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Preoperative vs Postoperative Radiotherapy in the Management of Rectal Cancer: A Systematic Review

Muhammad Fauzi Siregar
Radiation Oncologist, Radiation Oncology Department, RSUP Haji Adam Malik/Faculty of Medicine, University of Sumatera Utara

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Correspondence:
Muhammad Fauzi Siregar
E-mail:
fauzi_aja@yahoo.com

Abstract

Purpose. The objective of this study is to review randomized clinical trials systematically that compared the outcomes of preoperative and postoperative radiotherapy in the management of rectal cancer regarding locoregional recurrence, disease free survival and overall survival.

Methods. The relevant randomized clinical trials were searched via online databases such as Pubmed, EBSCO, and Proquest. RCTs published in English between 2000 until 2020 were selected and reviewed systematically.

Result. Locoregional recurrence at 5 years was statistically lower in preoperative radiotherapy group than in postoperative radiotherapy group based on two studies. Disease free survival at 5 years was statistically higher in preoperative radiotherapy group than the postoperative one based on two studies. Overall survival at 5 years was not statistically significant between two groups for each study.

Conclusion. Preoperative radiotherapy is superior to postoperative radiotherapy for controlling locoregional recurrence and disease-free survival, but both are equal in overall survival.

Keywords: Rectal cancer, preoperative radiotherapy, postoperative radiotherapy, chemoradiation.

Introduction

Colorectal cancer is the third most found cancer world-wide after lung and breast cancer. In 2018, 1.8 million new cases of colorectal cancer were found contributing of 10.2% of cancer worldwide. Number of deaths caused by colorectal cancer is second after lung cancer. The incidence and mortality of rectal cancer itself was approximately 704,376 and 310,394 cases worldwide. The highest incidence of rectal cancer was in the very high human development index country (1.3%) such as Central and Eastern Europe, Australia, New Zealand, and Eastern Asia. In Indonesia, colorectal cancer is the fourth most common cancer for both sexes but the second most common cancer for male.[1]

Rectal cancer is a malignancy that is originated from rectal tissue. Anatomically, the rectum is final part of large intestine and located between sigmoid colon and anal canal. The rectum starts from recto-sigmoid junction (as level as third sacral or sacral promontory) and ends at the anorectal ring.[2,3] It has been postulated that rectal cancer is associated with several syndromes such as familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC) and MUTYH-associated polyposis (MAP). Ulcerative colitis dysplasia may also play a role in the development of rectal carcinoma.[4,5] Clinical manifes-tations of rectal cancer vary regarding the extent of the disease. The signs and symptoms of rectal cancer are rectal bleeding, tenesmus, anemia, abdominal pain, and incomplete stool evacuation. In the early-stage, rectal cancer may also be asymptomatic.[6] The most common histologic findings of rectal cancer are adeno-carcinomas (>90%), other types are neuroendocrine, squamous cell, adenosquamous, spindle cell and undifferentiated carcinomas. Adenocarcinomas are

graded by its glandular formation. In well differentiated adenocarcinoma >95% of the tumor is gland forming. Moderately differentiated adenocarcinoma shows 50-95% gland formation. Poorly differentiated adenocarcinoma is mostly solid with <50% gland formation. Moderate differentiated adenocarcinoma is the most found in practice.[7]

The treatment modalities of rectal cancer consist of surgical, chemotherapy and radiotherapy. Surgical resection still the definitive treatment for rectal cancer, especially for the case without distant metastasis.[8] However, surgical resection alone resulted in high local recurrence. Thus, surgery and radiotherapy or chemoradiotherapy were combined in the management of rectal cancer and showed improvement in term of local recurrence.[9]

The role of radiotherapy has evolved gradually since the '80s when radiotherapy was performed as an adjuvant therapy after surgical resection to reduce pelvic recurrence. Survival rate also improved if radiotherapy combined with 5-FU based chemotherapy. In the '90s, total mesorectal excision (TME) was introduced and showed lower locoregional recurrence. Therefore, the role of radiotherapy was debatable. However, several studies stated that short course radiotherapy combined with TME resulted in lower locoregional recurrence compared to TME alone.[10]

Recently, chemoradiotherapy has been used to improve local control and survival.[11] According to Bosset's study, chemoradiotherapy was effective to reduce locoregional recurrence but not overall survival.[12,13] Nowadays, NCCN recommends preoperative chemoradiotherapy for rectal cancer patients staged II/III. On the contrary, previously, postoperative chemoradiotherapy was used as standard treatment in USA for rectal cancer patients staged II/III that has been completely resected.[3] Therefore, this systematic review compared the efficacy of preoperative to postoperative radiotherapy (including locoregional recurrence, disease-free survival and overall survival).

Methods

The included studies consisted of randomized clinical trials, that compared preoperative and postoperative radiotherapy, published between 2000 until August 2020. The literatures were searched via online database such as Pubmed, EBSCO, and Proquest. Keywords used were rectal cancer, adenocarcinoma, neoplasm, radiotherapy, chemotherapy, chemoradiation, radio-chemotherapy, preoperative, postoperative, and neoadjuvant. The minimum follow-up of the study were 5 years. Only articles published in English were reviewed. The flowchart for identification of studies was described on **Figure 1** and presented based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline.

Eligibility Criteria

The inclusion criteria for this review were rectal cancer patients aged 18 years or more, with adenocarcinoma histopathologic finding and tumor location no more than 16 cm from anal verge. The exclusion criteria were evidence of distant metastasis or other malignancy and history of getting chemotherapy or radiotherapy.

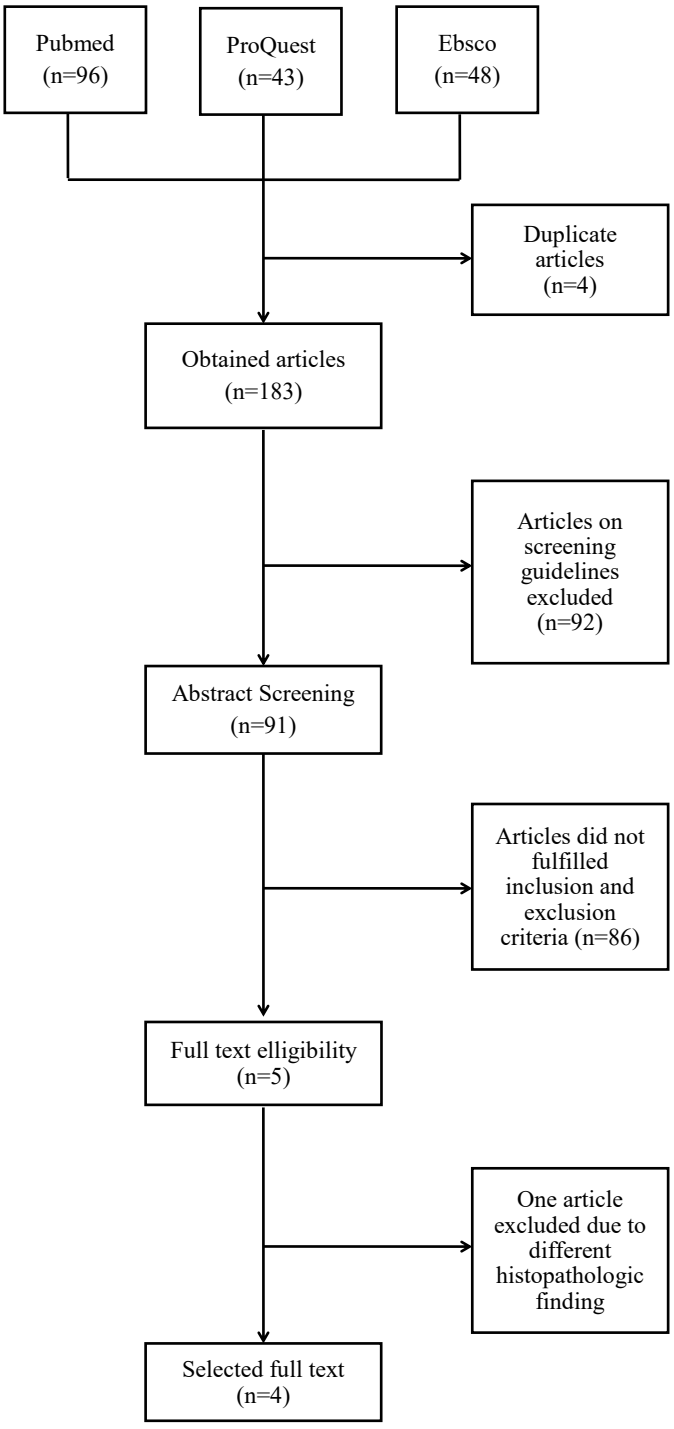

Figure 1. Flowchart for identification of studies

Interventions and comparators

The interventions for both groups were radiotherapy, chemotherapy and surgery. Radiotherapy was given before or after surgery. The protocol for chemoradiation and procedure of surgery were not considered in this review.

Outcomes

The definition of locoregional recurrence was the development of intraluminal tumor that was confirmed either by biopsy, imaging, subtle imaging finding with elevated carcino-embryonic antigen serum, without distant metastasis. Disease free survival is the time for randomization to any evidence of local recurrence, distant metastasis or death because of the disease itself or the treatment. Overall survival was defined as the time from randomization to death due to any reason.

Results

The initial literature search identified 187 studies with 91 RCTs. After screening for eligibility criteria, 5 RCTs were evaluated nut one study was excluded due to subtle locoregional recurrence rate data and variation in histopathology findings. Finally, only 4 studies were reviewed: Park et al in 2011[14], Roh et al in 2009[15], Sauer et al in 2012[16] and Sebag-Montefiore et al in 2009[17]. All four studies compared preoperative and postoperative radiotherapy for rectal cancer based on locoregional recurrence, overall survival and disease-free survival. Characteristic for each study described at **Table 1**.

All studies used endoscopic ultrasonography, CT scan or MRI to determine the stage of the disease. Stage II-III or cT3-cT4 or N were included in the studies, except Sebag-Montefiore whose study did not mention the stage as inclusion criteria. This study limited the criteria that the primary tumor was not fixed to the pelvis and complete excision was feasible. All patients in these studies were assessed as sufficiently fit to receive all treatment. It is concluded that all patients were estimated in the same level performance before the treatment. The total number of patients analyzed in each studies are 219 patients (Park, 2011), 254 patients (Roh, 209), 791 patients (Sauer 2012) and 1350 patients (Sebag-Montefiore, 2009).[14-17]

Interventions for both groups in each study were identical except for Sebag-Montefiore's study. In Park's study, preoperative and post-operative groups received 50 Gy in 25 fractions. In Roh's and Sauer's study, both groups received 50.4 Gy in 28 fractions. In Sebag-Montefiore's study, preoperative group received 25 Gy in 5 fractions and postoperative group received 45 Gy in 25 fractions. Chemotherapy used in these studies varies. Park's study used oral Capecitabine along with radiation (chemoradiation), but 5FU and Leucovorin or Capecitabine were also used for adjuvant chemotherapy. Sauer's and Roh's study used 5FU as chemoradiation and adjuvant chemotherapy. In Sebag-Montefiore's study 5FU and Leucovorin were used in postoperative chemoradiation and no chemotherapy were given during preoperative radiation. The operation procedure performed in these studies are generally total mesorectal excision.[14-17]

Locoregional recurrence

Locoregional recurrence at 5 years was significantly lower in preoperative radiotherapy group than in postoperative radiotherapy group based on two studies. Locoregional recurrence at 5 years in Sauer's study was 5% and 9.7% for preoperative group and postoperative

Table 1. Characteristic of the studies.

Author	Year	Total number of analyzed patients	Number of patients in preoperative radiotherapy group	Number of patients in postoperative radiotherapy group	Procedure of Operation	Chemotherapy	Radiotherapy
Park et al, 2011	2004-2006	219	107	112	TME	Capecitabine Adjuvant: Capecitabine or Leucovorin	50Gy/25 Fraction
Roh et al, 2009	1993-1996	254	123	131	Not mandatory	Leucovorin Adjuvant: Leucovorin	50.4Gy/28 Fraction
Sauer et al, 2012	1995-2002	791	404	387	TME	5-FU Adjuvant: 5-FU	50.4Gy/28 Fraction
Sebag-Montefiore et al, 2009	1994-1999	1350	674	676 (60 got RT)	Not mandatory	5-FU and Leucovorin	25Gy/5 Fraction

Source: Reference no. 14-17

group respectively (p=0,048) and in Sebag-Montefiore's was 4.7% and 11.5% (p<0,0001). Locoregional recurrence rate was not significantly different between two groups in Park's and Roh's studies.[14-17]

Disease free survival

Disease free survival at 5 years were not significantly different between two groups in Sauer's and Parks's study, but statistically higher in preoperative radiotherapy group than in postoperative one based on Roh's and Sebag-Montefiore's study. The disease free survival was 64.7% and 53.4% (p=0,011) for preoperative group and postoperative group respectively in Roh's study; whereas 4.7% and 11.5% (p<0,013) in Sebag-Montefiore's study.[14-17]

Overall survival

Overall survival at 5 years was not significantly different between two groups for each study.[14-17] Summary of the results are described at **Table 2**.

Discussion

Modality for management of rectal cancer included surgery, chemotherapy and radiotherapy.[18] Recently, management of rectal cancer has evolved with better technique, either in operative procedure, chemotherapy and radiotherapy. Total mesorectal excision improved survival and decreases morbidity.[19] Capecitabine are nowadays used as oral chemotherapy concurrent in radiotherapy as an alternative to intravenous 5-FU. According to NCCN guideline based on phase III RCT showing Capecitabine was not inferior to 5 FU.[3] Neoadjuvant short-course radiotherapy or long-course chemoradiotherapy before surgery improved treatment outcomes for locally advance rectal cancer.[20] But, recommendation of US National Institutes for Health in 1990 for completely resected stage II or III rectal cancer was postoperative chemoradiotherapy.

According to several randomized trials before, combination of 5-FU based chemotherapy and radiotherapy gave a best result but, these trials did not compare the efficacy of preoperative chemo-radiotherapy to postoperative chemoradiotherapy.[21,22]

In this review, two studies (Sauer et al. and Sebag et al.) showed lower locoregional recurrence at 5 years (statistically significant) in preoperative radiotherapy group compare to postoperative radiotherapy.[16,17] This can be explained by several reasons. First, chemoradiotherapy may reduce the volume of the tumor therefore the operation procedure may become easier to performed and increasing the possibility to maintain the sphincter. Second, pre-operated tissue in the pelvis may be more oxygenated than post-operated one, therefore radiation will be more effective to the pre-operated tissue than the post operated-one. Third, preoperative radiotherapy may reduce the possibility of radiation induce small bowel injury as occurred in postoperative radiotherapy due to small bowel trapped in the pelvis by post-surgical adhesion. Fourth, if the preoperative radiotherapy included all the tissue that will be resected, the healthy tissue will be remained therefore anastomose can be performed. And fifth, preoperative radiotherapy may eliminate micro-metastases tumor cell earlier than postoperative one.[16,17,22-25]

Surgery for rectal cancer usually performed 6 weeks after administration of neoadjuvant therapy so that the tumor may have enough time to respond to chemoradiotherapy and the patient may also had sufficient time to recover from toxicity. Study by Wang showed that the rectal cancer patient responded to chemoradiation in time-dependent manner, and it was usually needed several months to get complete

Table 2. Summaries of the results

Author	5 years-Locoregional recurrence			5 years-Disease free survival			5 years-Overall survival		
	Pre-operative group (%)	Post-operative group (%)	P value	Pre-operative group (%)	Post-operative group (%)	P value	Pre-operative group (%)	Post-operative group (%)	P value
Park et al, 2011	5	6	0.392	73	74	0.865	83	85	0.620
Roh et al, 2009	10.7	10.7	0.693	64.7	53.4	*0.011	74.5	65.6	0.65
Sauer et al, 2012	5	9.7	*0.04	68	65	0.65	76	74	0.85
Sebag-Montefiore et al, 2009	4.7	11.5	*<0.0001	73.6	66.7	*<0.013	70.3	67.9	0.4

Source: Reference no. 14-17

tumor regression.[26] So, prolonging the time between chemoradiation and surgery may have benefit of increasing pathological complete response. Nevertheless, many surgeons hesitate to delay the surgery until 6-8 weeks because of occurrence of pelvic fibrosis due to radiation of pelvic area. This may complicate the operation area and related to not only surgical complication but also locoregional recurrence.[27] In Sauer's and Park study, surgery was performed 4 to 6 weeks after completing chemo-radiation. Roh's study did not mention the time interval between completion of chemoradiation to surgery, while in Sebag's study surgery was performed within 7 days of the last fraction of short course radiotherapy.

Despite many advantages of preoperative radiotherapy, over staging may occur and that early-stage tumor got radiotherapy when it actually did not require it. MRI may play a role for accurate staging before operation but it cannot eliminate the risk of overstaging. After concerning the advantages over the disadvantages of preoperative radiotherapy, NCCN recommend preoperative chemoradiotherapy for rectal cancer patient staged II/III, and postoperative chemo-radiotherapy for rectal cancer patients that upstaged from stage I to stage II/III after histopathological finding of surgical specimen.[16,28,29]

Disease free survival at 5-years was not significantly different between two groups in Sauer's and Parks's study but significantly different in Roh's and Sebag-Montefiore's study. This can be explained that disease free survival mostly correlated to decreasing number local recurrence although there is a small non-significant decreasing in both the number of patients with distant metastasis and with deaths related to rectal cancer.[17]

The limitation of this review is limited number of RCTs included, but the samples from Sauer's and Sebag-Montefiore's study were sufficient to be evaluated. Another limitation is different regiment of radiation given for each study, Sebag-Montefiore's study using short course radiotherapy (25 Gy/5 fraction) whereas other three studies using long course radiotherapy (50 Gy/25 fractions). In Sebag-Montefiore's study, for non-preoperative radiotherapy group, only selected patients got postoperative radiotherapy. Besides, the eligibility criteria regarding stage of the tumor in four RCT's were unidentical. In Park's and Sauer's the stage of the tumor were clearly stated as T3-T4 with or without lymph node involvement, whereas in Roh's and Sebag's were not. But in Roh's and Sebag's the tumour were stated as resectable or potentially resectable tumour with no evidence of fixation to the pelvis or to surrounding organs.

The objective of this review is to evaluate locoregional recurrence, disease free survival and overall survival for preoperative radiotherapy and postoperative radiotherapy group. However, Sauer's study showed that either acute toxicity and severe chronic toxicity of radiation was statistically lower in preoperative radiation than the postoperative one. But this was not supported by Roh's and Park's study. Sebag-Montefiore's study did not evaluate toxicity of radiation at all.

There is one meta-analysis by Song et al in 2017 that compared preoperative chemoradiotherapy and postoperative chemoradiotherapy before, but our study did not consider whether the participants got chemotherapy or not.[30] Therefore Sebag's study, that was not included in Song's, was included in this review. Besides, we also did not consider the radiation dose and whether the radiation was performed in short or long course.

We also found one RCT by Taher et al in Egypt that compared preoperative radiotherapy and postoperative chemoradiation in locally advanced rectal carcinoma.[31] We did not include this study to our review because they included histopathologic findings of not only adenocarcinoma but also mucinous and Signet ring while the histopathologic findings in other 4 RCTs were confirmed to be adenocarcinoma. We also found subtle locoregional recurrence rate data. Additionally, the follow up of this study was long enough up to 10 years to evaluate the outcome of the disease and the result of this RCT showed that there was no significant difference between preoperative radiotherapy and postoperative chemoradiation in term of overall survival and disease free survival.

According to these 4 RCTs, it is concluded that preoperative radiotherapy is superior to postoperative radiotherapy for controlling locoregional recurrence and disease free survival, but both are equal in overall survival after 5 years follow up.

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