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REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

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DOI: 10.5603/RPOR.a2023.0051

Article type: Research paper

Published online: 2023-07-29

Stereotactic MR-guided adaptive radiotherapy (SMART) for primary rectal cancer: evaluation of early toxicity and pathological response

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Abstract

Background: The purpose of this study is to measure the effects of stereotactic MR-guided adaptive radiotherapy (SMART) for rectal cancer patients in terms of early toxicity and pathological response.

Materials and methods: For this prospective pilot study, patients diagnosed with locally advanced rectal cancer (LARC) with positive lymph node clinical staging underwent SMART on rectal lesion and mesorectum using hybrid MR-Linac (MRIdian ViewRay). Dose prescription at 80% isodose for the rectal lesion and mesorectum was 40 Gy (8 Gy/fr) and 25 Gy (5 Gy/fr), respectively, delivered on 5 days (3 fr/week). Response assessment by MRI was performed 3 weeks after SMART, then patients fit for surgery underwent total mesorectal excision. Primary endpoint was evaluation of adverse effect of radiotherapy. Secondary endpoint was pathological complete response rate. Early toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Results: From October 2020 to January 2022, twenty patients underwent rectal SMART. No grade 3–5 toxicity was recorded. Twelve patients were eligible for total mesorectal excision (TME). Mean interval between the completion of SMART and surgery was 4 weeks. Pathological downstaging

occurred in all patients; rate of pathological complete response (pCR) was 17%. pCR occurred with a prolonged time to surgery (> 7 weeks).

Conclusion: To our knowledge, this is the first study to use stereotactic radiotherapy for primary rectal cancer. SMART for rectal cancer is well tolerated and effective in terms of tumor regression, especially if followed by delayed surgery.

Key words: stereotactic radiotherapy; MR-guided RT; rectal cancer

Introduction

Short-course irradiation of locally advanced rectal cancer (LARC) as neoadjuvant treatment reduces the risk of local recurrence and showed overall survival improvement.

Advantages of short course radiotherapy (RT) for rectal cancer are huge. First of all, the short overall treatment time involves high compliance, related to the onset of toxicity generally after the end of the treatment. The small number of fractions makes it quick to administer and acceptable also to those patients with a poor performance status [24]. It is a flexible schedule that can be used with a palliative intent as well as a part of a neoadjuvant strategy**.**

The standard treatment of LARC typically consists of a combined-modality therapy, which includes a preoperative long-course chemoradiation of about 5 weeks followed by surgery and adjuvant chemotherapy. The overall treatment duration of approximately 1 year, a distant and local failure rate over 20% and a not-negligible high grade toxicity rate around 6–10% have, however, prompted the search for other more effective and more compliant alternative approaches [29].

In a recent phase III RAPIDO trial, short-course therapy and long-course therapy in patients with locally advanced rectal cancer showed similar efficacy. The rate of locoregional failure, the R0 resection rate and OS at 3 years were comparable in both arms. Adding sequential chemotherapy to short-course treatment, rates of distant metastasis and disease-related treatment failure were lower in the short-course therapy arm compared with the long-course therapy arm (respectively, 20.0% vs. 26.8%, p = 0.005; and 23.7% vs. 30.4%, p = 0.019) [4–6]. Short-course RT without sequential chemotherapy can be generally applied for operable rectal cancer (i.e. that with no involvement of mesorectal fascia), reducing local recurrence with acceptable toxicity [7]. This radiation treatment, used with a palliative intent, also demonstrated to successfully control rectal bleeding and pain in most cases and allowed colostomy to be avoided in majority of patients, without substantial acute toxicity[28]. Therefore, patients for a neoadjuvant program, upfront resectable or unfit for chemotherapy, and inoperable patients for a palliative intent were selected to perform SMART.

Pathological complete response (pCR) is a prognostic factor for disease-free survival [1, 2] and increased response rates have been reported with higher radiation doses [3]. Achievement of a pCR

has been shown to confer a survival benefit in patients with local advanced rectal cancer and a dose-response relationship for rectal cancer has been confirmed, but escalated radiation doses must also result in reasonable toxicities without decreasing patient's quality of life.

MRI may prove a powerful tool in selective dose escalation for patients with rectal adenocarcinoma [23]. The use of MR-hybrid technology for dose escalation neoadjuvant radiotherapy, with a good soft-tissue contrast and with the opportunity to adapt the plan to the anatomy of the day and to control target motion during delivery, could potentially lead to improved outcomes with low toxicity, increasing precision.

The purpose of this study was to analyze tolerability and response of dose-escalated short-course radiotherapy for the treatment of locally advanced rectal cancer in terms of safety and efficacy, using advanced stereotactic MR-guided adaptive radiotherapy (SMART) techniques.

Materials and methods

Patient selection

Patients newly diagnosed with histological proven primary adenocarcinoma of the rectum with positive lymph node clinical staging, resectable (cT3 with > 5 mm extramural invasion and uninvolved MRF) or upfront unresectable (i.e., those with involvement of mesorectal fascia) unfit for chemotherapy or inoperable due to age and/or comorbidities were included in the study. The exclusion criteria included recurrent rectal cancer and being unfit for MRI examinations.

TNM staging

Staging of rectal cancer was carried out according to the Union for International Cancer Control/American Joint Committee of Cancer (UICC/AJCC) 8.0 [27]. The clinical stage of the neoplasm was assessed in preoperative examinations (colonoscopy, pelvic MRI and thoracic-abdominal CT) performed before radiotherapy.

Treatment modalities

Eligible patients received SMART on rectal lesion and mesorectum using hybrid MR-Linac (MRIdian ViewRay).

Treatment prescription at 80% isodose for the rectal lesion and mesorectum with clinical positive lymphnodes was 40 Gy (8 Gy/fr) and 25 Gy (5 Gy/fr), respectively, delivered on 5 days (3 fr/week). Figure 1 shows the targets' coverage from an original plan for rectal SMART. The gross target volume (GTV), the mesorectum (CTV) and the OARs were identified on a true fast imaging (TRUFI) MR scan acquired during simulation and prior to each fraction to adapt the treatment plan of the day. An isotropic 3-mm margin was added to CTV to obtain PTV. New plans were calculated and delivered every fraction because of rectal and bowel motion. Step-and-shoot intensity-

modulated radiotherapy (IMRT) using 6 MV FFF photons was used. An intrafraction motion management strategy was applied, consisting of an automated gating approach based on the real-time acquisition of a sagittal cine MRI during the whole delivery time (temporal resolution: 8 frames/s).

Response assessment

Response assessment by contrast-enhanced pelvic MRI was performed 3 weeks after SMART, then resectable patients fit for surgery underwent total mesorectal excision (TME). Radiological tumour response was evaluated for all patients, according to the MRI assessment of the Tumour Regression Grade (mrTRG) system [25, 26]. The rectal tumor was removed by TME surgery or more extensive surgery if required because of tumor extent. Histopathological examination of the resected specimen was performed according to an established protocol. The evaluation of the tumour response to neoadjuvant treatment on surgical specimen was performed based on Mandard's classification of tumor regression grade (TRG). T and N downstaging was recorded when the pathological stage was lower than the clinical stage before neoadjuvant treatment. Complete pathological response (pCR) was defined as the absence of a residual tumor at the time of the histological examination of the resected specimen.

Follow up

Patients were followed up every day during radiation treatment. After SMART, patients fit for surgery underwent a visit 15 days before and after surgery; inoperable patients were followed up at 3-monthly intervals. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Primary endpoint was evaluation of adverse effect of radiotherapy. Secondary endpoint was pathological complete response rate.

Results

From October 2020 to January 2022 twenty patients underwent rectal SMART. The median age of the patients was 66 years (range 36–93). Patients (pts) baseline characteristics, clinical stage and treatment are listed in Table 1. All patients completed the radiation treatment. Median follow-up time was 12 months (range 4–21). No grade 3 or higher toxicity was recorded. No genitourinary symptoms were reported. Six patients (30%) complained of slight fatigue. Regarding gastrointestinal toxicity, the following symptoms were recorded: grade 1 rectal pain in 3 pts (15%), mild rectal hemorrhage in 1 (5%) patient, grade 1 and grade 2 proctitis in 4 (20%) and 3 (15%) pts, respectively; no enteritis occurred. Tenesmus with mild pain was the most reported acute symptom. More details about radiation-related toxicity are explained in Table 2. A moderate or good

radiological response was observed: the mrTRG 1 or 2 were achieved in 9 pts (45%) and 11 pts (55%) achieved mrTRG 3; no mrTRG 4–5 was observed.

Eight patients were unfit for surgery due to age and/or comorbidities. Twelve patients were eligible for total mesorectal excision, 2 of whom had involvement of mesorectal fascia and were unfit for chemotherapy. All patients were completely resected (R0). Mean interval between the completion of SMART and surgery was 4 weeks (range 3–12). A tumor and/or nodal downstaging occurred in all resected patients: out of 12 patients (pts), 17% (2 pts) were TRG 1, 33% (4 pts) were TRG 2, 33% (4 pts) were TRG 3, 17% (2 pts) were TRG 4; 92% (11 pts) were staged ypN0, one (8%) patient had a single nodal involvement on a surgical specimen. Two (17%) patients achieved complete response (pCR). The pCR occurred with a prolonged time to surgery (> 7 weeks). No postoperative complications were observed after SMART. Patients' pathological stage and response are listed in Table 3.

Discussion

Short course radiation therapy may represent a safe and effective treatment option to manage patients with rectal cancer not amenable for curative treatment as well as patients capable of receiving a neoadjuvant treatment.

Pathologic complete tumor response after chemoradiation in patients with locally advanced rectal cancer is associated with a favorable prognosis. Multiple factors have been postulated to be correlated with the degree of response, such as association of chemotherapy, time to surgery and radiation dose escalation. Studies confirmed that higher radiation doses are associated with a higher probability of pathologic tumor regression [8, 9]. Furthermore, pCR rates and long-term survival are linked in a dose-dependent manner and there seems to be a trend toward increased pCR rates and disease-free survival with increasing dose [10–12]. In addition, a previous meta-analysis showed that patients undergoing chemoradiation with doses over 60 Gy had increased pCR rates [13]. A total dose of 60 Gy using standard fractionation is equivalent to 40 Gy using extreme fractionation (BED_{10} = 72 Gy). Therefore, in this study a dose of 8 Gy per fraction in 5 fractions was prescribed to treat rectal lesions.

In our study TME was planned to be performed at least 3 weeks after the end of SMART. Indeed, delaying surgery after short-course RT entailed similar oncological with lower postoperative complications, compared to short-course RT with early surgery in the interim report of the Stockholm III study [14]. Surgery performed between 10 and 21 days after the start of RT has also been reported to lead to increased toxicity due to an impaired leukocyte response after surgery [15].

With a median follow-up of 12 months (range 4–21), no postoperative complications were observed after SMART.

In Stockholm III trial [14], in the groups with a delay to surgery, about 6% of patients developed grade 3–4 radiation-induced toxicity. A recent metanalysis about neoadjuvant radiotherapy dose escalation for LARC using innovative radiotherapy techniques found a rate of grade 3 or higher toxicity near 11% [12]. In our study, tenesmus with mild pain was the most reported acute symptom. It's noteworthy that symptoms were mostly pre-existing before treatment. Furthermore, as other authors reported [28], patients not undergoing surgery experienced a gradual symptom improvement, as during follow up they reported a reduction of pain, bleeding and/or mass effect signaled prior to treatment. Despite higher dose delivered, no high-grade toxicity (grade 3–5) and no genitourinary toxicity was recorded after SMART. It could be related to the accuracy of real time adaptive treatment strategies. Peculiar benefits of the use of MR-Linac are on-line daily optimization of the plan to manage tumor motion, automated gating to control organ motion in addition to optimal soft-tissue contrast to identify and treat lesions using high RT doses precisely. Because of rectal lesions' inter-fractional movement, as shown in figure 2, and inter-fractional motion (i.e., when air passes throw the rectum), daily adaptation of the plan and automated gating during delivery are essential for a safe dose-escalation.

Studies observed pCR after chemoradiation in 10–27% of patients, with clusters of studies reporting rates closer to 10%[16,17,18,19]. In the latest RAPIDO trial, the rate of pathologic complete response was higher in the short-course arm (28.4% *vs.* 14.3%; $p < 0.001$). This study found a pCR rate of 17%. It occurred when time to surgery was extended beyond 7 weeks for non-clinical reasons. This result is in line with literature [20]. Veennhof et al. found a pCR rate of 12% with short-course RT followed by TME after 45 days, then 4 days. Short-term morbidity was comparable for both groups. However, significantly higher numbers of complete remissions (12 *vs.* 0%) and tumor downstaging (55 *vs.* 26%) were found when surgery was delayed [21].

SMART, using high doses per fraction, led to tumor and nodal radiological or pathological downstaging in all patients included in this study, probably related to higher BED. Interestingly, all patients had a clinical positive lymph node staging and all patients but 1 has a pathological nodal complete response. It can be related to a sort of bystander effect[22]. Further studies are required to demonstrate this hypothesis.

Adding subsequent chemotherapy after SMART and planning time-to-surgery longer than 6 weeks for all patients could improve these results. Larger studies with a longer follow-up are needed.

Conclusions

To our knowledge, this is the first study to use stereotactic radiotherapy for primary rectal cancer. SMART for rectal cancer is well tolerated and could help achieve a complete pathological response in selected patients, especially if followed by delayed surgery. Further study about the association of SMART with chemotherapy are warranted.

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Table 1. Patients baseline characteristic and treatment

	N = 20	%
Gender		
Male	14	70
Female	6	30
Age (years)		
Mean	66	
Range	36-93	
Clinical stage at diagnosis		
cT3 MRF–	10	50
cT3 MRF+	9	45
cT4	1	5
cN1	5	25
cN2	15	75
cM0	16	80
cM1	4	20
Treatment		
SMART + surgery	12	60
Only SMART	8	40

SMART — stereotactic MR-guided adaptive radiotherapy

Table 2. Radiation-related toxicity (CTCAE v.5)

Toxicity type	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gastrointestinal (n. pts)					
Proctitis	4 (20%)	3 (15%)	–	–	–
Rectal pain	3 (15%)	–	–	–	–
Rectal hemorrhage	1 (5%)	–	–	–	–
Enterocolitis	–	–	–	–	–
Genitourinary (n. pts)					

Dysuria	–				
General disorders (n. pts)					
Fatigue	6 (30%)	–	–	–	–

Table 3. Pathological stage and response

	N = 12	%
Time to surgery (weeks)		
Mean	4	
Range	3-12	
Pathological stage		
ypT0	2	17
ypT1	2	17
ypT2	4	33
ypT3	4	33
ypN0	11	92
ypN1	1	8
Pathological response (sec. Mandard)		
T1	2	17
TRG 2	4	33
TRG 3	4	33
TRG 4	2	17
TRG 5	0	0

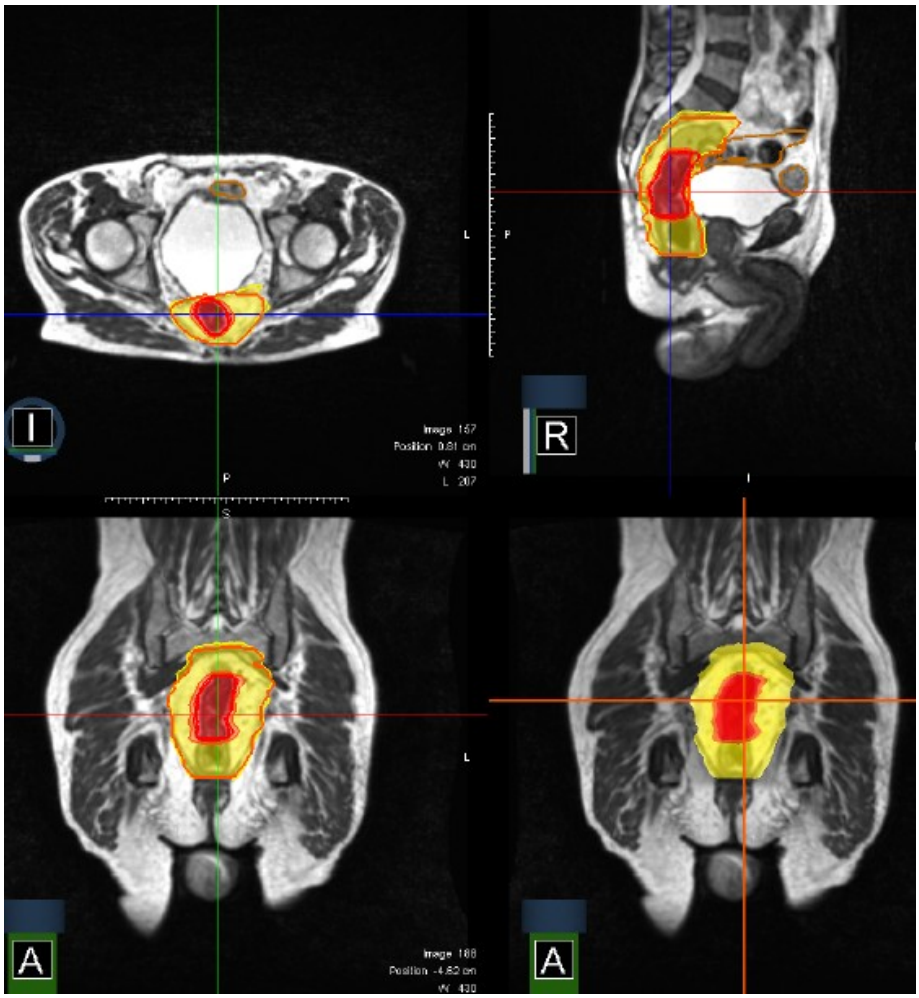

Figure 1. Original plan for rectal stereotactic MR-guided adaptive radiotherapy (SMART): mesorectum is covered by 25 Gy isodose (yellow area), gross target volume (GTV) is covered by 40 Gy isodose (red area)

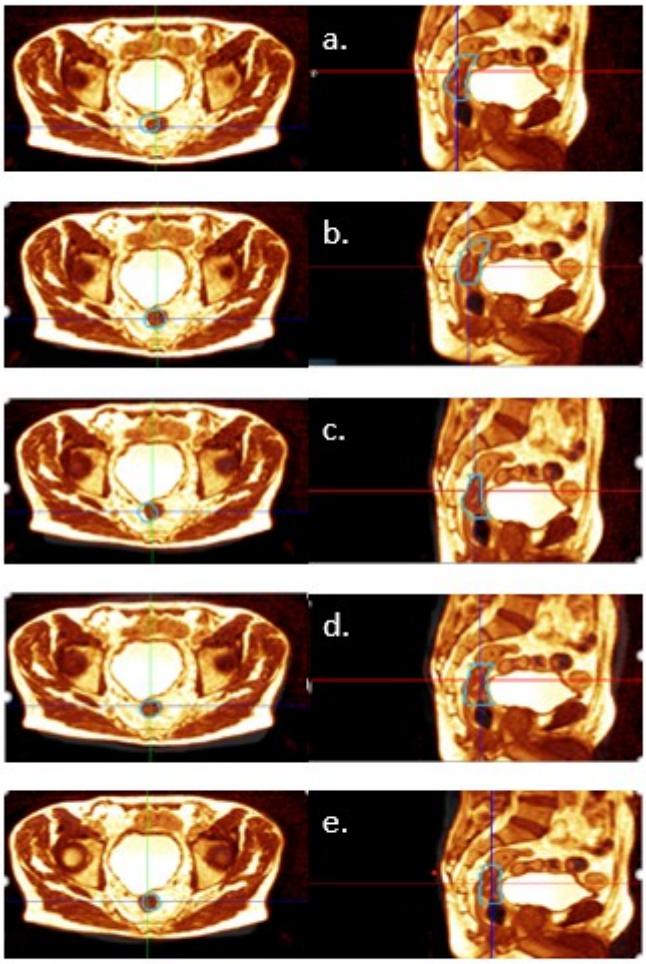

Figure 2. Inter-fractional motion of GTV : the rectal lesion (in cyan lines) assumes different positions from simulation MR for each fraction (a , b, c, d, e are fractions from first to fifth, respectively).