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ORIGINAL ARTICLE

Pathological Complete Response After Neoadjuvant Therapy in Rectal Adenocarcinoma: a 5-Year Follow-up

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Abstract

Neoadjuvant therapy is the gold standard treatment of locally advanced rectal cancer. It may induce complete sterilization of tumor cell and decreases its local recurrence rate. While 15–20% of patients were found to have pathological complete response (pCR) with combined multimodal therapy, Asian data were generally scarce. pCR rate can indicate the suitability of applying the "watch-and-wait" strategy, which advocates deferment of surgery that can alleviate surgery-associated morbidity.To determine the percentage of pCR of rectal cancer after neoadjuvant therapy. Patients diagnosed with rectal cancer underwent treatment from 2013 to 2017 were retrieved retrospectively. Demographic data, tumor localization, pre- and post-operative pathological reports, neoadjuvant therapy, and pCR status were collected from patients' records. A total of 242 out of 259 patients were treated with definitive rectal surgery. Mean age was 67.1 years old. Chinese ethnicity and male gender were predominant (n = 131, 54.1% and n = 146, 64.3% respectively). More than half (n = 124, 51.2%) had tumor located at mid or low rectum. Histologically, moderate differentiated adenocarcinoma was predominant (n = 227, 93.8%). Merely half (n = 123, 50.8%) of the patients received neoadjuvant chemoradiation therapy, but only 12 (9.8%) had a pCR. From follow-up on these 12 pCR patients, most had 2-year disease-free survival but 1 (8.3%) of the pCR had distant metastasis within 1-year post-surgery. The pathological complete response rate in our center was lower than reported. Stringent patient selection with close follow-up for patients should be carried out if the "watch-and-wait" strategy is implemented in our population.

Keywords Rectal adenocarcinoma · Neoadjuvant therapy · Pathological complete response · Colorectal cancer

Highlights All locally advanced (T3 and T4, mesorectal nodes positive or mesorectal fascia involved or threatened) rectal adenocarcinoma with curative intention were subjected to neoadjuvant chemoradiation before curative surgical resection.
Near half (123 patients, 50.8%) received neoadjuvant therapy.
Pathological complete response (pCR) rate in our center was about 9.76% which is lower than what have reported implied that many factors could influence pCR rate.
More strict criteria to define complete clinical response (cCR) are required to adopt the "watch-and-wait protocol."

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Introduction

Colorectal cancer is the second most common cancer and a leading cause of death in Malaysia [1]. Surgical resection is the cornerstone of curative management, with total mesorectal excision (TME) plays a fundamental role in patients who undergo rectal surgery [2–4]. With advancement in oncological therapies, neoadjuvant therapy prior to surgical resection of rectal cancer increased overall survival, disease-free survival, and reduced local recurrence rate [5, 6]. Therefore, neoadjuvant therapy is now the gold standard of treatment for locally advanced mid and low rectal cancer before subjecting patients to curative surgery resection (with criteria of T3 and above, positive mesorectal nodes, mesorectal fascia involvement or when mesorectal fascia is threatened) [7]. Neoadjuvant therapy is given to downstage and downsize the rectal tumor, as well as possible for preservation of sphincters for distal rectal tumor.

Neoadjuvant therapy alone may lead to significant regression of tumor, which provides an opportunity for patients to

avoid radical surgery [8]. As such, a "watch-and-wait" protocol was suggested for patients with rectal cancer who received neoadjuvant therapy and showed clinical complete response (cCR). This protocol advocates monitoring of these patients frequently—both clinically and radiologically—while holding off the surgery and waiting for the natural progression of disease to take place. This watch-and-wait strategy can preserve patients' functionality and quality of life, as well as minimize surgical-related morbidities and post-operative mortality [8]. The adaptation of the watch-and-wait approach varies by practice [9]. Some centers tend to proceed with surgical procedure based on initial tumor signs, while some implement the watch-and-wait protocol as post-neoadjuvant restaging leads to the modification of the initial plan [10].

One challenge in implementing the watch-and-wait protocol is the definition of cCR, which is yet to be standardized but was recommended to be based on very strict clinical, endoscopical, and radiological criteria [11]. From the endoscopic perspective, cCR should harbor no more than whitening of the mucosa or telangiectasia with normal mucosa integrity. Clinically, the presence of any deep or superficial residual ulcer, any palpable nodule or any significant stenosis that impede the proctoscope from sliding through are features described as incomplete clinical response [12]. Radiologically, patients are considered to have a clinical complete response when there is shrinkage of the tumor with homogenous low signal intensity on the T2 magnetic resonance imaging (MRI) images characterizing fibrosis and no residual tumor signal. There must be no lymph node involvement and no signal of extramural vascular involvement [13].

It was reported that neoadjuvant therapy can induce up to 25% cCR, while 20–25% of cCR after surgery had pCR [9–11]. However, there are potential risks in applying this protocol, which are attributed to the absence of direct pathologic confirmation of cCR, as cCR patients do not undergo surgery unless they have a recurrence [13–17]. In addition, previous study has shown a poor concordance between pathological assessment of response to preoperative neoadjuvant therapy and clinical assessment based on digital rectal examination on top of sigmoidoscopy [18, 19]. Moreover, a recent study has shown that many patients who achieved pathological complete response (pCR) were found to have mucosal abnormalities that were inconsistent with a cCR [20].

Although there was information reported on pCR after neoadjuvant therapy, a Malaysian cohort from last decade showed low pCR rate compared with other countries, and there is no newer data to date, in which pCR rate might have improved due to medical advances [21]. This study aims in reporting the proportion of patients with rectal adenocarcinoma who had a pCR after treatment with neoadjuvant therapy in a colorectal surgery department, a tertiary care university hospital in Malaysia.

Method

Settings

This retrospective cohort study reviewed all patients who diagnosed with rectal adenocarcinoma and underwent treatment plans over 5 years from January 2013 to December 2017 in a colorectal center and major tertiary referral hospital in Central region of Malaysia, which is also an academic teaching hospital. This study was reported in line with the strengthening the reporting of cohort studies in surgery (STROCSS) criteria [22].

Eligibility Criteria

All patients who diagnosed with rectal adenocarcinoma and underwent curative treatment in our institution from January 2013 to December 2017 were included in analyses.

Surgical Procedures and Associated Care

All patients were diagnosed with rectal adenocarcinoma via histology from the biopsy during colonoscopy. Complete staging was done including computed tomography scan of thorax, abdomen, pelvis (CT TAP) for distance staging and pelvic MRI (magnetic resonance imaging) for local staging. Multidisciplinary discussion (MDT) involving radiologists, pathologists, oncologists, and colorectal team was done for each patient to discuss whether to proceed with upfront curative surgery or neoadjuvant chemoradiotherapy. Neoadjuvant therapy was decided based on distance and local staging of the rectal cancer according to National Comprehensive Cancer Network (NCCN) guideline, with mid and low rectal cancers locally staged T3 and above, or mesorectal nodes positive, or mesorectal fascia (MRF) involved or threatened (MRF < 1 mm) in MRI local staging [7].

Patients who decided with upfront neoadjuvant therapy were then referred to oncologists for administrative chemoradiation. Most of the neoadjuvant regimen were decided by oncologists and involved long course chemoradiation whereby long course radiation was given for 5 weeks with radiation dose of 45–50.4 G in 25 fractions with concurrent 5-fluorouracil-based chemotherapy (either oral or intravenous route) given in week 1 and week 5 of radiation. Some patients with bulky upper rectum involving surrounding structures were given systemic chemotherapy before curative surgery. After completing chemoradiation, patients were referred back to colorectal team with post-neoadjuvant therapy MRI performed for local restaging of the rectal cancer. Colorectal team scheduled the surgeries about 10–12 weeks post-neoadjuvant therapy for all rectal cancers.

Patients subjected to surgery were reviewed by anesthetists preoperatively with optimization of their comorbidities. We

adhered to Enhanced Recovery After Surgery (ERAS) protocol. All patients were given bowel preparation before surgery.

Surgeries were performed by colorectal team consisting of two colorectal consultants and colorectal fellows. Patients were operated under general anesthesia in supine lithotomy position. Surgery was performed via laparoscopic technique or open laparotomy depending on the suitability of the cases. The resected specimens were sent to Pathology Department for histopathological analysis. Patients were given standard post-operative care according to ERAS protocol.

Patients were followed up for at least 2 years post-surgery. pCR was defined as absence of tumor cell microscopically in a complete resected specimen.

Data Collection

All patients diagnosed with rectal adenocarcinoma in our institution, whose records were complete and who were treated between 2013 and 2017, were included. For the analysis, patients who did not undergo curative surgical resection were excluded (palliative resection, palliative stoma diversion, open, and closed all excluded).

Information was collected from patients' admission files which include the following information: patients' demographic data, histopathological characteristics of the tumor, tumor localization, neoadjuvant regimen, histopathological report of the resected specimens, and recurrence or metastasis during follow-up.

Sample Size Calculation and Statistical Analysis

Sample size estimation was calculated using the population proportion formulae [23]. Prior data indicated that the proportion of patients with rectal adenocarcinoma with pCR after neoadjuvant therapy was 0.105 [21] and population size is 300. With the type I error probability and precision of 0.05 and 0.05 and an additional 20% dropout rate, the sample size required was 123 samples.

The data obtained were entered in a database using Excel 2013. Patients were divided to two groups: those who received neoadjuvant and those who did not. The data analysis was performed by using the IBM SPSS Statistics for Windows version 23.0 (IBM Corp., New York). The categorical variables were summarized as frequencies and percentages, and the numerical variables as means and standard deviations (SD). Chi-square test was used to study association between categorical data, while Fisher's exact test was used if the assumptions for chi-square test were not met. Independent T test was used to compare continuous variables between both groups. All probability values were two-sided and a level of significance of less than 0.05 (p value < 0.05) was considered as statistically significant.

Results

From 2013 till 2017, a total of 259 patients were diagnosed with rectal cancer. However, 242 out of 259 patients (93.4%) successfully completed the definitive curative surgery whereby the tumors were resected out. Seventeen patients (6.6%) with advanced disease during surgery ended up with palliative surgery (defunctioning stoma) or did not proceed with the surgery.

Mean age of patients' population who had definitive surgery (n = 242) was 67.1 (SD 10.9) years. Chinese ethnicity was predominant in the study population at 60.3% (n = 146), followed by Malays (n = 69, 28.5%) and Indians (n = 27, 11.2%). There was a slight predominance of male gender (n = 131, 54.1%) (Table 1).

Half of the patients received neoadjuvant therapy (n = 123, 50.8%). Both groups did not show significant difference between gender, ethnicity, and when the surgery was performed (Table 1). Mean age of each group were 65.7 (SD 10.6) and 68.6 (SD 11.1) years old, respectively ($p = 0.036$), implying that patients with neoadjuvant therapy were younger than patients without the neoadjuvant therapy.

Histologically, most tumors were moderately differentiated adenocarcinoma (n = 227, 93.8%). Well-differentiated adenocarcinoma was only reported in five patients (2.1%). Poorly or undifferentiated adenocarcinoma was rather rare in our study population (n = 10, 4.1%). There was no statistically significant difference between both groups for the histological classification (Table 1) ($p = 0.92$).

Most of mid and low rectal cancer cases were given neoadjuvant therapy (n = 112, 90.3%), while the remaining mid and low rectal cancer cases (n = 12, 9.7%) were not given neoadjuvant therapy, whereby this was the group of mid and low rectal cancers which were in early stage. In contrast with patients with neoadjuvant therapy which comprised of mainly mid or low rectal cancer cases, most patients without neoadjuvant therapy had upper rectal cancer (n = 107, 89.9%) (Table 1) ($p < 0.001$). There was a small proportion of upper rectal cancers were subjected to neoadjuvant therapy (n = 11, 8.9%), as this was the group whereby the upper rectal tumors were bulky and threaten the surrounding structures in imaging (Table 1).

More than half of the patients who received neoadjuvant therapy were in stages N1-2 and M0 (n = 71, 57.7%). Most patients without metastasis received neoadjuvant therapy, except those without clear evidence of locally advanced rectal adenocarcinoma, whom were the majority of the cases which did not receive neoadjuvant therapy (Table 1).

Among patients who underwent neoadjuvant therapy (n = 123, 50.8%) followed by definitive surgery, 9.8% (n = 12) patients showed pCR in their resected full-post-operative histopathological report. The 2-year follow-up for these 12 pCR

Table 1 Characteristics of patients who underwent rectal cancer surgeries from 2013 till 2017 stratified by presence or absence of treatment with neoadjuvant therapy

	Overall (N = 242)	Neoadjuvant therapy (n = 123, 50.8%)	Without neoadjuvant therapy (n = 119, 49.1%)	p value
Age, years [mean (SD)]	67.1 (10.9)	65.7 (10.6)	68.6 (11.1)	0.036[a]
Number of cases by year, n (%)				
• 2013	38 (15.7)	16 (13.0)	22 (18.5)	0.288[b]
• 2014	53 (21.9)	25 (20.3)	28 (23.5)	
• 2015	50 (20.7)	25 (20.3)	25 (21.0)	
• 2016	50 (20.7)	32 (26.0)	18 (15.1)	
• 2017	51 (21.1)	25 (20.3)	26 (21.8)	
Gender, n (%)				
• Male	131 (54.1)	63 (51.2)	68 (57.1)	0.355[b]
• Female	111 (45.9)	60 (48.8)	51 (42.9)	
Ethnicity, n (%)				
• Malay	69 (28.5)	30 (24.4)	39 (32.8)	0.202[b]
• Chinese	146 (60.3)	81 (65.9)	65 (54.6)	
• Indian	27 (11.2)	12 (9.8)	15 (12.6)	
Lesion sites, n (%)				
• Upper rectum	118 (48.8)	11 (8.9)	107 (89.9)	< 0.001[b]
• Mid rectum	55 (22.7)	48 (39.0)	7 (5.9)	
• Low rectum	69 (28.5)	64 (52.0)	5 (4.2)	
Histological type, n (%)				
• Well differentiated	5 (2.1)	2 (1.6)	3 (2.5)	0.920[b]
• Moderately differentiated	227 (93.8)	116 (94.3)	111 (93.3)	
• Poor/undifferentiated	10 (4.1)	5 (4.1)	5 (4.2)	
Disease stage at diagnosis, n (%)				
• T1-T2 N0 M0	6 (2.5)	3 (2.4)	3 (2.5)	< 0.001[c]
• T3-T4 N0 M0	19 (7.9)	15 (12.2)	4 (3.4)	
• T1-T4 N1-2 M0	73 (30.2)	71 (57.7)	2 (1.7)	
• Unknown T and N + M0	99 (40.9)	18 (14.6)	81 (68.1)	
• T1-T4 any N M1	45 (18.6)	16 (13.0)	29 (24.4)	
Pathological complete response, n (%)	12 (5.0)	12 (9.8)	Not applicable	Not applicable

[a] Independent T test was performed with $p < 0.05$ as significant

[b] Chi-square test was performed with $p < 0.05$ as significant

[c] Fisher's exact test was performed with $p < 0.05$ as significant

patients showed that there was no local recurrence but 1 (8.3%) pCR patient was found to have distant liver metastasis without local recurrence during surveillance with CT thorax, abdomen, and pelvis (Table 2).

Table 2 Disease progression pattern among patients with pCR after neoadjuvant therapy (n = 12)

Disease status at 2 years	Number of patients, n(%)
Clinically well	11 (91.7)
Local recurrence	0
Distant metastasis	1 (8.3)

Discussion

Our population showed a mere 9.8% pCR that was lower than previously reported [9, 21]. This reflects a potential concern of utilizing the increasingly popular watch-and-wait protocol for these patients with low pCR rate to begin with, as most of these patients would eventually require surgery. As low pCR rates are indicative of prognostically unfavorable biological tumor profiles in our population, the study population might have higher propensity for local recurrence, distant metastasis and poorer survival [8]. Therefore, the watch-and-wait strategy might deprive these prognostically unfavorable patients of the opportunity for cure when the surgery is

not performed in the timely manner following the neoadjuvant therapy.

There are many factors influencing cCR and pCR rates post-neoadjuvant therapy. Timing interval between neoadjuvant therapy and curative surgery is a potential factor. Longer duration was shown to have better effects than the traditional 6-week interval [24]. NCCN guideline recommends that surgery to be performed within 5–12 weeks after the end of neoadjuvant therapy [7]. A meta-analysis observed higher pCR in those who waited longer than 7 weeks [9]. Some patients might take longer time to achieve cCR; up to 37% of cCR was reported with 10–16 weeks and 73% was reported with interval of more than 16 weeks [38]. As our center provides a 10- to 12-week interval before subjecting patients for curative surgery, the timing interval might be a factor of low pCR in our center.

Besides the timing of surgery, the disease severity and degree of tumor cell differentiation are important in determining pCR rate. According to a retrospective study, poorly differentiated or undifferentiated tumors had lower pCR rate [25]. Our study population were generally given neoadjuvant therapy in more severe stages of the disease (with most cases were locally advanced at stage T3 and above ± mesorectal nodes positive or MRF positive/threatened and with less than 10% of well-differentiated tumors), which possibly explains the lower pCR rate among our study population. The mid and low rectal cancer cases without neoadjuvant therapy were mainly early rectal cancer (T1 or T2, mesorectal nodes negative, or without involvement of MRF). This contrasts with previous studies that reported higher pCR rates as they recruited patients with milder stages of disease [17, 25, 26]. The criteria for neoadjuvant therapy vary across institutions; some centers would not prefer to expose patients with early stage rectal cancers to potential toxicities of neoadjuvant therapy as the benefits are yet to be confirmed [26]. The study findings highlighted the importance of care in interpreting reported pCR outcomes of existing literature with limited generalizability to local practice.

The location of rectal tumor can affect the pCR rate. Tumors in the lower end or upper third of rectum have been reported to be less likely to have pCR, which possibly explains the low pCR rate among our study population in which 61.0% of the tumors were located in the lower end and upper third of rectum [27]. Most mid and low rectal cancer cases in our study population were given neoadjuvant therapy as the tumors were locally advanced. Less number of patients with upper rectal cancer received neoadjuvant therapy, which was in line with European Society for Medical Oncology (ESMO) guideline in which upper rectal cancers (> 12 cm from the anal verge) above the peritoneal reflection do not benefit from preoperative short-course preoperative radiotherapy or chemoradiation [28]. In addition, resection was given to patients with upper rectal cancer that could be well resected, or that occurred outside the radiotherapy field of pelvis. A small number of upper rectal cancers were given neoadjuvant therapy based on MRI as the tumors were either appeared too bulky or involved surrounding structures (bladder, uterus, prostate, or pelvic side wall) or difficulty to obtain R0 resection, in which oncological safety was taken into consideration before subjecting to definitive surgery. Neoadjuvant therapy was given to downstage and downsize these tumors. The study findings suggest that patients with tumors at the lower end or upper third of rectum should be counseled on the potentially low pCR rate and the implications when deciding for curative surgery or watch-and-wait strategy.

Young age is a reported predictive factor of lower pCR rate following neoadjuvant therapy [29]. Our study population reported a relatively younger patient population who underwent neoadjuvant therapy, which possibly explains the low pCR rate in our study population. It was postulated that these younger patients had more aggressive pathological features, believed to be associated with a higher CD133+ cancer stem cell burden, which contributed to poorer response to neoadjuvant therapy [29]. This warrants more research to evaluate the need to optimize the neoadjuvant therapy in young patients.

In addition, pCR does not necessarily imply complete cure, as shown by the presence of metastasis post-pCR from our study findings. Hence, tumor biology or preoperative radiological staging should be considered during prescribing adjuvant therapy. The 3-year regrowth rate increases based on tumor T-staging. Longer follow-up should be recommended to detect early any recurrence or metastasis.

As pCR can only be confirmed by performing radical surgery, the assessment of tumor response post-neoadjuvant therapy in watch-and-wait protocol will be based on a surrogate measure (cCR) with poorer accuracy than direct histological examination, with only 25% of cCR patients reported to have pCR [19]. In addition, the long-term survival and local recurrence rates with watch-and-wait approach were inconsistent [17, 25]. Therefore, cCR classification must be based on very strict criteria [8]. To adopt watch-and-wait protocol, it is advocated that frequent follow-up should be done with MRI pelvis, colonoscopy, and digital examination every 1–2 months for the first year, every 3 months for the second year, and every 6 months thereafter [8]. Therefore, it is important to be careful in selecting patients for watch-and-wait protocol post-neoadjuvant therapy in rectal adenocarcinoma in population with low pCR, with a need of multidisciplinary approach and various assessments to measure cCR, without compromising the balance of quality of life and achieving good disease/survival outcomes.

Other challenges in implementing "watch-and-wait" strategy in our setting include potential poor patient compliance on the follow-up procedures, as well as potential of interobserver variability [21]. As such, implementation of "watch-and-wait" protocol among our patients might incur more costs with low

pCR rate that renders surgery eventually inevitable, while additional healthcare costs are to be incurred by various surveillance procedures at frequent intervals. Therefore, the benefits and cost-effectiveness of this protocol in our study population requires further investigation. Although a study observed decreased costs associated with watch-and-wait protocol, the generalizability is limited, given the lower pCR found among our population, as well as different healthcare costs in our country [30].

Despite the uncertainties and inconveniences of the watch-and-wait protocol, this approach might be required during the challenging times of the COVID-19 pandemic in which surgical prioritisation might be required due to limited healthcare resources [31]. In view of low pCR rates from our center, better tools with higher sensitivity are needed to stratify patients who are likely to benefit from non-operative management after neoadjuvant therapy [18–20]. This approach may be useful for to those who have cCR based on radiological and endoscopic criteria and refuse for surgery after thorough discussion and explanation about the risks and benefits [4].

This study had its limitations. This retrospective study was subjected to potential selection bias, but randomization of patients is ethically challenging, when potentially curative options can only be obtainable by chance. Variability in the neoadjuvant regimes exists, but the regimens were all based on the institutional protocols. In addition, cCR is not obtainable from the study population due to the scarcity of credentialed radiologists in our institution. Besides, this study was limited by the limited generalizability of the data to other settings, given that other institutions might have different criteria in providing neoadjuvant therapy for rectal cancer patients. There are other potential factors of low pCR that were not studied, such as genetic polymorphisms [32], as well as variation in gene expression related with tumor biology [33]. The study was not designed to identify the causative factors of low pCR. While the radiotherapy technique, machine, and skills might be related with pCR rate, future studies could be designed to identify the factors of low pCR in our population. In addition, the study was exploratory in nature and not intended for survival analysis (such as the Kaplan-Meier method) as the assumptions required were violated by the unavailability of the exact survival time for each patient.

Conclusion

The pathological complete response rate post-neoadjuvant treatment for rectal cancer in our center showed lower rate than reported, suggesting a need of stringent patient selection process with close surveillance if surgical resection post-neoadjuvant treatment has to be delayed in our population. The benefits must outweigh the risk if watch-and-wait strategy is offered to our patient population.

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Data availability Data are available upon request.

Code Availability Not applicable

Declarations

Ethics Approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by University Malaya Medical Centre Ethics Committee, Malaysia with protocol number MREC ID: 202074-8863, and registered with the National Medical Research Register, Malaysia, under the protocol number NMRR-20-1858-56252.

Consent to Participate Not applicable as this is a retrospective observational study.

Consent for Publication Not applicable as this is a retrospective observational study.

Conflicts of Interest The authors declare they have no conflicts of interest.

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