The comparison of late complications between 2D conventional radiotherapy and 3D conformal radiotherapy with adjuvant chemotherapy for patients with rectal cancer in Siriraj Hospital

การเปรียบเทียบผลข้างเคียงระยะยาวระหว่างการฉายรังสี 2 มิติ และการฉายรังสี 3 มิติ เมื่อให้เป็นการรักษาเสริมร่วมกับยาเคมีบำบัดในผู้ป่วยมะเร็งลำไส้ตรงที่รักษาที่โรงพยาบาลศิริราช

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Submitted: May 12, 2021

Revised: July 12, 2021

Accepted: July 15, 2021

Abstract

Background: The transition of adjuvant radiotherapy techniques in treating locally advanced rectal cancer had been developed from 2-dimension conventional radiotherapy (2D-RT) to 3-dimensional conformal radiotherapy (3D-CRT). Theoretically, the 3D-CRT technique showed the advantage of more target dose coverage in treating field and lessen normal tissue toxicity compared to 2D-RT technique.

Objectives: To compare late radiation complications and quality of life (QoL) between patients receiving 2D-RT and 3D-CRT.

Materials and Methods: Locally advanced rectal cancer patients (T2-4 and/or lymph node positive), who received adjuvant either pre- or post-operative concurrent chemoradiotherapy between January 2012 and December 2018, were divided into 2 treatment groups: 2D-RT or 3D-CRT. After long term follow-up, we evaluated the late radiation complications using the RTOG/EORTC Late Radiation Morbidity Scoring Schema, and the QoL using the FACT-C Questionnaires, version 4.

Results: 235 locally advanced rectal cancer patients, (2D-RT; n = 62 and 3D-CRT; n = 173), were enrolled in this study. The median follow-up time was 4.92 years in 2D-RT group vs. 2.18 years in 3D-CRT group. There was no significant difference in late small / large intestine and bladder complications between 2 treatment groups. However, the QoL measurement showed better scores in longer follow-up time.

Conclusion: The longer follow-up periods had a significant impact on greater daily living. While there was no difference in late small / large intestine and bladder complications between both radiation techniques.

Keywords: rectal cancer, 2D radiotherapy, 3D conformal radiotherapy, late complication

บทคัดย่อ

หลักการและเหตุผล: ในปัจจุบันได้มีการพัฒนาเทคนิคการฉายรังสีรักษามะเร็งลำไส้ตรง จากแบบสองมิติเป็นสามมิติ เนื่องจากเทคคการฉายรังสีแบบสามมิติมีประโยชน์ในการเพิ่มการคลอบคลุมอวัยวะเป้าหมายและสามารถช่วยลดผลข้างเคียงจากการฉายรังสีได้มากกว่าเมื่อเปรียบเทียบกับการฉายรังสีแบบสองมิติ

วัตถุประสงค์: เพื่อศึกษาเกี่ยวกับผลข้างเคียงระยะยาวจากการการฉายรังสี, และระดับคุณภาพชีวิตในผู้ป่วยมะเร็งลำไส้ตรง ในระยะลุกลามเฉพาะที่ โดยเปรียบเทียบระหว่างการฉายรังสีแบบสองมิติและแบบสามมิติ

วัสดุและวิธีการ: เก็บข้อมูลรายละเอียดของผู้ป่วยมะเร็งมะเร็งลำไส้ตรงระยะลุกลามเฉพาะที่ (T2-4 และ/หรือ มีการลุกลามต่อมน้ำเหลือง) ที่เข้ารับการรักษาด้วยยาเคมีบำบัดร่วมกับการฉายรังสีก่อน หรือหลังการผ่าตัดตั้งแต่เดือนมกราคม พ.ศ. 2555 ถึงธันวาคม พ.ศ. 2561 โดยแบ่งออกเป็น 2กลุ่มหลักคือกลุ่มที่ได้รับการฉายรังสีแบบสองมิติ และกลุ่มที่ได้รับการฉายรังสีแบบสามมิติ โดยผลลัพธ์หลักคือเปรียบเทียบผลการศึกษาผลข้างเคียง

ระยะยาวจากแบบทดสอบมาตรฐาน RTOG/EORTC Late Radiation Morbidity Scoring Schema และการศึกษาระดับคุณภาพชีวิตจากแบบทดสอบ the FACT-C Questionnaires (version 4.0)
ผลการศึกษา: จากการศึกษาผู้ป่วยมะเร็งมะเร็งลำไส้ตรงระยะลุกลามเฉพาะที่รวม 235 คน แบ่งออกเป็นกลุ่มที่ได้รับการฉายรังสีแบบสองมิติ 62 คนและกลุ่มที่ได้รับการฉายรังสีแบบสามมิติ 173 คน ค่ามัธยฐานของระยะเวลาติดตามหลังการรักษา (median follow-up time) พบว่าเท่ากับ 4.92 และ 2.18 ปี ตามลำดับ ผลลัพธ์หลักพบว่าไม่มีความแตกต่างของผลข้างเคียงระยะยาวที่เกี่ยวกับผลข้างเคียงของลำไส้ และกระเพาะปัสสาวะจากการการฉายรังสีอย่างมีนัยสำคัญ อย่างไรก็ตามจากการประเมินระดับคุณภาพชีวิตพบว่าระยะเวลาติดตามหลังการรักษาที่นานจะมีคะแนนคุณภาพชีวิตดีกว่าอย่างมีนัยสำคัญ
ข้อสรุป: กลุ่มที่มีระยะเวลาติดตามหลังการรักษาที่นานจะช่วยให้คุณภาพชีวิตที่ดีขึ้นอย่างมีนัยสำคัญ แต่ผลข้างเคียงระยะยาวของลำไส้ และกระเพาะปัสสาวะของทั้งสองกลุ่มไม่แตกต่างกัน
คำสำคัญ: มะเร็งลำไส้ตรง, การฉายรังสี 2 มิติ, การฉายรังสี 3 มิติ, ผลข้างเคียงระยะยาว

J Thai Assoc Radiat Oncol 2021; 27(2): R27-R42

Introduction

Colorectal cancer is the third most common cancer in the world according to National Cancer institution[1]. The same rank in Thailand[2] and Siriraj hospital[3] was reported. Most of them presented with locally advanced disease (Stage II-III). Universal practice in rectal cancer treatment uses multimodality approach which were combinations between surgical management, radiotherapy, and chemotherapy. The benefit of radiotherapy in rectal cancer is to decrease the rate of locoregional recurrence (LRR) compare with surgery alone.[4,5] However, there was no significant improvement in disease free survival (DFS) and overall survival (OS).

In the past 20 years, radiotherapy techniques had huge development, from 2-dimension conventional radiotherapy (2D-RT) using radiologic anatomical reference to 3-dimension conformal radiotherapy (3D-CRT) using CT-image mapping, which increasde accuracy in treatment field and decreased normal tissue toxicity. In long-term follow-up, the most common and severe late complications of locally advanced rectal cancer after received concurrent chemo-radiotherapy (CCRT) were small intestine and bladder complications which affected quality of life (QoL). Approximately 4-12% had postoperative small intestinal obstruction that required surgical management.[6] Previous studies had reviewed factors affecting severity of late complications after completed adjuvant rectal carcinoma treatment. Reduction of radiation dosage to small intestine by increasing numbers of radiation fields would help reduce these complications. Moreover, 3D-CRT technique had

significant higher planning target volume coverage and reduced volume of irradiated small intestine compared to 2D-RT technique.[7] At the Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, number of patients treated with 2D-RT was constantly declined since 2012 paralleled with an up-rise number of 3D-CRT to the present time. In this study, we analyzed the difference in late small / large intestine and bladder complications and the QoL between 2D-RT and 3D-CRT techniques in locally advanced rectal cancer patients receiving pre-operative or post-operative CCRT.

Materials & Methods

This is a retrospective cohort study conducted at the Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital. The candidates in this study were rectal cancer patients treated during January 2012 - December 2018, aged more than 18 years old with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. These patients had received complete course of either pre-operative or post-operative CCRT with the curative aim treatment. The radiotherapy energy in our institution was Linac 10MV in both arms. There was some difference in radiation fields that almost both arms used 3-fields radiation technique (PA/RL/LL) but some cases in 3D-CRT arm who had inadequate conformal dose used 4-fields radiation technique (AP/PA/RL/LL). The patients with second primary cancer, or distant metastasis were excluded from this study. The study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine Siriraj Hospital.

The demographic data consisted of general data, tumor characteristics (TNM Stage: categorized according to the staging of AJCC 7th edition), treatment contents, and follow-up details were collected from electronic medical records while late complications and QoL were interviewed at out-patient department or by telephone using case record forms. The late complications and the quality of life were collected by interview once, either by telephone or face to face conversation.

RTOG/EORTC Late Radiation Morbidity Scoring Schema were used for grading late small / large intestine and bladder complications. QoL was scored by Functional Assessment of Cancer Therapy for Patients with Colorectal Cancer (FACT-C) Scoring Guidelines, version 4. The SPSS version 24, State and R software version 3.5.1 were used for all statistical analyses. *P*-value < 0.05 was considered statistically significant.

Results

The study participants were treated during January 2012 and October 2018. This period was the transition of radiation techniques from 2D-RT to 3D-CRT. The number of 2D-RT was gradually declined during 2012-2014 correlated with dramatically increased in number of 3D-CRT to the present day. There were 427 patients diagnosed with locally advanced rectal cancer during this period. However, only 235 participants were enrolled in this study: 62 in 2D-RT arm and

173 in 3D-CRT arm. We only included patients with curative aim treatment who had completed the treatment and follow-up schedules.

Patient characteristics

All patients had histologic proven of adenocarcinoma of rectal cancer without history of secondary cancer or any other cancer. According to baseline background data, there were no differences in both groups, more than half of the patients were male with a median age of approximately 60 years old. The majority had an initial CEA at diagnosis less than 5 ng/ml. **(Table 1)**

Table 1 Patient characteristics: General

Parameter	2D-RT n = 62	3D-CRT n = 173	*P*-value
Age (year)			
Median (IQR) *	61 (54, 68)	63 (56, 69)	0.255
Sex			
Male	35 (56.5%)	101 (58.4%)	0.909
Female	27 (43.5%)	72 (41.6%)	
CEA (initial at diagnosis)			
< 5 ng/ml	33 (55.9%)	88 (52.4%)	0.638
> 5 ng/ml	26 (44.1%)	80 (47.6%)	

Note. * IQR= interquartile range

Pretreatment primary tumor staging were described using pathological TNM staging for post-operative CCRT patients and clinical TNM staging for pre-operative CCRT patients. The T-staging was significant different between both groups. T3 and T4 staging in 3D-CRT group was 96.5%, whereas only 82.3% was observed in 2D-RT group (*p*-value <0.001). Seventy percent of the patients in both groups had regional lymph nodes metastasis and the same number had stage III disease. In 3D-CRT group, 35.3% of primary tumor was located at less than 5 cm from anal verge versus only 17.7% in 2D-RT group (*p*-value 0.016). These depicted poorer prognosis of participants in 3D-CRT group. **(Table 2)**

We divided treatment characteristics into 2 parts, first was the radiotherapy and chemotherapy session. In the late years, pre-operative radiotherapy was scheduled only 6.5% in 2D-RT group. While in recent years, pre-operative radio-

Table 2 Patient characteristics: Primary tumor

Primary tumor	2D-RT n = 62	3D-CRT n = 173	*P*-value
Staging *			
T staging			
T2	11 (17.7%)	6 (3.5%)	< 0.001
T3	41 (66.1%)	148 (85.5%)	
T4	10 (16.2%)	19 (11.0%)	
N staging			
N0	19 (30.6%)	51 (29.5%)	0.900
N1	27 (43.6%)	81 (46.8%)	
N2	16 (25.8%)	41 (23.7%)	
Staging			
I	1 (1.6%)	2 (1.2%)	0.944
II	18 (29.0%)	48 (27.7%)	
III	43 (69.4%)	123 (71.1%)	
Distance from Anal verge			
Median (IQR) **	8 (6,10)	6 (5,10)	0.029
Primary tumor location			
Upper (>10 cm from AV)	29 (46.8%)	52 (30.0%)	0.016
Middle (5-10 cm from AV)	22 (35.5%)	60 (34.7%)	
Lower (<5 cm from AV)	11 (17.7%)	61 (35.3%)	

Note. * Staging = post-op CCRT patients use pathological staging, pre-op CCRT patients use clinical staging
** Anal verge (AV), IQR= interquartile range

therapy became the standard treatment of rectal cancer in Siriraj Hospital. Correlation with the up-rise number of 3D-CRT treatment, pre-operative radiotherapy was significantly increased to 26.6% in 3D-CRT group (*p*-value 0.002). Most of the patients were prescribed with 45-50.4 Gy. However, booster dose of up to 54-60 Gy was used 19.6 % in 3D-CRT and 3.2% in 2D-RT (*p*-value 0.669). During radiotherapy treatment, the majority was set up in a prone position.

Chemotherapy was administered to all patients. For CCRT, Fluorouracil regimen was mostly prescribed. But there was higher number of Capecitabine regimen usage; 20.8% in 3D-CRT group versus 4.8% in 2D-RT group (*p*-value 0.011). For adjuvant chemotherapy, both Fluorouracil and Capecitabine regimens were proportionately used. **(Table 3)**

Table 3 Patient characteristics: Treatment; RT and Chemotherapy

Treatment	2D-RT n = 62	3D-CRT n = 173	*P*-value
Radiotherapy			
RT Schedule			
Postoperative RT	58 (93.5%)	127 (73.4%)	0.002
Preoperative RT	4 (6.5%)	46 (26.6%)	
Total dose (1.8-2.0 Gy / F)			
45 - 50.4 Gy	59 (95.2%)	137 (79.2%)	0.669
54 - 60 Gy	2 (3.2%)	34 (19.6%)	
> 60 Gy	1 (1.6%)	2 (1.2%)	
Treatment position			
Prone	53 (85.5%)	154 (89.0%)	0.611
Supine	9 (14.5%)	19 (11.0%)	
Chemotherapy			
Concurrent regimens			
Fluorouracil regimens *	53 (85.4%)	133 (76.9%)	0.011
Capecitabine regimens **	3 (4.8%)	36 (20.8%)	
NA	6 (9.8%)	4 (2.3%)	
Adjuvant regimens			
Fluorouracil regimens *	30 (48.4%)	96 (55.5%)	0.59
Capecitabine regimens **	26 (41.9%)	67 (38.7%)	
NA	6 (9.8%)	10 (5.8%)	

Note. * Fluorouracil, Fluorouracil / Leucovorin, or Fluorouracil / Leucovorin / Oxaliplatin

** Capecitabine or Capecitabine / Oxaliplatin

Abbreviation: NA = not available

The second part of treatment characteristic was surgical management. Most of the patients in both radiation techniques underwent anterior resection. The second most used procedure was abdominal perineal resection (APR). There was an insignificant difference in higher performed APR in 3D-CRT and 2D-RT, 31.8% and 17.8%, respectively. The surgical pathology was similar in both groups, in details of surgical margin positive, perineural invasion, and lympho-vascular space invasion. However, poorer predictors were higher in 3D-CRT group: tumor deposit 22.5% versus 6.5% (*p*-value 0.009), poor differentiation 6.4% versus 1.6%, and mucinous typed 5.8% versus 3.2% (*p*-value 0.018). On the other hand, the pathological complete response rate was 13% in 3D-CRT. **(Table 4)**

Table 4 Patient characteristics: Treatment; Surgery

Treatment	2D-RT n = 62	3D-CRT n = 173	*P*-value
Surgery			
Surgical procedure			
Anterior resection	49 (79.0%)	113 (65.3%)	0.063
Abdominal perineal resection	11 (17.8%)	55 (31.8%)	
Hartmann's operation	2 (3.2%)	3 (1.7%)	
Transanal excision	0	2 (1.2%)	
Pathology			
Surgical margin positive	8 (12.9%)	19 (11%)	0.861
Perineural invasion	27 (43.5%)	87 (50.3%)	0.445
Lymphovascular invasion	20 (32.3%)	48 (27.7%)	0.611
Tumor deposit	4 (6.5%)	39 (22.5%)	0.009
Differentiation type			
Well differentiation	8 (12.9%)	5 (2.9%)	0.018
Moderate differentiation	51 (82.3%)	138 (79.8%)	
Poor differentiation	1 (1.6%)	11 (6.4%)	
Mucinous	2 (3.2%)	10 (5.8%)	
NA	0	9 (5.2%)	
yp Staging*			
0	0	6 (13.0%)	1.000
I	1 (25%)	6 (13.0%)	
II	2 (50%)	21 (45.7%)	
III	1 (25%)	13 (28.3%)	

Note. * Preoperative chemoradiotherapy; 2D-RT n = 4, 3D-CRT n = 46

Abbreviation: NA = not available

Late radiation complications and QoL were evaluated after a median follow-up time of 4.92 (4.32, 5.54) years in 2D-RT group and 2.18 (1.53, 3.07) years in 3D-CRT groups.

Late Radiation Morbidities

We categorized patients into 2 subgroups: patients with permanent colostomy and without colostomy. The scoring was divided into 5 grades from 0 to 4. The higher they graded, the worsen of those complications.

Most of the patients were living without permanent colostomy; 75.8% in 2D-RT and 52.6% in 3D-CRT. Late small / large intestine and bladder complications occurred at the same rate, mostly mild symptoms. For colostomy patients, all 2D-RT candidates had none to mild symptoms of small / large intestine and bladder morbidity. While a few numbers of 3D-CRT patients were graded 2 or higher. There was no statistically significant difference between two radiation techniques. For non-colostomy patients, bladder complication grading was in the same trend. But for the late small / large intestinal morbidities, there was significant different outcome between these radiation techniques (*p*-value 0.007). 41.8% of 3D-CRT non-colostomy patients had graded 0 whereas only 17% had in 2D-RT group. Twenty two percent of 3D-CRT and 21.3% of 2D-RT groups experienced grade 2-4 small and large bowel complications. **(Table 5, 6)**

Quality of life

Quality of life (QoL) was classified by Functional Assessment of Cancer Therapy for Patients with Colorectal Cancer (FACT-C)

Table 5 RTOG/EORTC Late Radiation Morbidity: Small/Large intestine

Small/Large intestine	2D-RT	3D-CRT	*P*-value
Colostomy	n = 15	n = 82	
Grade 0	6 (40.0%)	55 (67.1%)	0.069
Grade 1	9 (60.0%)	19 (23.2%)	
Grade 2	0	1 (1.2%)	
Grade 3	0	6 (7.3%)	
Grade 4	0	1 (1.2%)	
Non-colostomy	n = 47	n = 91	
Grade 0	8 (17.0%)	38 (41.8%)	0.007
Grade 1	29 (61.7%)	33 (36.2%)	
Grade 2	7 (14.9%)	17 (18.7%)	
Grade 3	2 (4.3%)	3 (3.3%)	
Grade 4	1 (2.1%)	0	

Table 6 RTOG/EORTC Late Radiation Morbidity: Bladder

Bladder	2D-RT	3D-CRT	*P*-value
Colostomy	n = 15	n = 82	
Grade 0	15 (100%)	79 (96.4%)	1.000
Grade 1	0	1 (1.2%)	
Grade 2	0	2 (2.4%)	
Grade 3	0	0	
Grade 4	0	0	
Non-colostomy	n = 47	n = 91	
Grade 0	43 (91.5%)	89 (97.8%)	0.125
Grade 1	1 (2.1%)	0	
Grade 2	2 (4.3%)	2 (2.2%)	
Grade 3	1 (2.1%)	0	
Grade 4	0	0	

Questionnaires and sub-scaled in to 5 domains: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and colorectal cancer sub-scale (CCS). The scoring was reported in median and interquartile range (IQR). Equation of total scoring system: FACT-C, FACT-G, and trial outcome index (TOI) was described at the bottom of **Table 7-8**. Higher score reflected better quality of life. We analyzed quality of life by 2 factors: radiation techniques and follow-up time.

All total scoring system, 2D-RT patients significantly scored higher than 3D-CRT patients: FACT-C 117 versus 111 (*p*-value 0.021), FACT-G 96 versus 90 (*p*-value 0.008), and TOI 73 versus 69 (*p*-value 0.013). As same as FACT-C sub-scale, 2D-RT group tended to score better in all domains. **(Table 7)**

Analysis of follow-up time, we divided all patients regardless of treatment techniques into 3 groups: 52 patients of </=2 years follow-up, 80 patients of 2-4 years follow-up, and 68 patients of > 4 years follow-up. Duration of follow-up time had an impact on the QoL. The longer follow-up period, the better scoring in all modalities was observed with *p*-value <0.05. **(Table 8)**

However, social/family well-being (SWB) was the only aspect that reported insignificant difference either by radiation techniques (*p*-value 0.509) and follow-up time (*p*-value 0.146).

Discussion

We could presume that the group of patients

Table 7 The median score of FACT-C by Radiation technique

Treatment group	2D-RT n = 62	3D-CRT n = 173	*P*-value
FACT-C Subscale domains			
Physical well-being (PWB)			
Median (IQR)	27 (25, 28)	26 (23, 28)	0.120
Social / Family well-being (SWB)			
Median (IQR)	20 (17, 26)	21 (18, 23)	0.509
Emotional well-being (EWB)			
Median (IQR)	23 (22, 24)	23 (20, 24)	0.025
Functional well-being (FWB)			
Median (IQR)	26 (23, 27)	22 (16, 27)	0.004
Colorectal cancer subscale (CCS)			
Median (IQR)	22 (19, 25)	21 (19, 24)	0.307
Total score			
FACT-C * (Total score = 0 - 136)			
Median (IQR)	117 (106, 124)	111 (100, 121)	0.021
FACT-G ** (Total score = 0 - 108)			
Median (IQR)	96 (88, 100)	90 (82, 98)	0.008
TOI *** (Total score = 0 - 84)			
Median (IQR)	73 (69, 78)	69 (60, 77)	0.013

Note. * FACT-C = Functional Assessment of Cancer Therapy - Colorectal cancer, the sum score of all subscale domains

** FACT-G = Functional Assessment of Cancer Therapy - General (Health related general quality of life, assessment for chronic illness), the sum score of all subscale domains except CCS

*** TOI = Trial outcome index, the sum score of the PWB and FWB from the FACT-G and the disease- specific subscale items

receiving 3D-CRT had poorer prognostic features. Significant higher number of T3 and T4 pretreatment staging, and primary tumor located at lower rectum (<5 cm from anal verge) might had affected the treatment option on higher total radiation dose (up to 54 – 60 Gy) and more APR rate. Histology also reported more tumor deposition in 3D-CRT than 2D-RT patients. There

Table 8 The median score of FACT-C by Follow-up time

Duration of follow up	<2 Yrs n = 52	2-4 Yrs n = 80	>4 Yrs n = 68	*P*-value
FACT-C Subscale domains				
Physical well-being (PWB)				
Median (IQR)	26 (22, 28)	26 (24, 28)	27 (26, 28)	0.014
Social / Family well-being (SWB)				
Median (IQR)	20 (19, 21)	21 (17, 23)	22 (18, 26)	0.146
Emotional well-being (EWB)				
Median (IQR)	22 (20, 24)	22 (21, 23)	24 (22, 24)	0.009
Functional well-being (FWB)				
Median (IQR)	19 (16, 23)	23 (17, 27)	26 (23, 28)	< 0.001
Colorectal cancer (CCS)				
Median (IQR)	21 (18, 24)	21 (19, 24)	23 (20, 26)	0.037
Total score				
FACT-C (Total score = 0 - 136)				
Median (IQR)	105 (98, 116)	112 (101, 121)	119 (109, 126)	< 0.001
FACT-G (Total score = 0 - 108)				
Median (IQR)	84 (79, 92)	90 (82, 97)	97 (90, 102)	< 0.001
TOI (Total score = 0 - 84)				
Median (IQR)	65 (59, 73)	70 (61, 78)	74 (70, 79)	< 0.001

Note. * FACT-C = Functional Assessment of Cancer Therapy - Colorectal cancer, the sum score of all subscale domains

** FACT-G = Functional Assessment of Cancer Therapy - General (Health related general quality of life, assessment for chronic illness), the sum score of all subscale domains except CCS

*** TOI = Trial outcome index, the sum score of the PWB and FWB from the FACT-G and the disease-specific subscale item

was also distinction between cellular differentiation type. Higher amount of poor differentiation and mucinous were found in 3D-CRT.

Influenced by the poorer baselines in pathologic tissue in 3D-CRT, there were nearly a half of patients with APR in 3D-CRT more than in 2D-RT. And for chemotherapy detail, the trend of using capitabine was increased in 3D-CRT which might be convenient in daily life and minimal in side effect, however, beyond the

scope of this study. There were two previous studies comparing 2D-RT and 3D-CRT in locally advanced rectal cancer. Corner reported that 3D-CRT was superior to 2D-RT in terms of better target coverage of the tumor volume and lessen the volume of small intestine.[8] Supported by Cella 3D-CRT also improved target coverage of the tumor without affecting normal tissue complication probability for small intestine and bladder.[9] Although 3D-CRT technique could increase accuracy in treating field and decrease normal tissue toxicity, it would also have an influence on late radiation complications and QoL.

Intestinal toxicity was the most frequent complication and serious side effect following radiotherapy in rectal cancer patients. It usually occurred within the first 6-18 months after treatment. Komori reported 13% of advanced rectal cancer patients receiving post-operative radiotherapy had experienced intestinal complication as early as 2 to 3 months and 25% as late as 10 years.[10] The sequelae included diarrhea, ileus, intestinal perforation, and pelvic inflammation. However, pelvic small intestinal volumes and radiation target volume were determined of late small intestinal complication. Guckenberger revealed that patients who underwent surgery especially APR likely to develop small intestine fixation but prone position and belly board used during radiation may helped reduced volume of small intestine in the treatment field.[11] Multiple field treatment technique, even in 2D-RT that reduced dose to small intestine which showed benefit in reduced small intestine complication rate to lesser than 5-10%.[5,7,12] However, in our study, 2D-RT group showed less moderate late intestine and bladder complications. We assumed that it was an effect of time. The median follow-up time of 2D-RT was 4.92 years while only 2.18 years in 3D-CRT groups.

Quality of life (QoL) was an important factor reflecting treatment outcome. In colorectal cancer patients, intestine problems and stoma had an impact on daily living. Diarrhea and incontinence may interfere with family and social life. To improve quality of life, we need to facilitate post-radiation treatment adaptation. Education, self-help group, behavioral therapy such as anal training may help patients coped with their changes.[13]

According to Yoo's study, FACT-C was a valid disease specific tool responsible to change in functional status over period of time. QoL decreased during the first few months after treatment while over 6 months period, it recovered to baseline level.[14] These supported our outcome that regardless of radiation techniques, FACT-C scoring may increase over the period of time. Moreover, the number of patients who had worsened baseline features as mentioned above tended to receive higher radiotherapy doses which might induce more discomfort in daily life and bring lower QOL in 3D-CRT, which need further investigation to clarify this suspicion. The high percentage of APR rate in 3D-CRT increased the amount of patients who had permanent colostomy which was not habituated to them, thus result in reduction of QOL point in 3D-CRT group in our study.

There were some limitations in our study. First, there were some differences in baseline characteristics of both arms in which patients in 3D-CRT had poorer prognostic features. This might make the 3D-CRT had the aggressive treatment which could be followed by the more severe complications and poorer quality of life. Secondly, this study might illustrate the results in different points of time compared between both arms. To describe the reason, there was the transition of 2D-RT to 3D-CRT technique from the past to present time which would be better if the author could further collect the data of 3D- CRT longer enough to compare them in the same period. Third, there was a difference in beam directions which might have influenced the bowel complication. The radiotherapy treatment planning system in the 3D-CRT era could adapt the dose distribution to conform almost in target organs and limit the dose constraints to normal tissue. Owing to those reasons, some cases had raised AP-beam direction and the increasing dose treatment which might presume to increase the bowel complications whereas the results of the late bowel complication in this study were no significant difference in both arms. Nevertheless, the colostomy dependent group showed the trend of increasing grade 2 or more of late small/large intestine complication in 3D-CRT (8 patients (9.7%)) vs. 2D-RT (0 patient(0%)). In our opinion, the benefit of the CT simulation in 3D-CRT had more potential, although AP beam direction was more frequently used in 3D CRT group. This factor could be further studied to show the resolution. Lastly, the limitation of results in some cases of telephone interviews might affect the quality of life's evaluation. There might be more accurate result by making the face-to-face interview.

Conclusion

The 2D-RT was not inferior to 3D-CRT in term of late bowel and bladder toxicities. There was no significant difference in late intestine and bladder complications between both radiation techniques. As an effect of longer follow-up time, 2D-RT patients tended to have lesser moderate intestine and bladder complications and significant better QoL. We suggested that the longer follow-up in 3D-CRT group would get some further profitable outcomes about the timing effect and other influential factors.

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