Radioterapi & Onkologi Indonesia
Journal of the Indonesian Radiation Oncology Society

Preoperative Radiotherapy in Rectal Cancer

Irwan Ramli, Sudibio, Fitri Anugrah
*Radiation Oncology Department, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia

Article Information :
Accepted : December 2018
Approved : January 2019

Corespondency:
Sudibio

E-mail:
sudibio_su@yahoo.com

Abstract

Rectal cancer is the third most common types cancer in the world and rank second as a cause of cancer related deaths in 2018. Surgical is the main modality in treatment of rectal cancer, however preoperative radiotherapy significantly reduces local recurrence risk after surgery. At present there are two different schedules of preoperative radiotherapy, short-course preoperative radiotherapy (25 Gy at 5 fractions) followed by immediate surgery and long-course chemoradiotherapy (45-50 Gy at 25-28 fractions) followed by delayed surgery. Although the purpose and local control rate of both schedules is the same, it is indicated in different conditions.

Keywords: Rectal cancer, preoperative, radiotherapy, short-course radiotherapy, long-course radiotherapy, chemoradiation, radiation

INTRODUCTION

Rectal cancer is a common malignancy, together with malignant tumors affecting the colon, colorectal cancer rank as the third most common cancer worldwide and the second-leading cause of death, with an estimated 1,800,000 new cases diagnosed and 881,000 death in 2018. Colorectal cancer incidence rates are about 3-fold higher in transitioned versus transitioning countries, however fatal case rate higher in lower human development index settings.[1]

Rectal cancer treatment is one of the best examples in oncology how patients derives benefits from multidisciplinary strategies. These strategies are as variable as the clinical presentations of the disease. The main modality of the rectal cancer therapy is radical surgery with total mesorectal excision (TME) has emerged as the surgical technique that can reduce local reccurences, however the risk of distant and local reccurences continue to threaten rectal cancer patients. Radiotherapy has a well established role in rectal cancer treatment and is used in the definitive, adjuvant, neoadjuvant and palliative settings.[2]

Preoperative radiotherapy has potential advantages over postoperative radiotherapy, it can lead to the shrinkage of tumor size to facilitate surgery, reduce the risk of tumor spread, hypoxia problems and higher toxicity in postoperative setting. Nowadays, there are two different schedules of preoperative radiotherapy, short-course preoperative radiotherapy (SCRT) 25 Gy at 5 fractions followed by immediate surgery and long-course chemoradiotherapy (LCRT) 45-50 Gy at 25-28 fractions followed by delayed surgery.[3-5] Identifying which patients may benefit most from SCRT and LCRT would be best for which individual patient. This review is aimed to provide a summary role of preoperative radiotherapy in rectal cancer.

ETIOLOGY

In general, the development of the colorectal cancer is an interaction between environmental factors and genetic factors. Approximately 75% of colorectal cancer are sporadic, 15%-20% develop in positive family history or a personal history of colorectal cancer or polyps. The remaining cases occur in people with genetic predispositions such as hereditary nonpolyposis colorectal cancer (HNPCC) or familial adenomatous

polyposis (FAP) or in people with inflammatory bowel disease (IBD) particularly chronic ulcerative colitis.[6-8]

One of modifiable risk factors of colorectal cancer is a high-fat, low-fiber diet. High-fiber diet is associated with the protection effect over colorectal cancer development by decreasing colonic transit time, therefore allowing less time of encounter between carcinogenic subtances and colorectal mucosa. The more sedentary lifestyle such as cigarette smoking and alcohol consumption also appear to be linked with the risk of colorectal cancer. [6-8]

There are likely three main pathways that lead to colorectal cancer : chromosomal instability (CIN), microsatellite instability (MSI) and CpG island methylator phenotype (CIMP). These pathways are not mutually exclusive, tumor can occasionally exhibit features of multiple pathways.[6]

HISTOPATHOLOGY

More than 90% of colorectal cancer are adenocarcinomas originating from epithelial cells of the colorectal mucosa. Adenocarcinoma have mucin, which can be extracellular (colloid) or intracellular (signet-ring cell). Signet-ring cell occurs in 1%-2% of adenocarcinomas. Other rare types of colorectal cancer include neuroendocrine, squamous cell, adenosquamous, spindle cell, undifferentiated carcinomas and lymphomas. The degree of differentiation (well, moderate and poor) is the basis for the grading of colorectal carcinomas. Signet-ring cell carcinoma and poorly differentiated cancer associated with a worse prognosis.[8,9]

CLINICAL MANIFESTATIONS

Rectal cancer often produces minimal or no symptoms, emphasizing the need for screening programs. Common symptoms include abdominal pain, hematochezia/melena sometimes accompanied by the passage of mucus. Change of bowel habits such as unexplained constipation, diarrhea, or reduction in stool caliber. In a few cases, nausea symptoms present, vomiting or abdominal distension indicative a signs of tumor-related obstruction. Urgency, inadequate emptying, tenesmus, urinary symptoms and buttock or perineal pain is indicative of locally advances tumor.[7,8]

PRE-TREATMENT EVALUATION AND IMAGING

Detailed history and through physical examination should be included in the workup. Digital rectal examination (DRE) is mandatory, on DRE tumors can be assessed for size, location, distance from the verge, ulceration and fixation to surrounding structures, permits evaluation of sphincter function, which is important in determining whether the sphincter–sparing procedure is indicated. Pelvic exam should be performed in women diagnosed with rectal cancer to assess for vaginal involvement where appropriate. Pretreatment evaluation should include pathologic confirmation of adenocarcinoma, colonoscopy to evaluate extent of tumor and rule out of synchronous primaries, and baseline laboratory test including blood counts, liver function tests (LFTs) and carcinoembryonic antigen levels (CEA) which sometimes produced by colon cancer.[3-5]

With the shift to preoperative therapy, clinical staging to accurately identify both T and N category is critical. The principal imaging modalities to assess the extent of the primary tumor are endorectal ultrasonography (ERUS), MSCT scan and MRI. Pelvic MRI is the modality of choice and the most reliable test to define locoregional clinical staging. MRI staging of rectal cancer comprises the assessment of tumor location and relation to mesorectal fascia (MRF) and sphincter complex, peritoneal reflection, extramural vascular invasion (EMVI), and lymph nodes. MRI should be carried to select patients for respective preoperative management.[3-5,10] In bulky tumor or locally advanced tumor due to limited acoustic penetration of ERUS, CT scan and MRI are better evaluate the tumor than ERUS. MRI can identify the anal sphincter, puborectalis and especially mesorectal fascia, CT scan can't see true involvement of the anal sphincter and levator ani muscles. CT scan and MRI can evaluate iliac, mesenteric and retroperitoneal nodes but ERUS can evaluate perirectal node only.[2,8]

PREOPERATIVE RADIOTHERAPY VS POST-OPERATIVE RADIOTHERAPY

Preoperative radiotherapy has emerged as the standard of care, although both preoperative and postoperative radiotherapy can be effective. Until 1990, most patients underwent surgery and if needed, received postoperative radiotherapy, the primary advantage of postoperative approach was pathological staging and avoiding overtreatment with preoperative setting. Traditionally, postoperative radiotherapy was administrated for all patients with pT3-4,pN+ tumors or positive circumferential resection margin (CRM), perforation in the tumor area, incomplete mesorectal resection, extranodal deposits or nodal deposits with extracapsular spread

close to MRF if preoperative radiotherapy has not been given.[2,4,5]

Table 1. Sensitivity & Specificity of ERUS, Pelvic CT, and MRI in Evaluating Rectal Cancer[8]

Tumor Extent	Imaging Modality	Sensitivity (%)	Specificity (%)
Muscularis propria invasion	ERUS	94	86
	MRI	94	69
	CT Scan	NA	NA
Perirectal tissue invasion	ERUS	90	75
	MRI	82	76
	CT Scan	79	78
Adjacent organ invasion	ERUS	70	97
	MRI	74	96
	CT Scan	72	96
Lymph node involvement	ERUS	67	78
	MRI	66	76
	CT Scan	55	74

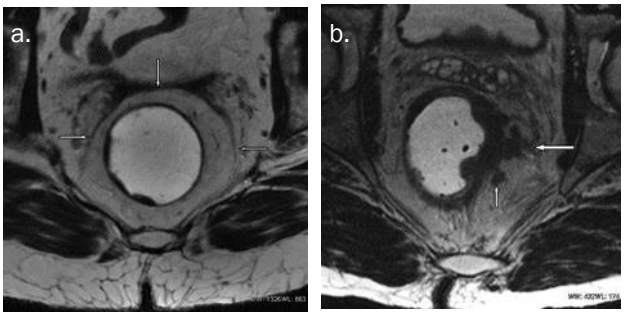

Figure 1. (a) Axial T2-weighted MR image mesorectal fascia as a thin hypointense line (arrows) which encircles the hyperintense mesorectal fat on axial T2 weighted MRI. (b) tumor that extends into the surrounding mesorectal fat and reaches the perirectal fascia (arrow) that represents MRF involvement on axial T2 weighted MRI[2]

Compared with postoperative radiotherapy, preoperative radiotherapy reduces risk of local recurrence, increases sphincter preservation, increases resectability and/or prevent tumor spread viabillity. The peripheral extension of the tumors are relatively better oxygenated and hence are killed effectively by radiotherapy, making the tumor circumscribed. This may reduce tumor spillage and implantation during surgery. Further preoperative radiotherapy may reduce the number of tumor cells disseminating systematically at the time of surgery and the tumor cells entering the circulation are possibly damaged by radiotherapy.[11] German Rectal Cancer Study Group reported the 5-year local recurrence (LR) rate increased from 6% to 13% with use of preoperative radiotherapy. The sphincter preservation increased to 39% from 19% and reduction of grade 3—4 acute and late toxicity and late anastomic strictures.[12] NSABP R-03 confirmed findings of the German rectal cancer study group, preoperative radiotherapy improve 5-year disease free survival (DFS) from 53,7% to 64,7% and this trial also showed a trend toward improved overall survival rate to 74,5% from 65,6%.[13] Gondhowiardjo in retrospective study reported 38% of unresectable patients became resectable after receiving a high dose preoperative irradiation. Complete regression of the tumor mass followed by sphincter preserving surgery was about 30%.[14]

PREOPERATIVE RADIOTHERAPY

Preoperative radiotherapy gets to act on the cancer cells in the well vascularized and thus better oxygenated which increases the efficacy of radiotherapy.[15] Preoperative radiotherapy has been evaluated in a large number of studies.

The EORTC trial compared 37,5 Gy in 2-3Gy fractions preoperative radiation therapy with surgery only. The result of this trial was an increase of local control but not overall survival rate favoring preoperatively irradiated patients. 5-year survival rates in a group of patients younger than 55 years old favoring preoperatively irradiated patients (80%) than those with surgery only (48%). In the EORTC trial, reported the use of preoperative radiotherapy increased the 5-year survival rate to 69% from 59%.[16]

There are two approaches to preoperative radiotherapy. The first, developed in Northern Europe and Scandinavia is SCRT (25 Gy in 5 fractions). The second is LCRT (45-50 Gy in 25-28 fractions with or without boost with a further 5,4 Gy in 3 fractions). Preoperative radiotherapy is indicated in locally advanced tumor (cT3-T4). The selection of preoperative approach is based more regarding risk of CRM at surgery. If CRM are predicted at risk, LCRT is advised. Otherwise either SCRT or LCRT can be administered. CRM can be predicted by MRI, if tumor distance to the MRF ≤ 1mm was recorded as an MRI-involved CRM or positive MRF.[17]

Current guidelines recommended choice of treatment options , such as :[3-5]

a. cT3 [MRF(-)], N0, M0 à SCRT followed by immediate surgery (<10 days from the first radiation fraction) or LCRT followed by delay surgery (6-8 weeks after last fraction of radiotherapy)
b. cT3 [MRF(-)], N+, M0 à SCRT or LCRT. If

SCRT was chosen, adjuvant chemotherapy is recommended after surgery

c. cT3 [MRF(+)], N0/+, M0 or cT4, N0/+, M0 à LCRT

A number of RCT have show that for patients with locally advanced disease who didn't undergo total mesorectal excision (TME) preoperative, radiotherapy improves survival. For patients treated with TME, the local recurrence risk is reduced by preoperative radiotherapy but not survival. According to Swedish Rectal Cancer Trial that compare preoperative 25 Gy fractions RT-non TME surgery vs non TME surgery alone, preoperative radiotherapy improved 5-year local recurrence rate of 11% to 27% in favor of the irradiated group. Dutch TME study compare preoperative RT-TME surgery vs TME Surgery, preoperative surgery improved 5-year LR 5.6% to 10.9% in favor of the irradiated group, in conclusion preoperative radiotherapy reduced cancer specific survival but not overall survival in TME surgery era.[14-15]

PREOPERATIVE SCRT VS LCRT

A number of study to determine whether a SCRT approach is better than LCRT was undertaken. In a study from Polish rectal cancer group compared SCRT and LCRT approach, although a higher pathological complete response (pCR) rate was seen with LCRT (16% vs 1%) along with fewer positive radical margins (4% vs 13%) and considerable tumor size reduction by the tumor. No difference in sphincter preservation rate, local control or OS was seen.[16]

In the TROG 01.04 an Australian intergroup trial, 326 patients with cT3nxM0 randomized between SCRT and LCRT. There wasn't any difference in 3-year LR (7.5% vs 4.4%0, 5-year OS (74% vs 70%) or late toxicity. There was no distinction in rates of sphincter-sparing surgery, despite tumor downstaging. Fractionation and timing after radiotherapy to surgery were both evaluated in the more recently published Stockholm III trial. All patients were randomized to SCRT followed by surgery within 1 week, after 4-8 weeks and LCRT followed by surgery after 4-8 weeks. The main outcome was time to local recurrence, there was no difference between all three arms. The post operative complication rates were 46% vs 40% vs 32% (p=0.164). Among patients receiving SCRT, patients with delayed surgery had lower pT stages, higher rates of pCR (11.85% vs 1.7%) and higher likelihood of tumor regression. This suggest that SCRT with delayed surgery may be an option to conventional SCRT followed by immediate surgery.[17-18]

FUTURE DIRECTION – PREOPERATIVE RADIOTHERAPY AS A ORGAN PRESERVATION THERAPY

After an interval of 12 weeks from the start of the treatment, clinical complete response (cCR) can be obtained in 10%-40% patients following SCRT or LCRT. A cCR is defined as the disappearance of all signs of cancer in response to treatment. It can be assessed clinically including DRE, endoscopy and by MRI. A cCR marked as the absence of any palpable tumor or irregularity at DRE, no visible lesion in endoscopic modalities except a flat scar, telangiectasia or whitening of the mucosa. These minimal criteria can be complemented by absence of any residual tumor in the primary site and draining lymph nodes on imaging with CT scan or MRI, and negative biopsies from the scar, although this definition not universally agreed. Some centers in the world have reported encouraging oncological and functional outcome results for selected patients treated with LCRT and non-operative strategy. Limited clinical series report favorable results with non-operative management among patients who achieve cCR with LCRT. A single institution retrospective study by Habr-Gama et al reported that patients with cCR after LCRT were enrolled on a nonoperative management, reserving surgery for salvage therapy. 90 (49%) patients from 183 patients achieved cCR, of these the 5-year LR was 31% and salvage therapy was possible in 93% of failures.[19] Same study was done by Renehan et al in UK. 30% patients treated with LCRT had cCR and were observed for nonoperative management, 3-year LR 38% and 88% were salvaged. Compared to matched who had surgical resection, a greater portion of cCR patients after LCRT were colostomy free at 3 years (74% vs 47%) and have better quality of life.[20]

In order to confirm this watch and wait approach, more follow-up and larger number of patients treated within properly controlled prospective studies are required.

CONCLUSION

With the shift to preoperative therapy, clinical staging to accurately identify both T and N category is critical and MRI pelvic is the modality of choice. It is the most accurate test to define locoregional clinical staging. Selection preoperative approach in rectal cancer is based on regarding of MRF status and prediction of resection status. LCRT is advised for rectal cancer with MRF ≤1mm or cT4. Otherwise, either SCRT or LCRT can be administered.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I. Global Cancer Statistics 2018 : GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. 2018;00(00):1–31.
2. Valentini V, Schmoll H. Multidisciplinary Management of Rectal Cancer. 2nd ed. Valentini V, Schmoll H, editors. Multidisciplinary Management of Rectal Cancer. Springer; 2018.
3. NCCN. Rectal Cancer. Clin Pract Guidel Oncol. 2018
4. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(July):iv22-iv40.
5. Velde CJH Van De, Boelens PG, Borras JM, Coebergh J, Cervantes A, Blomqvist L, et al. EURECCA colorectal : Multidisciplinary management : European consensus conference colon & rectum. 2014
6. K.Libutti S, G.willet C, B.Saltz L. Cancer of the Rectum. In: T.Devita V, S.Lawrence T, A.Rosenberg S, editors. Cancer Principles & Practice of Oncology. 9th ed. Philadelphia: LIPPINCOTT WILLIAMS & WILKINS; 2011.
7. M.Liu M, G.willet C, G.CZito B. Cancer of the Colon and Rectum. In: Halperin EC, Wazer DE, A.Perez C, W.Brady L, editors. Principles and Practice of Radiation Oncology. 6th ed. Philadelphia: LIPPINCOTT WILLIAMS & WILKINS; 2013. p. 1215–31.
8. D.Minsky B, M.Rodel C, Valentini V. Rectal Cancer. In: Gunderson LL, Joel E. Tepper, editors. Clinical Radiation Oncology. 4th ed. Philadelphia: elsevier; 2016. p. 992–1018.
9. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: Pathologic aspects. J Gastrointest Oncol. 2012;3(3):153–73.
10. Jhaveri KS, Hosseini-Nik H. MRI of rectal cancer: An overview and update on recent advances. Am J Roentgenol. 2015;205(1):W42–55.
11. Ramli I, Gondhowiardjo S, Dhamiyati W. Radiation Treatment in Rectal Cancer: Indonesian Perspective. In: Sudoyo AW, Gondhowiardjo S, Hutagallung EU, Panegoro SS, Phillipi B, Sekarutami SM. The Multidisciplinary Cancer Management of Solid Tumors: Breast, Colorectal and The Sarcomas Today and Tomorrow. Jakarta: The Information and Publication Center of the Department of Internal Medicini, University of Indonesia, Faculty of Medicine; 2004. p.73-82.
12. Rödel C, Wittekind C, Fietkau R, Martus P, Ph D, Tschmelitsch J, et al. Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer. N Engl J Med [Internet]. 2004;351:1731–40. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa040694
13. R- N, Roh MS, Colangelo LH, Connell MJO, Yothers G, Deutsch M, et al. J OURNAL OF C LINICAL O NCOLOGY Preoperative Multimodality Therapy Improves Disease-Free Survival in Patients With Carcinoma of the Rectum : 2009;27(31).
14. Gondhowiardjo S, Pusponegoro AD. The Role of Irradiation in The Treatment of Rectal Cancer. A Literature Review and Some Experience. In: Berkel H, Kresno SB, Susworo R, eds. Book of Proceeding Jakarta International Cancer Conference '95. Jakarta: Gaya Baru: 1997; 342-8.
15. Shukla NH, Seenu V, Goel AK, Deo SVS, Lal P. et al. Cancer of The Colon, Rectum and Anal Canal. In: Rath GK, Mohanti BK, eds. Textbook of Radiation Oncology Principles and Practice. New Delhy: Churchill. Livingstone: 2000; 407-43.
16. Lavery IC, Lopez-Kostner F, Peley RJ, Fine RM. Multidiciplinary Approach to Cancer. Treatment of Colon and Rectal CAncer. Survg Clin of North America 2001;15:1-8.
17. Taylor FGM, Quirke P, Heald RJ, Moran BJ, Blomqvist L, Swift IR, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-Year follow-up results of the MERCURY Study. J Clin Oncol. 2014;32(1):34–43.
18. Swedish Rectal Cancer Trial. Improved Survival with Preoperative Radiotherapy in Resectable Rectal Cancer. N Engl J Med [Internet]. 1997;336:980–7. Available from: https://www.nejm.org/doi/full/10.1056/NEJM199704033361402
19. Kapiteijn E, Marijnen CAM, Nagtegaal I, Putter H, Steup WH, Wiggers T, et al. Preoperative Radiotherapy Combined with Total Mesorectal Excision fot Resectable Rectal Cancer. N Engl J Med. 2001;345 (9):638–46.
20. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93(10):1215–23.
21. Solomon M, Alfred RP, Ngan SY, Burmeister B, Fisher RJ, Solomon M, et al. JOURNAL OF CLINICAL ONCOLOGY Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer : Trans-Tasman Radiation Oncology Group Trial 01 . 04. 2012;30 (31):3827–33.
22. Erlandsson J, Holm T, Pettersson D, Berglund Å, Cedermark B, Radu C, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre , randomised , non-blinded , phase 3 , non-inferiority trial. (Stockholm III).

23. Habr-gama A, Gama-rodrigues J, Proscurshim I, Sabbagh C, Sa GP, Lynn PB, et al. Local Recurrence After Complete Clinical Response and Watch and Wait in Rectal Cancer After Neoadjuvant Chemoradiation : Impact of Salvage Therapy on Local Disease Control. 2014;
24. Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol [Internet]. 2015;2045(15):1–10. Available from: http://dx.doi.org/10.1016/S1470-2045(15)00467-2