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อุบัติการณ์การตอบสนองทางพยาธิวิทยาแบบสมบูรณ์ในผู้ป่วยมะเร็งลำไส้ตรงที่ได้รับยาเคมีบำบัดร่วมกับการฉายรังสีในโรงพยาบาลวชิรพยาบาล

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Incidence of Pathological Complete Response after Neoadjuvant Treatment in Current Vajira Hospital Rectal Cancer Practice

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บทคัดย่อ

หลักการและวัตถุประสงค์: มะเร็งลำไส้ใหญ่และลำไส้ตรง เป็นมะเร็งที่พบได้มากที่สุดเป็นอันดับสามทั่วโลก การรักษาที่ได้รับการยอมรับในปัจจุบันในผู้ป่วย locally advanced rectal cancer คือการให้ยาเคมีบำบัดร่วมกับการฉายรังสี (concurrent chemoradiation therapy; CCRT) ตามด้วยการผ่าตัด total mesorectal excision (TME) ซึ่งผลการตอบสนองต่อ CCRT ในแต่ละงานวิจัยมีความแตกต่างกันอย่างมาก และมีผู้ป่วยประมาณร้อยละ 15-30 ที่มีการตอบสนองทางพยาธิวิทยาแบบสมบูรณ์ (pathological complete response; pCR) โดยงานวิจัยนี้จึงมีเป้าหมายที่จะศึกษาเกี่ยวกับอัตราการตอบสนองทางพยาธิวิทยาแบบสมบูรณ์ (pCR rate) และปัจจัยที่มีผลต่อการตอบสนองทางพยาธิแบบสมบูรณ์ ในผู้ป่วยมะเร็งลำไส้ตรงที่ได้รับยาเคมีบำบัด ร่วมกับการฉายรังสีในประเทศไทย

วิธีการศึกษา: เป็นการศึกษาแบบย้อนหลัง (retrospective review of a prospectively collected database) โดยศึกษาจากผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งลำไส้ตรง ระยะที่ 2-3 ที่มี cT3-4, N0 หรือ any cT, cN1-2 เท่านั้น และผู้ป่วยต้องได้รับการรักษาด้วยการให้เคมีบำบัดร่วมกับฉายรังสีก่อนการผ่าตัด (neoadjuvant CCRT) ในช่วงปี พ.ศ. 2557-2563

ผลการศึกษา: ผู้ป่วยมะเร็งลำไส้ตรง ทั้งสิ้น 234 ราย มีผู้ป่วย 101 ราย (ร้อยละ 43.1) ที่ได้รับ neoadjuvant CCRT โดยมีผู้ป่วยชาย 68 ราย (ร้อยละ 67.3) อายุเฉลี่ย 58.5±11.5 ปี ตำแหน่งก้อนที่พบมาก ที่สุดคือ lower rectum 60 ราย (ร้อยละ 59.4) มี clinical T staging เป็น cT3 76 ราย (ร้อยละ 75.2) และ clinical N staging เป็น cN1-2 54 ราย (ร้อยละ 53.5) มีผู้ป่วยทั้งสิ้น 14 ราย (ร้อยละ 13.9) ที่มีการตอบสนองทางพยาธิวิทยาแบบ pCR เมื่อคำนวณ univariate analysis และ multivariate analysis แล้วพบว่า CEA>2.5, cN1-2 และการให้ยา capecitabine เป็น radiosensitizing agent มีผลต่อการเกิด pCR โดยมี OR 0.23 p = 0.04 (95% CI 0.59-0.93), OR 0.15 p = 0.02 (95% CI 0.03-0.79) และ OR 9.89 p = 0.01 (95% CI 1.62-60.25)

สรุป: อัตราการตอบสนองทางพยาธิวิทยาแบบ pCR คือ ร้อยละ 13.9 โดยมีปัจจัยที่มีผลต่อ pCR คือ CEA>2.5; OR 0.23, p = 0.04 (95% CI 0.59-0.93), cN1-2 OR 0.15 p = 0.02 (95% CI 0.03-0.79) และการได้รับยา capecitabine เป็น radiosensitizing agent OR 9.89 p = 0.01 (95% CI 1.62-60.25)

คำสำคัญ: มะเร็งลำไส้ตรงขั้นสูง, การตอบสนองที่สมบูรณ์ทางพยาธิวิทยา, ปัจจัยพยากรณ์โรค, เคมีบำบัด

Abstract

Background and Objective: Colorectal cancer is the third most common cancer worldwide. The current standard treatment for locally advanced rectal cancer is neoadjuvant concurrent chemoradiation therapy (CCRT) followed by total mesorectal excision (TME). The responses to CCRT differ significantly in each study, and approximately 15-30% of patients have pathological complete response(pCR). This research aims to investigate the pCR rate and the factors affecting the pCR after neoadjuvant CCRT in rectal cancer.

Method: A retrospective study of locally advanced rectal cancer, diagnosed with cT4-3, N0 or any cT, cN2-1, who underwent neoadjuvant CCRT during 2020-2014.

Results: A total of 234 rectal cancer patients, there were 101 (43.1%) patients treated with neoadjuvant CCRT, with 68 (67.3%) male patients and a mean age of 58.5±11.5 years The most common cancer location was the lower rectum, 60 (59.4%). For clinical staging, 76 patients had cT3 (75.2%) and 54 patients had cN1-2 (53.5%). A total of 14 patients (13.9%) had pCR. When univariate analysis and multivariate analysis were calculated, it was found that CEA> 2.5, cN1-2 and capecitabine as a radiosensitizing agent affected pCR with OR 0.23 p = 0.04 (95% CI 0.59-0.93), OR 0.15 p = 0.02 (95% CI 0.03-0.79) and OR 9.89 p = 0.01 (95% CI 1.62-60.25), respectively.

Conclusion: The pCR rate was 13.9%, with factors affecting pCR were CEA>2.5, cN1-2 and capecitabine as a radiosensitizing agent.

Keywords: Locally advanced rectal cancer, pathological complete response, prognostic factor, neoadjuvant concurrent chemoradiation therapy

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Introduction

Colorectal cancer is the third most common cancer worldwide.[1] Concurrent chemoradiation therapy (CCRT) followed by total mesorectal excision (TME) is considered as standard treatment in locally advanced rectal cancer (T3-4, N0 or anyT, N 1-2)[2-4] which causes tumor downsizing and greatly reduced local recurrence rate.[5-8]

The response to CCRT varies widely from study to study and approximately 11-30% of patients achieve pathological complete response(pCR).[9-12] According to several studies, it is found that these patients had better treatment outcomes and survival rates[13] which led to the new theory of treatment for rectal cancer, “a watch and wait approach”, believing that patients with complete response may not require surgery and gave a therapeutic effect that was comparable to that of surgery.[9-12]

Currently, in Thailand, there has not been a precise study of the incidence of pCR. Based on current studies, T staging, N staging, initial CEA, initial Hb level, the interval from complete CCRT to surgery, endoscopic circumferential rate affect pCR rate[14-21], which factors such still haven't had a clear conclusion. This research aims to study the pCR rate and factors affecting the pathological complete response in patients with locally advanced rectal cancer who received neoadjuvant CCRT in Thailand.

Methods

This research was a retrospective review of a prospectively collected database by studying patients diagnosed with stage 2-3 rectal cancer with cT3-4, N0 or any T, N1-2 who underwent neoadjuvant CCRT followed by TME during 2014-2020. The primary outcome was the incidence of pCR rate and the secondary outcomes were the predictive factor for pCR.

Using SPSS version 22 program for data analysis. Continuous data were presented in mean +/- SD and Categorical data were presented as a percentage. Binary logistic regression analysis was used to analyze factors associated with pCR for univariate and multivariate analysis. P-value <0.05 was defined for a significant statistical difference.

Results

There were 234 cases of rectal cancer between 2014 and 2020. One hundred and one patients (43.1%) were treated with neoadjuvant CCRT prior to surgery. There were 68 (67.3%) male patients with a mean age of 58.5 ± 11.5 years. The most common tumor location was lower rectum (59.4%).

Table 1 Patient characteristic

Patient characteristics	Number (%) N=101
Sex	
Male	68 (67.3)
Female	33 (32.7)
Age (mean ± SD)	58.5 ± 11.5
BMI (mean ± SD)	23.1 ± 4.8
Underlying	55 (54.5)
Diabetes mellitus	18 (17.8)
Hypertension	32 (31.7)
Dyslipidemia	17 (16.8)
Ischemic heart disease	4 (3.9)
Chronic kidney disease	5 (4.9)
HIV	2 (1.9)
Other	27 (26.7)
CEA (mean)	14.6
Hb (mean)	12.1
Tumor site	
Upper rectum	11(10.9)
Mid rectum	30 (29.7)
Lower rectum	60 (59.4)
Distant from AV (mean ± SD)	6.2 ±3.5
cT staging	
cT3	76 (75.2)
cT4	25 (24.8)
cN staging	
cN0	47 (46.5)
cN1-2	54 (53.5)
Total radiation dose	
50Gy	81 (80.2)
50.4Gy	13 (12.9)
> 50.4Gy	7 (6.9)
Dose per fraction	
1.8 Gy/Fr	15 (14.9)
2 Gy/Fr	86 (85.1)
Radiosensitizing agent	
5FU	93 (92.1)
Capecitabine	8 (7.9)
Total neoadjuvant therapy(TNT)	8 (7.9)
Induction chemotherapy	5 (62.5)
Consolidation chemotherapy	2 (25)
Induction + consolidation	1 (12.5)
TNT regimen	
FOLFOX4	8 (100)
TNT cycle (mean)	5 cycle
Interval to surgery (wk) (mean± S/D)	10.2 ± 4.6

The clinical stage was cT3 in 76 cases (75.2%) and cN1-2 in 54 cases (53.5%). Most of the cases (80.2%) received total radiation dose of 50 Gy with dose per fraction 2 Gy/Fr (85.1%). Ninety-three patients (92.1%) received 5FU where 8 patients (7.9%) received capecitabine as the radiosensitizing agent. (Table 1)

Eight patients (7.9%) received total neoadjuvant therapy, 5 in 8 patients (62.5%) with induction chemotherapy, 2 in 8 patients (25%) with consolidation chemotherapy, and 1 in 8 patients (12.5%) with induction plus consolidation chemotherapy. All patients received FOLFOX as a chemotherapy regimen, 2 cycles in 2 patients, 4_cycles in 2 patients, 6_cycles in 2 patients, and 8_cycles in 2 patients. (Table 1)

Mean interval after CCRT to surgery was 10.7 weeks (4-32 weeks). Most of the cases (62.4%) underwent laparoscopic surgery. There were 47 (46.5%) patients undergoing Low Anterior Resection (LAR), 23 (22.8%) patients with Intersphincteric Resection(ISR)/Coloanal Anastomosis (CAA) and there were 31 patients (30.7%) undergoing Abdominoperineal Resection(APR), in which only 3 patients (2.9%) did not have a protective ostomy. A total of 40 patients (39.6%), had a loop transverse colostomy before CCRT. (Table 2)

Table 2 Operative technique

Patient characteristics	Number (%) N=101
Approach	
Open	38 (37.6)
Laparoscopy	63 (62.4)
Procedure	
LAR	47 (46.5)
ISR/CAA	23 (22.8)
APR	31 (30.7)
Stomal formation	98 (97.0)
Type of stoma	
Loop transverse colostomy	49 (48.5)
Loop ileostomy	18 (17.8)
End colostomy	31 (30.7)
Stoma formation before CCRT	40 (39.6)

Table 3 Pathological outcome

Patient characteristics	Number (%) N=101
pCR	14 (13.9)
yT staging	
T0	16 (15.8)
T1	6 (5.9)
T2	23 (22.8)
T3	48 (47.5)
T4	8 (7.9)
yN staging	
N0	65 (64.3)
N1	21 (20.7)
N2	15 (14.8)
Staging	
Stage 0	14 (13.9)
Stage 1	22 (21.8)
Stage 2	29 (28.7)
Stage 3	36 (35.6)
Tumor grading	
Well differentiate	16(15.8)
Moderately differentiate	72 (71.3)
Poor differentiate	11 (10.9)
Mucinous	2 (1.9)
LVI	17 (16.8)
PNI	13 (12.9)
Tumor deposit	4 (3.9)
Lymph node harvested (mean ± SD)	10.7 ± 6.1
< 12 nodes	64 (63.4)
≥ 12 nodes	37 (36.6)

A total of 14 patients (13.9%) had a pathological complete response (pCR) (Table 3). The results of the univariate among pCR patients are demonstrated in Table 4.

The Result from the univariate analyses indicates that CEA> 2.5; OR 0.27 p = 0.03, cN1-2. ; OR 0.11, p = 0.006 and capecitabine as radiosensitizing agent; OR 8.3 p = 0.007 had a significantly associate with pCR. And when using the above data to study multivariate analysis, it was found that CEA> 2.5, cN1 / 2 and capecitabine as a radiosensitizing agent were significantly associate with pCR with OR 0.23 p = 0.04 (95% CI 0.59-0.93), OR 0.15 p = 0.02 (95% CI 0.03. -0.79) and OR 9.89 p = 0.01 (95% CI 1.62-60.25), respectively. (Table 5)

Table 4 Univariate analysis of predictors for pCR using logistic regression models.

Variable	Total cases	pCR cases (%)	OR	p value
Sex				
Female	33	5 (15.2)	1	
Male	68	9 (13.2)	0.85	0.79
Age				
<60yr	53	8 (15.1)	1	
≥60yr	48	6 (12.5)	0.8	0.7
Obesity				
No	67	11 (16.4)	1	
Yes	34	3 (8.8)	0.49	0.3
Underlying disease				
No	46	9 (19.6)	1	
Yes	55	5 (9.1)	0.41	0.13
CEA level				
≤ 2.5	26	7 (26.9)	1	
> 2.5	75	7 (9.3)	0.27	0.03
Hb level				
>10	88	13 (14.8)	1	
≤10	13	1 (7.7)	0.48	0.49
Distant from AV				
> 5cm	48	4 (8.3)	1	
≤ 5cm	53	10 (18.9)	2.55	0.13
cT stage				
cT3	76	13 (17.1)	1	
cT4	25	1 (4)	0.2	0.13
cN stage				
cN0	47	12 (25.5)	1	
cN1-2	54	2 (3.7)	0.11	0.006
Tumor grading				
Well/ Moderately differentiate	88	13 (14.1)	1	
Poor/ Mucinous differentiate	13	1 (7.7)	0.48	0.49
Total radiation dosage (Gy)				
≤ 50.4 Gy	94(93.1)	13 (13.8)	1	
> 50.4 Gy	7 (6.9)	1 (14.3)	1.03	0.97
Interval to surgery				
≤12 wk	83	10 (12.0)	1	
>12 wk	18	4 (22.2)	2.08	0.26
Radiosensitizing agent				
5FU	93	10 (10.8)	1	
Capecitabine	8	4 (50.0)	8.3	0.007
Total neoadjuvant therapy				
No	93	13 (14)	1	
Yes	8	1 (12.5)	1.13	0.9

Table 5 Multivariate analysis of predictors for pCR using logistic regression models.

Variable	OR	p value	95% CI
CEA > 2.5	0.23	0.04	0.59-0.93
cN1-2	0.15	0.02	0.03-0.79
Capecitabine as radiosensitizing agent	9.89	0.01	1.62-60.25

Discussion

According to the previous studies, the pCR rate was approximately 11-30%[9-12] and was also found to have a significant effect on the better oncological outcome.[13] In this study, the incidence of pathological complete response was 13.9%. The factors affecting pCR were CEA> 2.5, cN1-2 and capecitabine as a radiosensitizing agent. Currently, the factors affecting pCR are widely studied and there is still much debate. Tan et al.[22] found that CEA> 5 was associated with pCR rate OR 0.83 p = 0.01 (95% CI 0.71-0.97), which was found in the same way as our study where CEA> 2.5 affected pCR rate. In addition, clinical T4, N2 was found to affect pCR rate, but there was no correlation between clinical T staging and pCR in this study, which may be due to the preoperative staging limitations of the research. Since CT scans are used for pre-treatment evaluation in the research institutes, a small number of patients use MRI to assess the clinical T staging, so the clinical T staging assessment may not be accurate for seperating T3a, b, c, d, and the limitations to evaluate threatened CRM and EMVI.

Total neoadjuvant treatment (TNT) is currently in widespread study and interest. Current data support that TNT, whether induction or consolidation chemotherapy

increases the incidence of pCR.[23-28] Garcia-Aguilar et al. was administered post-CCRT consolidation chemotherapy in rectal cancer patients[23]. The study groups were divided into 2, 4, 6 mFOLFOX6 cycles. It was found that the pCR rate was up to 38% in the 6 cycle group compared with 18% of the control group. However, in our study, TNT did not affect the incidence of pCR, possibly because the number of our TNT patients was only 7.9%; therefore may cause the study results to be inaccurate because such treatments are not yet widely available in Thailand.

For interval to surgery, it is debated whether or not it affects pCR. Kalady et al.[29] found that interval> 8 weeks had a more significant effect on pCR rate, but The GRECCAR-6 trial[4], which compared interval to surgery between 7 and 11 weeks, showed no difference in pCR rates (15% vs 17.4%, p = 0.59) This study is consistent with our research showing that interval to surgery did not affect pCR rate.

This research has limitation, retrospective study with relatively few participants. It mays have a discrepancy with the secondary outcome, which is the factor that affects pCR itself. In the future, multi-center study in Thailand could result in a more significant number of patients enrolled and making it possible to get more significant information.

Conclusion

The pCR rate of the study was 13.9%, with factors affecting pCR were CEA> 2.5, cN1-2, and capecitabine as the radiosensitizing agent.

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