High-Dose-Rate brachytherapy (HDR-BT) with neoadjuvant chemoradiation for advanced rectal cancer

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Abstract*—Colorectal cancer is leading cancer-related public health problem. This study was conducted to determine the effect of High-Dose-Rate intraluminal brachytherapy (HDR-BT) with or without interstitial brachytherapy during neoadjuvant chemoradiation for locally advanced rectal cancer. This randomized contrial was conducted on 28 patients attended with locally advanced rectal cancer (T3, T4 or N+) treated initially with concurrent capecitabine (800 mg/m2 twice daily for 5 days per week) and pelvic external beam radiation therapy (45Gy in 25 Fractions) after one week MRI for all patients; received intraluminal HDR-BT with 4Gy x 2 Fractions with one week interval for those had gross residual disease within 1cm of rectal wall and receiveed intraluminal and interstitial brachytherapy with 4Gy x 2 Fractions with one week interval for those had gross residual disease far from 1cm of rectal wall. All patients underwent surgery within 4-8 week after completion of neoadjuvant therapy. In the control group which were not randomized, twenty-eight patients underwent neoadjuvant chemoradiation (45Gy in 25 Fraction with concurrent capecitabine 800mg/m2 twice daily for 5 days per week) followed by surgery. It was found that in HDR-BT group pathologic complete response (pCR), pathologic partial response (pPR) and pathologic response rates (pCR+pPR) based on AJCC TNM staging for colorectal cancer were %35.7, %35.7, and %71.4 respectively. The pCR, pPR, and pRR were %25, %17, and %42 in the control group respectively. pCR, pPR, and pRR were improved with HDR-BT. However, only response rate improvement was statistically significant (p=0.031). There was no a statistically significant difference in the complications between the two groups (p > 0.05). So it can be concluded that HDR intraluminal with or without interstitial brachytherapy may be an effective method of dose escalation technique in neoadjuvant chemoradiation therapy of locally advanced rectal cancer with higher response rate and manageable side effects.*

Key words: HDR, Brachytherapy, Neoadjuvant, Chemoradiation, Rectal cancer

I. INTRODUCTION

Colorectal cancer is leading cause of cancer-related mortality and morbidity worldwide.[1-3] The incidence of colorectal cancer in Iranian population is currently very low compared with western population, the younger generation is experiencing an accelerated rate approaching the western rates and the burden of disease will increase dramatically in future.[4] Accordingly, beside the preventive approaches, use of the most recent effective treatment is of importance.[5-6] However, the surgery remains the cornerstone of rectal cancer treatment, most rectal cancer cases present at advanced stage and are not indicated to curative surgery. Recent evidence demonstrates that neoadjuvant

chemoradiation is superior to postoperative chemoradiation for treatment complications, local control and sphincter saving in patients with stage 2-3 of rectal cancer.[7-8] It has been shown that brachytherapy results are appreciated in clinical and pathological response rates with manageable treatment complications.[9] The aim of the study was determining the effect of High-Dose-Rate intraluminal brachytherapy (HDR-BT) with or without interstitial brachytherapy during neoadjuvant chemoradiation for locally advanced rectal cancer.

II. METHODOLOGY

A hospital based randomized control study was conducted on twenty-eight patients who were referred for neoadjuvant treatment for rectal cancers between August 2012 and September 2014 in a tertiary health care center were enrolled. The inclusion criteria were histologicaly confirmed rectal adenocarcinoma, distal end of tumor located within 12-15 cm from anal verge on lower gastrointestinal endoscopy, tumor stage 2-3 (T3, T4 or N+) on pelvic MRI or endoscopic ultra sonography without systemic metastasis (M0), Eastern Cooperative Oncology Group (ECOG) performance status 0-2, and normal laboratory profile (WBC >4000 with absolute neutrophil count>1400, Hb >10, Platelet count > 100000, serum creatinine <1.2 mg /dl , SGOT < 3 times upper normal limit). Exclusion criteria were poor performance status (ECOG > 3), abnormal blood cells count or liver function test or renal function test, history of previous pelvic radiotherapy, and history of inflammatory bowel disease. Furthermore, the patients with the same clinical stage during the same time that were referred to this center, although not randomized, were selected as the control group.

2.1 Radiotherapy

Pelvic irradiation was delivered by high energy linear accelerator (18 MV) machine. A CT simulation was achieved for all patients in prone position with a belly board. Rectal field designed to cover tumor with margin, presacral and internal iliac nodes (for T4 tumors, internal iliac nodes should be covered) using three filed technique with following borders:

For AP-PA fields the lateral borders extended to cover pelvic sidewalls, i.e. 1.5 cm outside pelvic inlet. The superior border was at the L5-S1 inter-vertebral space, and the lower border was kept at 3-5 cm below tumor volume. Anterior border of lateral fields was 3-5 cm anterior to sacral promontory and posterior border was behind bony sacrum to cover presacral tissues. All ethical issues were considered in this study and written informed consent was obtained from all patients before treatment.

HDR-BT technique: One week after completion of external beam radiation therapy, MRI was performed for all the patients and based on residue, ILBT with or without IST-BT was done with 4Gy x 2 Fractions with one week interval.

Intraluminal BT was performed using rectal cylinder applicator implant. A rectal cylinder is a hollow cylinder that is placed into the rectum by local anesthesia. The cylinder itself is not radioactive; the radioactive source is placed into the cylinder once treatment plan is completed. Interstitial BT was performed using fine needles inserted via perineum according to the tumoral invasion and lymph node involvement under the guide of ultrasound.

Machine used for HDR-BT was a Flexitron remote after loading unit with an Iridium-192 source. Prescribed dose was 4Gy at 1 cm of rectal catheters. The above-mentioned irradiation was concurrent with capecitabine (800mg/m2 twice daily for 5 days per week). Weekly laboratory data was obtained

during treatment. If there were hematological, renal or liver toxicities, dose modification was considered and Capecitabin was hold until the abnormalities were resolve. All patients underwent surgery within 4-8 week after completion of neoadjuvant therapy. The same treatment protocol was administered for the control group but EBRT was delivered instead of brachytherapy.

2.2 Toxicity profile

Treatment toxicities were graded based on National Cancer Institute (NCI) criteria and were checked weekly for next 3 months during the treatment time.

2.3 Statistical Analysis

Data analysis was performed by SPSS software (version 16.0) [Statistical Procedures for Social Sciences; Chicago, Illinois, USA]. Response rate and toxicity profile were summarized with 95% confidence interval. Paired-sample-T and chi-square tests were used and were considered statistically significant at p-values less than 0.05.

III. RESULTS

3.1 Patient's characteristics

Among total 28 patients were selected as HDR-BT group and 28 patients as the control group, although randomization was not performed. Patients' information is summarized in table 1. There was no significant ($p>0.05$) difference between the two groups in terms of median age, sex, clinical stage and site of primary tumor.

Table 1- Patients Characteristics

Variables		Group A (N=28) ((HDR-BT group)	Group B (N=28) (Control group)	P Value LS
Mean age (year)		60.5±6.2	62±6.7	0.388 NS
Gender	Male	14	12	0.789 NS
	Female	14	16	
Site of tumor	Lower	6	7	0.864 NS
	Middle	13	11	
	Upper	10	11	
Clinical stage	T2N1	4	3	0.358 NS
	T3N0	4	3	
	T4N0	2	2	
	T3N1	1	10	
	T3N2	4	5	
	T4N1	1	2	
	T4N2	3	3	

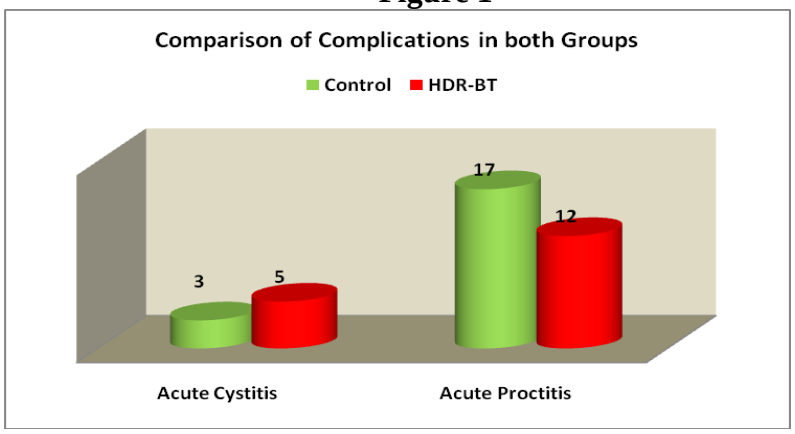
3.2 Surgery and pathologic response

Type of surgery was at the discretion of the surgeon. When type of surgery and pathologic response was observed it was revealed that there was no significant improvement of proportion of the patients who underwent sphincter-preserving surgery (Low Anterior Resection). pCR, pPR and pRR were improved with HDR-BT, however only the response rate improvement was statistically significant ($p=0.031$).

3.3 Complications

Grade 1-2 of acute cystitis was registered in 5 patients in HDRBT group and 3 patients of the control group. Grade 1-2 of acute proctitis was registered in 12 patients in HDRBT group and in 17 patients of the control group. Grade 3 of acute cystitis/proctitis was not registered in both groups. All complications were medically manageable. There was no statistically significant ($p>0.05$) difference in the complications between the two groups. (Figure 1)

Figure 1



IV. DISCUSSION

This study was performed to determine the effect of High-Dose-Rate intraluminal brachytherapy (HDR-BT) with or without interstitial brachytherapy during neoadjuvant chemoradiation for locally advanced rectal cancer. It was seen that pCR, pPR, and pRR indices in HDR-BT group were %3.7, %35.7, and %71.4 respectively. They were also %25, %17, and %42 in the control group respectively.

A complete response to neoadjuvant chemoradiation is associated with improved patient survival and local control in patients with rectal malignancy.[10] However, it is reported in different amounts in various studies. García-Aguilar et al.[10] reported 58 percent complete response which is higher than 36 percent obtained in our study. Also Theodoropoulos and colleagues[11] reported a complete response rate of 18 percent which is conversely less than the obtained response rate in our study. These differences are predominantly due to various chemoradiation therapy regimens used in various studies. Differed inclusion criteria are also other potential causes of various response rates in different studies. The study by Corner et al. showed 58 percent complete response rate among patients with advanced inoperable rectal carcinoma.[12]

The worldwide population is ageing and it may be predicted that the majority of the patients with rectal cancer will be above 75 years in the early future[13]. So, a revision in treatment options with a mild shift from surgical treatments to non-surgical approaches such as chemoradiation is inevitable. The management protocols for rectal cancer have been changed considerably in recent years due to some reasons; countries with high prevalence of rectal cancer are using national bowel cancer screening programs which target earlier stage rectal malignancies compared with cancers in more advanced stages.[14-15] Therefore, the surgical techniques that were aimed in treating of advanced rectal tumors would be inapplicable.

One important finding in this study was similar rate of adverse effects between the two groups. The side effects were also mild and transients. The study by Chuong et al[16] similarly demonstrated no major side

effect in ten studied patients. More attempts should be made to choose the patients with advanced tumors for treatment in specialized referral centers to reduce the rate of side effects and better management of occurred adverse effects.[17]

HDR intraluminal with or without interstitial brachytherapy may be an effective method of dose escalation technique in neoadjuvant chemoradiation therapy of locally advanced rectal cancer with higher response rate and manageable side effects. One of the main limitations in our study was lack of long-term follow-up of the patients.

V. CONCLUSIONS

It can be concluded from this study that HDR intraluminal with or without interstitial brachytherapy may be an effective method of dose escalation technique in neoadjuvant chemoradiation therapy of locally advanced rectal cancer with higher response rate and manageable side effects.

CONFLICT

Authors declare no conflict of interest.

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