# Outcomes of preoperative radiotherapy in rectal cancer: a single institute experience

# รายงานการวิเคราะห์ผลการรักษามะเร็งลำไส้ตรง ด้วยวิธีฉายรังสีก่อนการผ่าตัด

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## Abstract

**Background:** The combination of preoperative radiotherapy, total mesorectal excision surgery and systemic chemotherapy contributed to improved disease control of rectal cancer in modern era. Different radiotherapy fractionation has been used in clinical practice in Thammasat hospital.

**Objective:** To evaluate treatment outcomes of rectal cancer patients who underwent preoperative radiotherapy at Thammasat hospital.

**Materials and methods:** Retrospective chart review of rectal cancer patients who underwent preoperative radiotherapy at Thammasat hospital from October 1,2015 to January 31,2021.

**Results:** A total of 70 rectal cancer patients underwent preoperative radiotherapy. Most patients were in a locally advanced stage. Sixty-three patients received conventional fractionation radiotherapy concurrent with intravenous 5-fluorouracil or oral capecitabine followed by surgery and adjuvant chemotherapy. The median dose of conventional fraction was 50.4 Gy. Preoperative short-course radiotherapy of 25 Gy in 5 fractions followed by surgery and adjuvant chemotherapy was given in seven patients. All of the patients who received short course radiotherapy and 80.95% of patients who received long-course radiotherapy achieved complete resection. Pathological complete response was found in 11.4% with all being the subset that received long course radiotherapy. From the median follow-up time of 20.5 month, 2-year overall survival was 88.5%, 2-year progression-free survival was 49.3%, 2-year locoregional recurrence free was 70.5% and 2-year distant metastasis free survival was 58%. A total of 30 patients developed disease failure. Eight patients (11.4%) had loco-regional recurrence as the first recurrence, 4 of them had persistent disease (5.7%); 22 developed distant metastasis (32.8%) including one who had synchronous loco-regional and distant metastasis (1.4%). Complete resection was shown to improve progression free survival in multivariate analysis (HR 0.11, 95%CI 0.05-0.27, p value<0.001).

**Conclusions:** Preoperative radiotherapy, both short course and long course fractionation, facilitate complete resection in rectal cancer. Distant metastasis is the most common cause of disease recurrence.



**Keywords:** preoperative radiotherapy, short course radiotherapy, rectal cancer



## บทคัดย่อ

**หลักการและเหตุผล:** การรักษามะเร็งลำไส้ตรงด้วยการฉายรังสีก่อนการผ่าตัดแบบเลาะเนื้อเยื่อรอบลำไส้ออกร่วมกับการให้ยาเคมีบำบัด มีส่วนช่วยให้ผลการรักษาในยุคปัจจุบันได้ผลดีมากขึ้น การฉายรังสีด้วยสูตรปริมาณรังสีที่ต่างกันได้ถูกนำมาใช้ในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

**วัตถุประสงค์:** เพื่อวิเคราะห์ผลการรักษาโรคมะเร็งลำไส้ตรง ของผู้ป่วยในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติที่ได้รับการฉายรังสีก่อนเข้ารับการผ่าตัด

**วัสดุและวิธีการ:** การทบทวนเวชระเบียนย้อนหลังของผู้ป่วยมะเร็งลำไส้ตรง ที่ได้รับการฉายรังสีก่อนการผ่าตัดในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ตั้งแต่ ตุลาคม 2558 ถึง มกราคม 2564

**ผลการศึกษา:** ผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งลำไส้ตรงจำนวนทั้งสิ้น 70 ราย ได้รับการรักษาด้วยการฉายรังสีก่อนการผ่าตัด โดยส่วนใหญ่เป็นโรคระยะลุกลามเฉพาะที่ ผู้ป่วยจำนวน 63 รายได้รับการฉายรังสีก่อนการผ่าตัดแบบสูตรยาว ร่วมกับเคมีบำบัด5-Fluorouracil ทางหลอดเลือดดำ หรือยา Capecitabine ทางปาก ตามด้วยการผ่าตัดและยาเคมีบำบัดหลังการผ่าตัด ค่ามัธยฐานปริมาณรังสีที่ได้รับคือ 50.4 เกรย์ ผู้ป่วยจำนวน 7 รายได้รับการฉายรังสีก่อนการผ่าตัดแบบสูตรสั้น 25 เกรย์ใน 5 ครั้ง ตามด้วยการผ่าตัดและยาเคมีบำบัดหลังการผ่าตัด โดยผู้ป่วยทุกรายที่ได้รับการฉายรังสีสูตรระยะสั้นและ 80.95% ของผู้ป่วยที่ได้รับการฉายรังสีสูตรระยะยาวสามารถเข้ารับการผ่าตัดออกได้หมด ผลชิ้นเนื้อจากการผ่าตัดพบว่า 11.4% ไม่พบรอยโรคมะเร็งหลงเหลือ โดยทั้งหมดเป็นผู้ป่วยที่ได้รับการฉายรังสีสูตรระยะยาว จากค่ามัธยฐานเวลาการติดตาม 20.5 เดือน อัตราการรอดชีวิตที่สองปีอยู่ที่ 88.5%, อัตราการรอดชีวิตโดยปราศจากการกำเริบที่สองปี 49.3%, อัตราการควบคุมโรคเฉพาะที่ต่อมน้ำเหลืองใกล้เคียง 70.5% และอัตราการรอดชีวิตโดยไม่มีการแพร่กระจายที่สองปี 58% ในผู้ป่วย 30 รายที่มีโรคกลับเป็นซ้ำ 8 ราย (11.4%) เกิดโรคกลับเป็นซ้ำเฉพาะที่ โดย 4 รายเป็นรอยโรคเดิมที่ไม่ตอบสนองกับการรักษา มีผู้ป่วยจำนวน 22 ราย (32.8%) มีโรคแพร่กระจาย โดยที่ 1 ราย (1.4%) มีกลับเป็นซ้ำเฉพาะที่ร่วมด้วย ปัจจัยที่สัมพันธ์กับการเพิ่มโอกาสรอดชีวิตโดยปราศจากการกำเริบในการวิเคราะห์แบบหลายตัวแปร ได้แก่ การผ่าตัดก้อนออกได้หมด (HR 0.11, 95%CI 0.05-0.27, p value<0.001)

**ข้อสรุป:** การฉายรังสีก่อนการผ่าตัดมะเร็งลำไส้ ไม่ว่าด้วยสูตรระยะยาวหรือระยะสั้น ช่วยทำให้สามารถผ่าตัดก้อนมะเร็งออกได้หมด การแพร่กระจายของโรคมะเร็งไปยังอวัยวะอื่นคือสาเหตุหลักของการล้มเหลวของการรักษา

**คำสำคัญ:** การฉายรังสีก่อนการผ่าตัด, การฉายรังสีสูตรระยะสั้น, มะเร็งลำไส้ตรง

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## Backgrounds

In Early 2000s, extra-fascial excision of rectal cancer by removing rectum and the surrounding mesorectum was proven to improve disease control and overall survival[1-2]. In locally advanced stage rectal cancer, postoperative radiotherapy therapy was recommended until studies including randomized controlled trial identified that preoperative radiotherapy achieved better local control with fewer toxicities[3-4] Adding concurrent chemotherapy during preoperative radiotherapy decreased locoregional recurrence[5] and even improved cancer-specific survival in locally advanced disease[6-7]. The combination of effective total mesorectal excision the addition of preoperative radiotherapy and systemic chemotherapy contributed to improved outcomes of locally

advanced rectal cancer treatment and become a standard in the modern era[8-9].

Radiotherapy treatment volume of rectal cancer includes added margin of primary tumor, lymphadenopathy and potential microscopic disease in pelvic cavity. Conventional fractionation or long-course radiotherapy concurrent with systemic chemotherapy was the most common regimen as this had been in the established studies[3-4]. Short course radiotherapy given to the same treatment volume followed by immediate surgery within one week was another approach that was used[10]. Studies found no different disease outcomes in either preoperative short-course and long-course radiotherapy[11-12]. Interdepartmental communication is important to determine the sequence of treatment plan in multidisciplinary team. There has been more discussion to encourage usage of short course radiotherapy regimen during pandemic as it required less radiotherapy treatment time and resources while yielding comparable oncologic outcomes[13].

The study goal is to analyze outcomes comparing to literature data and determine feasibility of each regimen in our institution in order to further improve treatment protocol.

## Materials and methods

### Patient

We studied rectal cancer patients who underwent preoperative radiotherapy at Thammasat university hospital from October 1,2015 to December 31,2020. Retrospective chart review was performed to collect demographic data and treatment outcome.

### Treatment

Two well-established preoperative radiotherapy regimens were used in rectal cancer treatment; long course concurrent radiotherapy and short course radiotherapy. Either long course or short course radiotherapy can be administered unless potential circumferential margin involvement or unresectable tumor are predicted, then long course radiotherapy is preferred. Preoperative long course radiotherapy patients received radiotherapy concurrent with intravenous 5-fluorouracil or oral Capecitabine followed by surgery after 8-12 weeks and received four months of adjuvant chemotherapy. For patients who received preoperative short course radiotherapy, surgery was performed within one week followed by six months of adjuvant chemotherapy. Adjuvant chemotherapy regimens included FOLFOX, XELOX, 5-FU/LV, Capecitabine and CapeOx.

### Radiotherapy

Patient underwent computed tomography (CT) simulation in supine position with foot support immobilization. A series of axial images was obtained on a CT simulator (Siemens SOMATOM Definition AS) with continuous 3-mm slice thickness. Additional deformable image registration with axial MRI T2-weighted FS was performed if available. Contour of target tumor and organ at risk was performed by radiation oncologists. Three-dimensional radiotherapy

planning was calculated using Elekta's Monaco treatment planning system (version 5.11.03) which was subsequently treated with Versa HD Linear accelerator.

Clinical target volume (CTV) included primary rectal cancer and regional lymph nodes; perirectal, internal iliac, pelvic side wall and presacral node. For patients who received short course radiotherapy, radiation dose of 25 Gray (Gy) in 5 fractions was prescribed. For patients who received long course radiotherapy, the initial 45 Gy in conventional fraction was prescribed to the same CTV. Sequential boost of 5.4-9 Gy was then prescribed to cover clinical target volume of gross primary tumor plus 2 centimeters. Additional 5 millimeters margin was used for planning target volume (PTV).

**Outcome measurement**

The overall survival (OS) was calculated from the day of pathological diagnosis until death from any cause. Progression-free survival (PFS) was calculated from the day of pathological diagnosis until death from any cause or any cancer events, including locoregional and distant recurrence. Distant metastasis free survival (DMFS) rate was calculated from the day of pathological diagnosis until death from any cause or distant metastasis. Loco-regional control (LRC) was calculated from the day of pathological diagnosis until local and/or regional recurrence or death from any cause. Patients without mortality or any cancer events were censored at the time of last follow-up.

Pathological complete response (pCR) was defined as no viable tumor cell in both primary tumor (T) and nodal (N) disease. Partial pathological response included any regression of T or N or extramural vascular invasion (EMVI) from initial clinical staging. No pathological response was progression or no detectable pathological change from baseline. Unresectable cases were classified as no pathological response. The AJCC 8th edition was used to classify TNM stages.

**Statistical analysis**

Time-to-event analyses for OS, PFS, LRC and DMFS were calculated by the Kaplan-Meier method.

Univariate and multivariate models were used to identify clinical risk factors influencing treatment outcomes by calculating hazard ratios (HR) in Cox regression models. Results with two-sided $p$ values of $\leq 0.05$ were regarded as statistically significant. Analyses and calculation were performed using R software (R core team, version 3.5.3, Vienna, Austria).

**Ethics**

Study protocol was reviewed and data access was approved by the Human Research Ethics Committee of Thammasat university (MTU-EC-RA-0-029/64).

**Results**

A total of 70 locally advanced rectal cancer patients underwent preoperative radiotherapy at

Thammasat hospital from October 1, 2015 to January 31, 2021. Patient characteristic was shown in **Table 1**. The average age was 61 years (range, 27-81 years) and most of the patients were male (50, 71.4%). Most patients were in nonmetastatic locally advanced stage; Tumor stage three to four, positive nodal disease without distant metastasis.

**Table 1.** Patient characteristics

| Demographic | | Number | Percentage |
|---|---|---|---|
| Age | ≤50 | 11 | 15.7% |
| Mean = 61 (range 27-81) | 51-70 | 47 | 67.1% |
| | >70 | 12 | 17.2% |
| Sex | Male | 50 | 71.4% |
| | Female | 20 | 28.6% |
| T stage | T1 | 0 | 0% |
| | T2 | 2 | 2.8% |
| | T3 | 51 | 72.9% |
| | T4 | 17 | 24.3% |
| N stage | N0 | 8 | 11.4% |
| | N1 | 46 | 65.7% |
| | N2 | 16 | 22.9% |
| M stage | M0 | 61 | 87.1% |
| | M1a | 9 | 12.9% |
| Pathology | Adenocarcinoma | 69 | 98.6% |
| | Mucinous | 1 | 1.4% |
| Radiotherapy Long course RT | 5FU/LV | 17 | 24.3% |
| | Capecitabine | 44 | 62.8% |
| | RT alone | 2 | 2.9% |
| Short course | | 7 | 10% |
| RT dose fractionation | 25 Gy | 7 | 10% |
| (25-60 Gy) | 50.4-54 Gy | 48 | 68.6% |
| | >54 Gy | 15 | 21.4% |
| Adjuvant chemotherapy | Completed | 51 | 72.9% |
| | No/incompleted | 19 | 27.1% |

| Demographic | | Number | Percentage |
|---|---|---|---|
| Surgery | Low anterior resection | 39 | 55.7% |
| | Abdominoperineal resection | 18 | 25.7% |
| | Pelvic exenteration | 4 | 5.7% |
| | No surgery | 9 | 12.9% |
| Resectability | R0 resection | 58 | 82.9% |
| | R1 resection | 0 | 0% |
| | R2 resection/unresectable | 12 | 17.1% |
| Pathological response | Complete | 8 | 11.4% |
| | Partial | 46 | 65.7% |
| | No | 16 | 22.9% |

**Abbreviation:** RT = radiotherapy, 5-FU = Fluorouracil, LV = Leucovorin

**Treatment**

Sixty-three patients received conventional fractionation radiotherapy concurrent with intravenous 5-fluorouracil or oral capecitabine; two of 63 received radiotherapy alone. The median dose of conventional fraction was 50.4 Gy (range, 50.4-60 Gy). Median time from the end of radiation to surgery was 62 days (range, 22-134 days)

Preoperative short course radiotherapy of 25 Gy in 5 fractions was given in seven patients followed by surgery and adjuvant chemotherapy. Three out of seven patients underwent surgery within one week per protocol (range, 4-71 days). Regardless of radiotherapy regimen, 19 (27.1%) patients failed to complete planned adjuvant chemotherapy due to following reasons; postoperative complication (3), chemotherapy toxicities (5), denial of treatment (2) and rapid progression of disease before completion of adjuvant chemotherapy (9).

**Oncologic outcomes**

From the median follow-up time of 20.5 month (range, 1-78 months), 2-year overall survival was 88.5% ( 95%CI 79.8-98.1%) and 2-year progression free survival was 49.3% (95%CI 38.1-63.8%). 2-year locoregional recurrence control was 70.5% (95%CI 58.1-85.7%). 2-year distant metastasis free survival was 58% (95%CI 46.6-72.3%) (figure 1). A total of 30 patients developed disease failure. Eight patients (11.4%) had loco-regional recurrence as the first recurrence with four had persistent disease (5.7%); 22 developed distant metastasis (32.8%) and one had synchronous loco-regional and distant metastasis (1.4%). Gastrointestinal toxicities as follows; anastomosis leakage, bowel obstruction, bowel fistula and radiation proctitis was found in three, one, one and one patients respectively. The following genitourinary toxicities; bladder fistula, ureteral stenosis and radiation cystitis was reported in three, one and one patients, respectively.

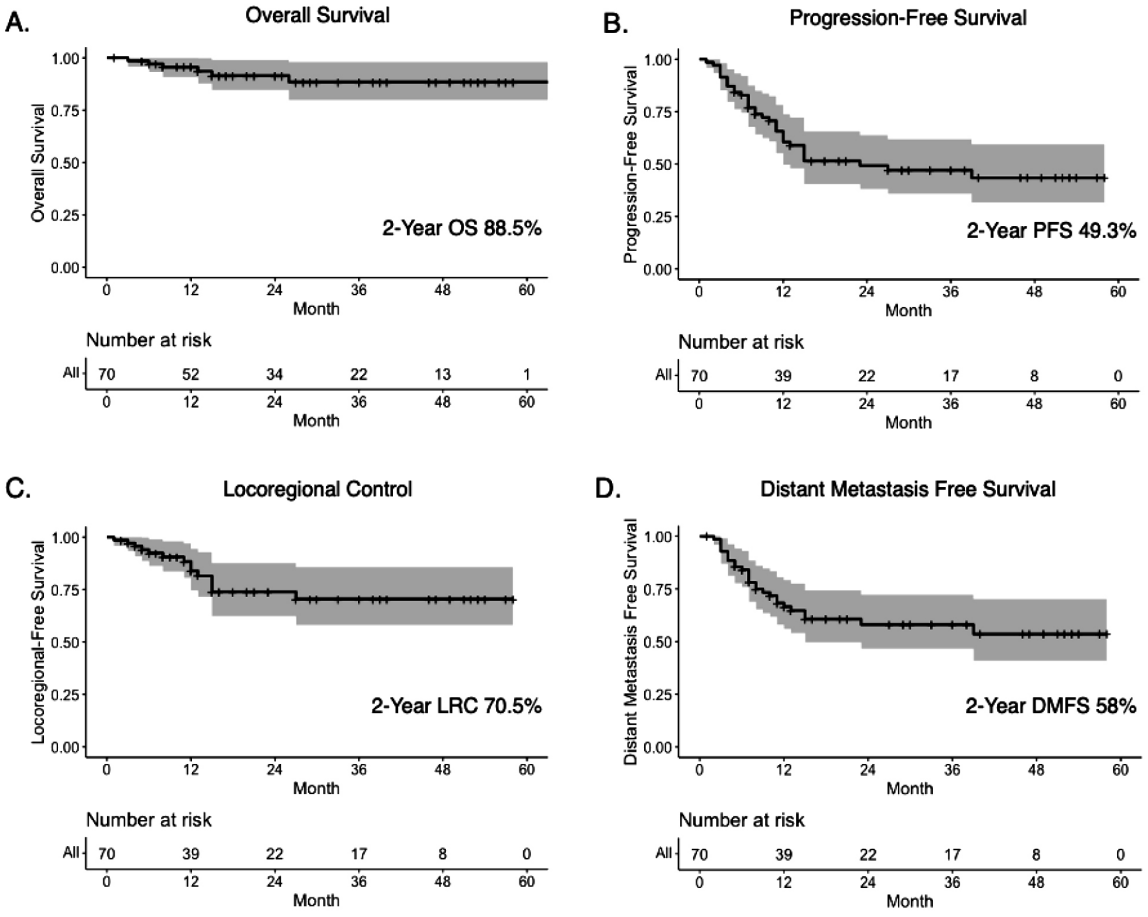


**Figure1.** Kaplan Meier plots of disease outcomes. (A) Overall survival. The 2-year overall survival was 88.5%, (88.5%, 95%CI 79.8-98.1%); (B) Progression-free survival. The 2-year progression free survival was 49.3%, (49.3%, 95%CI 38.1-63.8%); (C) Loco-regional control. The 2-year locoregional recurrence control was 70.5%, (70.5%, 95%CI 58.1-85.7%); (D) Distant metastasis free survival. The 2-year distant metastasis free survival was 58%, (58%, 95%CI 46.6-72.3%)

Overall, preoperative radiotherapy achieved complete resectability in 58 out of 70 patients (82.9%). All of patients who received short course radiotherapy achieved complete resectability (100%,7 out of 7) while 80.95% (51 out of 63) of patients who received long course radiotherapy underwent complete resection. Pathological complete response was found in 11.4% overall (8 out of 70 patients). All of these patients were the subset that received long course radiotherapy (8 out of 63 patients,12.7%). None of the patients in short course preoperative subgroup achieved complete pathological response.

Correlation of clinical risk factors with progression free survival were calculated using cox regression analysis. The risk factors were age, sex, ECOG performance status, Tumor stage, nodal positivity, complete resection, pathological complete response and preoperative radiotherapy regimen. The result was shown in **table 2**. Complete resection was the only factor that shown to improve progression free survival in univariate analysis (HR 0.15, 95%CI 0.07-0.32, *p* value<0.001) as well as in multivariate analysis (HR 0.11, 95%CI 0.05-0.27, p value<0.001).

**Table2.** Cox proportional hazard ratio of risk factors and progression free survival.

| Covariates | Univariate Cox HR (95%CI) | p-value | Multivariate Cox HR (95%CI) | p-value |
|---|---|---|---|---|
| Age | 1.10 (0.76-1.60) | 0.61 | 1.11 (0.75-1.66) | 0.60 |
| Sex female vs male | 1.63 (0.80-3.32) | 0.17 | 2.11 (0.97-4.61) | 0.06 |
| ECOG 1 vs 0 | 1.29 (0.45-3.68) | 0.63 | 0.67 (0.22-3.07) | 0.78 |
| T3-T4 vs T1-T2 | 0.90 (0.27-2.94) | 0.86 | 1.62 (0.31-8.39) | 0.57 |
| Positive nodal disease | 1.01 (0.35-2.87) | 0.98 | 1.32 (0.36-4.78) | 0.68 |
| Complete resection | 0.15 (0.07-0.32) | <0.001 | 0.11 (0.05-0.27) | <0.001 |
| pCR | 1.19 (0.42-3.37) | 0.75 | 1.24 (0.29-5.25) | 0.77 |
| Short course vs Long course | 1.21 (0.43-3.45) | 0.71 | 1.78 (0.56-5.68) | 0.33 |

**Abbreviations:** HR= Hazard Ratio, CI = confidence interval, ECOG= Eastern Cooperative Group performance status, pCR= pathological complete response.

## Discussion

The effectiveness of total mesorectal excision surgery, the addition of preoperative radiotherapy and systemic chemotherapy contributed to improved disease control in modern era [9,14]. The aim of preoperative radiotherapy, either a short course or long course RT, is to facilitate resection and reduces local recurrence[15-16].

The study included unresectable disease as a part of locoregional failure whether it was due to persistent disease or patient refusal of surgery. With the small total number of patients, this contributed to a relatively low locoregional control compared to previous data that excluded these population[5,6,8]. Overall treatment failure was predominantly due to distant metastasis as in the other studies[6, 8]. Contemporary data showed that long course CCRT achieved

pCR at 11.4-19.5%[14, 17] while short course radiotherapy achieved pCR around 0.7% although survival outcomes were not different[12].

Attention has been shifted toward hypofractionation radiotherapy especially when utilization of time and resources have to be optimized amid pandemic. Short course preoperative radiotherapy regimen showed comparable oncological outcomes compared to conventional fraction in many studies including the randomized controlled trial[18]. Although none of the patients who received short course radiotherapy in this study achieved complete pathological response, complete surgical resection was achieved in every case even though the total number was low. Since complete resection was the proven factor to increase chance of better PFS in both univariate and multivariate analysis, the effort of implementing this regimen was not futile. Short course radiotherapy shortened radiotherapy treatment time but it is important to have multidisciplinary cooperation to ensure surgical plan within one week. Four out of seven patients who received short course radiotherapy failed to undergo surgery within one-week interval but all patients still achieved complete resection. There were proven benefits of watch and wait or delayed surgery after short course radiotherapy to enhance tumor regression and decrease postoperative complication especially in elderly patients[19-20].

Any modality that is helpful for complete resectability as well as other variables that were proven to improve disease control such as complete pathologic response[8] should be encouraged.

Distant metastasis was the prominent cause of disease failure in this study even after excluding ones with initial M1a stage. This correlates with the previous study[21]. A significant number of patients in our study failed to receive complete adjuvant chemotherapy mostly because of chemotherapy toxicities and rapid development of metastasis. Justification of adjuvant chemotherapy was questioned as studies found no significant survival benefit in overall patients but in certain subgroup such as ones with primary tumor in upper rectum and ones with residual tumor after preoperative chemoradiation[22-23]. Unable to complete adjuvant chemotherapy was also an important factor contributed to suboptimal treatment result whether it was from postoperative complication that delayed the adjuvant chemotherapy or poor compliance of patients[24-25]. Novel studies[26-27] found a promising approach of using neoadjuvant chemotherapy to minimize distant metastasis and achieved pCR rate up to 28.4%. The result of this study, showing that distant metastasis was the main problem of disease failure, encouraged our team to consider incorporating total neoadjuvant therapy into our institutional protocol.

The limitation of this study is the retrospective approach. Direct comparison of different radiotherapy regimens requires a randomized controlled design. The relatively small number of sample size from a single institute study limits the generalization of the result from this study.

## Conclusion

Preoperative radiotherapy, both short course and long course fractionation, facilitate complete resection in rectal cancer. Distant metastasis is the most common cause of disease recurrence.

## Conflict of interest

None.

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