Original paper

Complication and response assessment of high-dose-rate endorectal brachytherapy boost in neo-adjuvant chemoradiotherapy of locally advanced rectal cancer with long-term outcomes

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Abstract

Purpose: To identify efficacy, complication, and pathologic response of high-dose-rate endorectal brachytherapy (HDR-BRT) boost in neo-adjuvant chemoradiotherapy (nCRT) of locally advanced rectal cancer.

Material and methods: Forty-four patients who met eligibility criteria were included in this non-randomized comparative study. Control group was recruited retrospectively. nCRT (50.40 Gy/28 fr. plus capecitabine 825 mg/m^2 twice daily) was administered to both groups before surgery. In the case group, HDR-BRT (8 Gy/2 fr.) was supplemented after chemoradiation. Surgery was done 6-8 weeks after completion of neo-adjuvant therapy. Pathologic complete response (pCR) was the study's primary endpoint.

Results: From 44 patients in the case and control groups, pCR was 11 (50%) and 8 (36.4%), respectively (p = 0.27). According to Ryan's grading system, tumor regression grade (TRG) TRG1, TRG2, and TRG3 were 16 (72.7%), 2 (9.1%), and 4 (18.2%) in the case, and 10 (45.5%), 7 (31.8%), and 5 (22.7%) in the control group (p = 0.118). T down-staging was found in 19 (86.4%) and 13 (59.1%) patients in the case and control groups, respectively. No grade > 2 toxicity was identified in both the groups. Organ preservation was achieved in 42.8% and 15.3% in the case and control arm (p = 0.192). In the case group, 8-year overall survival (OS) and disease-free survival (DFS) were 89% (95% CI: 73-100%) and 78% (95% CI: 58-98%), respectively. Our study did not reach median OS and median DFS.

Conclusions: Treatment schedule was well-tolerated, and neo-adjuvant HDR-BRT could achieve better T down-staging as a boost comparing with nCRT, without significant complication. However, the optimal dose and fractions in the context of HDR-BRT boost needs further studies.

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Key words: brachytherapy, neo-adjuvant chemoradiotherapy, boost, dose escalation, rectal cancer.

Purpose

Colorectal cancer is the third most common malignancy, and the second most lethal cancer disease. The most recent cancer epidemiology data reported an incidence of 1.9 million cases and 935,000 deaths worldwide [1]. Neo-adjuvant chemoradiotherapy followed by total mesorectal excision (TME) is the treatment of choice in rectal adenocarcinoma [2]. Neo-adjuvant chemoradiotherapy (CRT) is commonly applied with 50-50.4 Gy in 25-28 fractions plus capecitabine 825 mg/m^2 daily during treatment [2, 3].

Neo-adjuvant chemoradiotherapy has been shown to improve response rate, loco-regional control, and overall survival (OS), and various approaches to this therapy are under investigation [3], including intensified concurrent chemotherapy, additional consolidation and/or induction chemotherapy, and application of external radiation boost to the standard radiation protocols [3].

Several studies have addressed the role of contact brachytherapy as a boost to external beam radiotherapy (EBRT), or as a monotherapy in non-operative management of early-stage rectal cancer [4]. Lyon R96-02 trial showed that 50 kV contact X-ray brachytherapy is effective and safe in non-operative management of clinical T1 and early T2-3 rectal cancers to improve complete clinical response and local control [5, 6]. High-dose-rate

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endorectal brachytherapy (HDR-BRT) was first utilized for palliative or adjuvant treatment of rectal malignancies [7]. The use of remote afterloading techniques and novel imaging modalities enabled more precise dose distribution treatment planning [8]. Moreover, the advantages of HDR-BRT in achieving pathologic complete response (PCR) as a neo-adjuvant monotherapy in early stage [9], or as a boost to EBRT in locally advanced rectal cancer [10], have been reported. However, due to the lack of long-term outcomes and mixed results of different trials, the definite benefit of pre-operative HDR-BRT for locally advanced rectal cancers remains to be established.

Here, we aimed to investigate the efficacy of intra-luminal HDR-BRT boost to neo-adjuvant chemoradiotherapy in patients with locally advanced rectal adenocarcinoma by assessing the complications and pathologic complete response, presenting long-term results of our group of patients.

Material and methods

In this non-randomized prospective cohort study, we evaluated patients with rectal cancer at the Radiation Oncology Department of Tehran University of Medical Sciences, between 2011 and 2012. A cohort of locally advanced rectal adenocarcinoma patients without intra-luminal HDR-BRT boost was used as a comparator group. The present study was designed and performed under the ethical codes of Helsinki Declaration, and approved by the Ethics Committee of Tehran University of Medical Sciences (approval code: IR. TUMS.IKHC.REC.1400.224).

Inclusion criteria

Patients with T2-4 and/or N+ (node-positive) rectal adenocarcinoma, Karnofsky performance status (KPS) > 70, and normal renal function were eligible for inclusion into the study. Additionally, all eligible patients had to be candidates for neo-adjuvant chemoradiotherapy followed by surgery with proximal edge of the rectal tumor located up to 10 cm from the anal verge.

Exclusion criteria

Patients with synchronous colon and rectal cancer, history of previous pelvic radiation or distant metastasis, and tumor location of more than 10 cm distance from the anal verge were excluded.

Pre-treatment evaluation

Patients were evaluated according to endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) using the 7th edition of the American Joint Committee on Cancer (AJCC) guidelines for colorectal cancer [11]. A spiral chest, abdominal, and pelvic computed tomography (CT) scan was performed to exclude metastasis. Lab data and serum carcino-embryonic antigen (CEA) were assessed.

Treatment description

Patients were treated with neo-adjuvant 3-dimensional radiotherapy (3D-RT) using four-field box to pelvis with high energy linear accelerator. Rectal exam was done before chemoradiotherapy and before brachytherapy, and the changes were noted. A retrospective arm to compare complications and outcomes of surgery, in which patients received similar treatments, except brachytherapy, was applied. Radiation dose in both groups was 50.4 Gy in 28 fractions, with capecitabine 825 mg/m^2 twice daily during RT concurrently given. Lab data evaluated patients in both groups weekly, with interviews and data recorded.

Patients were referred to surgery 6-8 weeks after termination of neo-adjuvant CRT in the control group and after the last fraction of brachytherapy in the case group, if metastatic events did not occur. At surgery ward, repeated endoscopy was done in all patients as well as DRE and restaging scans to assess patients' response to neo-adjuvant therapy and surgical approach (low anterior or abdominal peritoneal). Almost all patients received adjuvant capecitabin plus oxaliplatin every 3 weeks for 6 months post-operatively.

Brachytherapy protocol

A week after completion of external beam RT, patients received ^{192}Ir source HDR-BRT with two fractions of 4 Gy prescribed to a 0.5 cm depth from the mucosal surface weekly. Patients were sedated with 2 mg midazolam before each treatment session. Brachytherapy was done in the lateral decubitus position, and digital rectal exam was performed to evaluate the location of tumor and to select the best diameter for intra-luminal cylinder. A rigid single-channel cylinder with 2 or 2.5 cm diameter was chosen according to patient's anatomy and comfort. The length of cylinder was determined following pre-treatment MRI or EUS staging, with a 2 cm proximal and distal margin. The length and width of the cylinder in both fractions were the same. All treatment planning was performed with the aid of Flexiplan (ELEKTA AB, Stockholm, Sweden). Moreover, all patients were treated using the same brachytherapy unit (Flexitron, ELEKTA, AB, Stockholm, Sweden).

Outcomes' response evaluation

Staging system was based on AJCC, 7th edition [11]. Pathologic reports were evaluated using central histopathological review of the specimens, and tumor regression scoring was classified according to Ryan's grading system [12]. Acute toxicities were evaluated using common toxicity criteria adverse events (CTCAE, v. 3.0) [13].

Post-treatment follow-up

After completion of adjuvant chemotherapy, patients underwent follow-up with physical examination and serum CEA every 3 months. Thoraco-abdominopelvic CT scanning was done every six months in first two years, every 6-12 months up to 5 years, and annually thereafter, if indicated. In the surveillance protocol, a total colonoscopy was performed one year after surgery and every 3 years, if normal. OS was defined as the time of surgery to death or last follow-up, and disease-free survival was specified as the time of surgery to first tumor recurrence.

Statistical analysis

For evaluating PCR and surgical and chemoradiotherapy complications, χ^2 test and multivariate logistic regression were applied. A p-value of less than 0.05 was considered statistically significant.

Results

Patients and tumor characteristics

This study included 22 patients in each arm. The mean age of the enrolled patients was 53.57. Patient characteristics were well-balanced between the treatment groups, and there was no significant difference between the two groups regarding gender, tumor location, type of surgery, and clinical staging. Our study's patients mainly were T3N0. Most tumors in both the groups were located in the lower third of the rectum, 63.6% in the case group and 59.1% in the control group. Patients and tumor characteristics are showed in Table 1.

Treatment characteristics

The treatment schedule was well-tolerated. Two patients in the case group refused surgery, and chose non-operative management following clinical complete response. After surgery, most patients of the two groups were pathologically T0-2 and N0-1. 50% and 63.6% of the patients underwent low anterior resection (LAR) in the case and the control groups, respectively. Abdomino-perineal resection (APR) was more commonly performed in lower-third tumors in both the groups. The patients completed all cycles of adjuvant chemotherapy. Treatment characteristics are described in Table 2.

Table 1. Patients and tumor characteristics

Parameter	Case group, *n* (%)	Control group, *n* (%)	*P*-value
Sex			0.179
Female	7 (31.8)	11 (50.0)	
Male	15 (68.2)	11 (50.0)	
Location			0.949
Upper third	1 (4.5)	1 (4.5)	
Middle third	7 (31.8)	8 (36.4)	
Lower third	14 (63.6)	13 (59.1)	
N clinical staging			0.293
N0	9 (40.9)	4 (18.2)	
N1	8 (36.4)	12 (54.5)	
N2	5 (22.7)	5 (22.7)	
Missing	0 (0.0)	1 (4.5)	
T clinical staging			0.455
T2	1 (4.5)	3 (13.6)	
T3	20 (90.9)	17 (77.3)	
T4	1 (4.5)	2 (9.1)	

Staging was done according to the American Joint Committee on Cancer (AJCC) guidelines for colorectal cancer, 7th edition

In terms of T down-staging, participants in the brachytherapy group were more likely to experience improvement at least one score in T staging after surgery (p = 0.044).

Sphincter preserving surgery was more often performed in T3 tumors. Sphincter preservation rate in lower third tumors in a post-hoc sub-group analysis was 42.8% and 15.3% in the case and the control groups, respectively (p = 0.19).

In our analysis, pathologic complete response was documented in 11 (50%) patients in the case group vs. 8 (36.4%) patients in the control group (p = 0.27). More-

Table 2. Treatment characteristics

Parameter	Case group, *n* (%)	Control group, *n* (%)	*P*-value
Type of surgery			
APR	9 (40.9)	8 (36.4)	0.184
LAR	11 (50.0)	14 (63.6)	
Refused surgery	2 (9.0)	0 (0.0)	
Partial response	8 (36.4)	9 (40.9)	0.27
Pathologic complete response	11 (50.0)	8 (36.4)	
No response	3 (13.6)	5 (22.7)	
T pathological staging			
0	12 (54.5)	11 (50.0)	0.177
1	1 (4.5)	0 (0.0)	
2	6 (27.3)	2 (9.1)	
3	3 (13.6)	8 (36.4)	
4	0 (0.0)	1 (4.5)	
N pathological staging			0.504
0	13 (59.1)	13 (59.1)	
1	6 (27.3)	6 (27.3)	
2	0 (0.0)	2 (9.1)	
3	1 (4.5)	0 (0.0)	
Missing	2 (9.1)	1 (4.5)	
TRG			0.118
I	16 (72.7)	10 (45.5)	
II	2 (9.1)	7 (31.8)	
III	4 (18.2)	5 (22.7)	
T down-staging			0.044
Yes	19 (86.4)	13 (59.1)	
No	3 (13.6)	3 (13.6)	
Cystitis			
Grade I	6 (27.3)	1 (4.5)	0.041
Proctitis			0.132
Grade I	7 (31.8)	13 (59.1)	
Grade II	8 (36.4)	1 (4.5)	
Overall	15 (68.2)	14 (63.6)	

** TRG – tumor regression grade, APR – abdomino-perineal resection, LAR – low anterior resection*

Table 3. Comparison of previous similarly designed studies with the current study

Study	Target population	Design	EQD_2, BED	Number of patients	TRG				Toxicity	PCR	DFS	OS
					TRG1	TRG2	TRG3	TRG4				
Jakobsen *et al.* 2012 [20] Appelt *et al.* 2014 [14]	T3-4N0-2 rectal ADC	CRT (50.4 Gy in 28 fr.) vs. CRT (50.4 Gy in 28 fr.) + 10 Gy/2 fr. BRT boost	(49.56, 59.47) vs. (62.06, 74.47)	248	28% vs. 44%, $p < 0.05$			ND	(Grade 2 or more), proctitis: 15% vs. 18%, diarrhea: 19% vs. 19%, cystitis: 7% vs. 6%	18% vs. 18%	5-year PFS (63.9% vs. 52.0%, $p = 0.32$), number of pts: 221	5-year OS (70.6% vs. 63.6%, $p = 0.34$), number of pts: 221
Sun Myint 2007 [10]	T3-4N0-2 rectal ADC	CRT (45 Gy in 25 fr.) + 10 Gy BRT boost	–	16		ND			No grade 3-4 toxicity	44%	20-month DFS: 100%	ND
Jakobsen *et al.* 2005 [22]	T3 rectal ADC	CRT (46.8 Gy in 26 fr.) + 5 Gy BRT boost	–	50	27%	27%	40%	ND	MILD	–	ND	ND
Our study	T3-4N0-2 rectal ADC	CRT (50.4 Gy in 28 fr.) vs. CRT (50.4 Gy in 28 fr.) + 8 Gy/2 fr. BRT boost	(49.56, 59. 47) vs. (58.89, 70.67)	44	45.5% vs. 72.7%	31.8% vs. 9.1%	22.7% vs. 18.2%	–	Cystitis grade 1: 4.5% vs. 27.3%, $p < 0.05$, overall proctitis: 63.6% vs. 68.2%	36.4% vs. 50%, $p > 0.05$	8-year DFS: 78% (case group only)	8-year OS: 89% (case group only)

ADC – adenocarcinoma, EQD_2 – equivalent total doses in 2 Gy fractions, BED – biologically effective dose, CRT – chemoradiotherapy, TRG – tumor regression grade, ND – not defined, PCR – pathologic complete response, OS – overall survival, DFS – disease-free survival

over, the most common score of TRG after surgery was TRG 1 found in 16 (72.7%) patients in the case group and 10 (45.5%) patients in the control group ($p = 0.118$).

With regard to the treatment toxicity, patients with urinary complications had only grade 1 cystitis and were significantly worse in the case group. Grade 1 and 2 proctitis were observed in both the groups, but there was no significant difference between the two groups in terms of gastro-intestinal complications.

Disease outcomes

The present study was the first long-term follow-up study, with a median follow-up of 99 months. Two patients who refused surgery underwent APR after 13 and 21 months, respectively, due to positive biopsy. During follow-up, three patients died, and five patients experienced recurrences, one loco-regional and four distant recurrences. 8-year overall survival and disease-free survival (DFS) was 89% (95% CI: 73-100) and 78% (95% CI: 58-98) in the case group, respectively. Our study did not reach median OS and median DFS. Since the control group patients were recruited retrospectively for a better understanding of complications and response assessment, long-term outcomes are not reported in this article.

Discussion

This study was a comparative, non-randomized study to evaluate the efficacy of HDR-BRT effect as a boost to neo-adjuvant chemoradiation in patients with locally advanced rectal adenocarcinoma. Despite that the pathologic complete response as the primary endpoint of this study was reached, a trend towards favorable outcome was observed. Additionally, T down-staging was higher in the HDR-BRT group, which indicated promising findings for brachytherapy in rectal cancer.

Comparison of our study with other similarly designed studies, in which HDR-BRT was applied as a boost to long course chemoradiotherapy are shown in Table 3. Various methods have been used to evaluate the effect of HDR-BRT as a boost. However, most studies have concluded that brachytherapy boost is an effective option to improve treatment response with low complications. Consistent with our study, Sun Myint *et al*. [10] reported a comparable PCR. However, regarding TRG, there is a contradiction as a result of different scoring systems incorporated by previous studies. With regard to the long-term outcome, our study revealed a higher survival rate compared with a study by Appelt *et al*. [14], and it might be attributed the low sample size in our study.

Dose escalated radiation therapy above 40 Gy had been showed to result in a higher PCR rate and improved 5-year DFS and OS [15]. Furthermore, since external radiation techniques have advanced, the role of adding a boosted dose to the tumor bed in rectal cancer has been investigated in various studies; however, despite their effectiveness in improving PCR, they did not show a significant difference between DFS and 5-year OS [2]. Also, a systematic review and meta-analysis demonstrated a rate of 25% improvement in PCR by adding a boosted

dose by modern inverse-planning techniques; however, there was no dose-response relationship [16].

These observations can be interpreted in different aspects. First, according to the sigmoid-like tumor control probability curve (TCP), the changes greater than 85% of biological effectiveness range add to modest benefits in controlling tumors while causing higher risk of complications [17]. It should be remembered that normal tissue tolerance limits the ability to determine the optimal dose-escalation range in rectal cancer. In our study, dose-escalation resulted in a higher rate of low-grade complications and minor PCR advantages. Second, to achieve the best ratio of cancer to normal tissue dose, the selection of an appropriate prescription point is essential. In fact, both the prescription point and tumor size affect the brachytherapy radiation dose [18]. As shown in Table 3, widespread differences exist in the practice of applying brachytherapy in both the fraction and dose. Therefore, additional investigations are required to clarify the optimal method.

Third, despite the demonstrated benefits of HDR-BRT in T1-2 disease [9], full tumor colonogen coverage in T3-4 patients is far from resolved. Consequently, it might be the reason for the insignificant TRG rate between the two arms in our study. However, Valentini *et al*. [19] in external radiotherapy techniques and Jakobsen *et al*. [20] in brachytherapy techniques, disclosed that adding a boosted dose in T3 disease had a significant advantage over T4 disease in improving TRG grades.

The significant benefit of T down-staging observed in this study may play an essential role in the management of lower-third rectal cancer, resulting in a higher rate of sphincter preservation. However, due to the lack of a randomized controlled trial focusing on oncologic outcomes of this event, efficacy data are unclear and needs further studies.

Apart from being practical, brachytherapy is a relatively less toxic modality with minimal complications. We found no case of severe cystitis or proctitis in the brachytherapy group. There was no significant difference in the rate of proctitis between the intervention and control groups. However, the intervention group showed a significantly higher rate of grade 1 cystitis, which could be managed by medications. Furthermore, implementation of 3D conformal brachytherapy techniques in the modern era, such as multi-channel flexible applicators, may help improve the toxicity profile by better tumor coverage and normal tissue sparing. However, prospective data are needed to further elucidate the benefits of these advances.

Both EBRT and BRT trials did not indicate a significant difference in 5-year DFS and OS by adding a boosted dose. Although in a recent meta-analysis, PCR correlated with a 10-year OS (80.5%) and 5-year DFS (90.1%) [21]. Our study was not designated and powered for OS and DFS; however, long-term outcomes were favorable in the brachytherapy arm.

Although our study provided useful findings that contributed to the literature, there are some limitations. This study was a single-center assessment with relatively low sample size, and a retrospective control group. Therefore, the results need to be analyzed in a randomized manner and a larger group of patients.

Conclusions

In conclusion, HDR-EBT was found as an effective treatment in locally advanced rectal cancer in achieving improved response rate and down-staging. Besides being efficient, this method had mild complications, and most adverse effects could be managed medically. However, the optimal brachytherapy technique, dose, and fractions as well as its possible role as a boost to locally advanced rectal cancer should be further investigated.

Disclosure

The authors report no conflict of interest.

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