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Case reports and case series

Cone-beam computed tomography-guided online-adaptive radiotherapy for inoperable right colon cancer: First in human

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A B S T R A C T

We report the case of a medically inoperable patient with localised colon cancer. Due to symptomatic bleeding, definitive radiotherapy (5 daily fractions of 5 Gy) has been performed using cone-beam computed tomography-based online-adaptive radiotherapy (ART). Online-ART enables compensation of interfraction motion of abdominal organs by performing daily delineation of organs at risk (OARs) and target volumes. Daily treatment replanning maximised target volume coverage while lowering the dose to OARs. Intrafraction variation of the tumour was still significant and had to be incorporated in the planning target volume margin computation. After the treatment, the patient did not develop any acute radiotherapy-induced adverse events and had no further rectal bleeding either at the end of the radiotherapy or at oncological follow-up 4 months later. Online-ART for colon cancer is feasible and is a valuable alternative when surgery is not an option.

Introduction

The recommended treatment for localised colon cancer is surgery [1]. However, it may be contraindicated in patients with high comorbidity. Radiotherapy (RT) is not currently part of the management of localised colon cancer due to the lack of clinical benefit and significant toxicity [1,2]. Hence, it is only considered a palliative haemostatic treatment in cases of tumoral bleeding [3]. Nevertheless, RT could improve the resection rate and the overall survival in selected patients, according to recent retrospective data [4,5]. Colon RT is challenging due to poor tumour visualisation on cone-beam computed tomography (CBCT) and the high inter- and intra-fraction motion of the tumour and abdominal organs, including the colon itself [2,5–8]. Online-adaptive radiotherapy (ART) offers an opportunity to overcome the challenges of colon RT as it facilitates daily replanning, compensating for anatomical interfraction variations.

Case report

Clinical data

A 71-year-old man presented with rectal bleeding and melena over the previous 15 days. His medical history is characterised by an oxygen-dependent chronic obstructive pulmonary disease (COPD GOLD IV), atrial fibrillation, for which he receives anticoagulant therapy, and obesity (body mass index = 30.5 kg/m^2). Blood tests revealed a grade 1 microcytic anaemia (Hb = 11.5 g/dL). A colonoscopy showed a tumour in the caecum. The contrast-enhanced thoraco-abdominal CT did not detect any distant lesions. Biopsies confirmed the diagnosis of microsatellite-stable adenocarcinoma, staged cT2N0M0 (TNM classification, 8th edition).

The patient was deemed inoperable and unfit for chemotherapy due to excessive comorbidities. Simple follow-up was proposed. During the following weeks, the ongoing rectal bleeding led to grade 3 anaemia (Hb = 7.9 g/dL), with a deterioration of the pre-existing grade 4 dyspnea, which required blood transfusions. RT treatment was suggested despite the lack of recommendations, aiming for haemostatic and local tumour control. This motivated us to develop an online-ART protocol tailored to these specific conditions using our o-ring gantry linear accelerator (ETHOS; Varian Medical Systems, Palo Alto, Calif., USA).

Online-ART technique

Based on the short-course neoadjuvant RT scheme recommended for rectal cancer, we prescribed a dose of 25 Gy in five consecutive daily fractions to the planning target volume (PTV) [9].

The planning-CT was acquired in fasting condition (nil by mouth for one hour prior to planning-CT acquisition), with oral butylhyoscine

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premedication, and an empty bladder. The patient was positioned in supine position without any immobilisation device besides soft immobilisation cushions (Orfit®, Belgium), arms above head. Abdominal compression was not used in order to avoid additional breathing difficulties for the patient.

Volume delineation was made on Raystation (clinical version 12A, RaySearch Laboratories, Stockholm, SE). The clinical target volume (CTV) consisted of the circumferential colonic wall on each of the transversal CT slices on which the tumour was apparent. An initial plan was created with the treatment planning system of the ETHOS (version 2.0).

During the online ART procedure, the CTV of the day was generated using the OARs-guided deformable registration algorithm of the ETHOS between the planning-CT and the CBCT. The volume of the CTV was then manually edited in order to include the entire colon wall, extending from the top of the most cranial radiopaque markers to bottom of the most caudal one.

Three important technical aspects were considered for the planning and the online-ART process of such an unusual location: the interfraction variation, the intrafraction variation, and the lack of visibility of the tumour on CBCT for the image-guided RT (IGRT) procedure.

The interfraction variation of the colon is the most significant one, with reported values reaching up to 35 mm [6]. The on-board treatment planning system of the ETHOS allowing online-ART can compensate for those interfraction variations [10]. It carries out online-ART with daily automatic delineation of OARs, OARs-guided deformable propagation of target volumes, and daily replanning within an acceptable time (23.8 min for this case in average, Fig. 1C). This way, online-ART suppresses interfraction variations and setup uncertainties.

Online-ART does not address intrafraction anatomical variations. We therefore considered three actions to minimise them. (1) Twenty milligrams of oral butylhyoscine were taken orally 30 min before each online-ART session to decrease bowel motility due to its antispasmodic action. (2) Three CBCTs were performed for repeated IGRT ("pelvis large fast" mode of the ETHOS – 25 s duration) during each online-ART session. The first CBCT was used for daily replanning. The second CBCT was made just before RT delivery to assess potential intrafraction displacement. At this point, no treatment was delivered yet and a subsequent table displacement or a new replanning could be made if required. The third CBCT, acquired after RT delivery, was used to evaluate if the final intrafraction displacements of the CTV did not extend outside the PTV. (3) Finally, an empirical isotropic PTV of 20 mm was added around the CTV. However, based on clinician medical decision, the PTV was reduced in the right direction down to 10 mm due to the abutment of the tumour with the abdominal wall (Fig. 1B).

Finally, to address the poor visibility of the tumour on CBCT, six radio-opaque markers (vascular clips) were implanted around the circumference of the tumour, including two at its upper and lower poles. This was performed during a colonoscopy, one day before the RT planning (Fig. 1A). These markers were used as surrogates for tumour position during the whole treatment.

Treatment assessment

We report here below the treatment time requested for all treatment sessions, regarding each step of the adaptive workflow. We also report the adaptive results of each sessions regarding dose to OARs and target volume coverage.

An additional retrospective analysis was performed in order to assess both intra- and inter-fraction variations based on the CTV delineation reported on all the CBCTs acquired during the treatment. We used two metrics: the mean distance-to-agreement (mDTA), which evaluates the

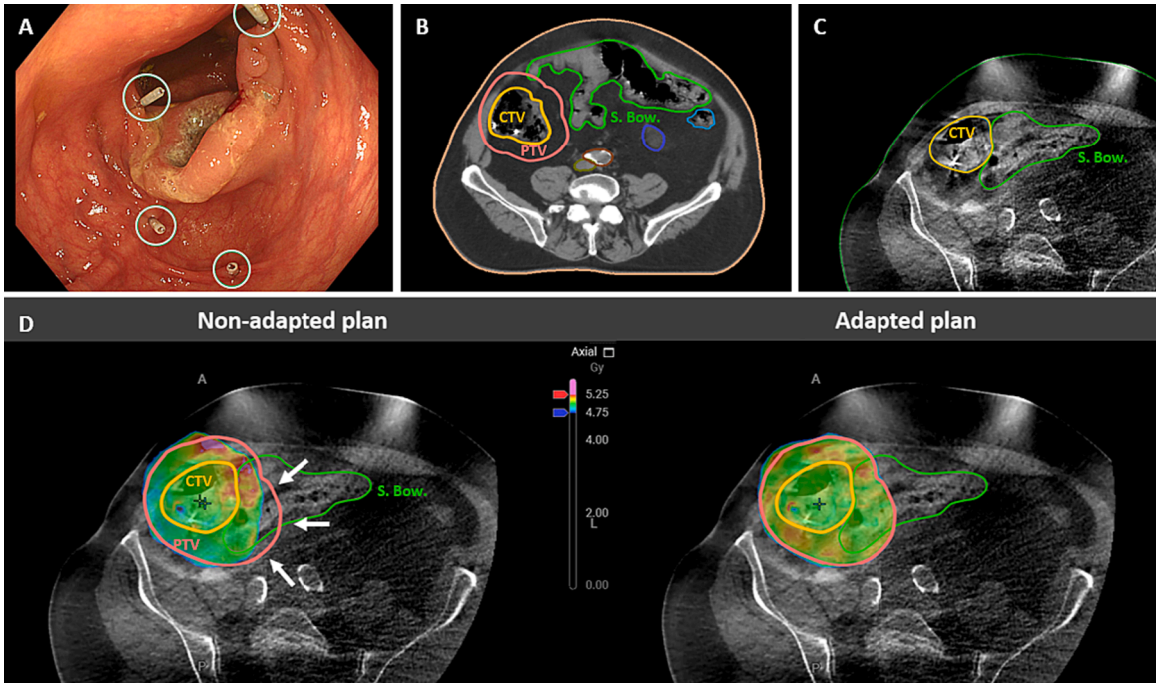


Fig. 1. (A) Six radio-opaque markers were inserted endoscopically in the normal colon mucosa around the tumour the day before the radiotherapy planning CT. (B) These markers were used to delineate the CTV on the planning CT. It is defined as the colonic wall from the CT-slice above the first visible marker to the CT-slice below the last marker in a craniocaudal direction along the colonic axis. PTV consisted of an isotropic margin of 20 mm in all directions except 10 mm in the right direction around CTV. (C) CTV position was propagated on the cone-beam CT of the day using the influencer-guided deformable image registration algorithm for each online-ART session. The small bowel (S. Bow.) was one of the organs at risk considered for this treatment. It was automatically delineated by the artificial intelligence-based algorithm. Manual corrections were done for both the CTV and organs at risk if required. (D) A new dosimetry was computed each day by the online-ART treatment planning system. This allowed the radiation oncologist to choose the best plan between non-adapted and adapted plans. Adapted plans allow for better coverage of the PTV compared to the non-adapted plan (white arrows). ART: Adaptive radiotherapy, CT: Computed tomography, CTV: Clinical target volume, PTV: Planning target volume.

average distance between structures, and the 95% Hausdorff distance (HD95), which is a surrogate for the largest distance between structures. For the interfraction variation, comparisons were made between the CTV delineated on the planning-CT and the CTV delineated on the first CBCT (CTV1) of each session after a rigid bony image registration. Additionally, we created a structure from the merging of all those CTV1, which was compared to the planning-CTV, to get an idea of the optimal margin that would be needed in a non-adaptive workflow to compensate for the interfraction variations. For the intrafraction evaluation, the same metrics were assessed by comparing CTV1 and the union of the CTV volumes delineated on all the CBCTs from the same session. Intrafraction tumoral motion was also quantified by analysing the displacement of radio-opaque markers during each session. We delineated a volume including all the radio-opaque markers on the three daily CBCTs and reported the distance between the centres of mass (ΔCoM) of these structures as a function of time from the first CBCT.

Finally, patient's tolerance to the treatment was also assessed by a physician following each RT sessions. The evolution of the initial rectal bleeding and the RT-induced adverse events were reported using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. at 4 timepoints: at treatment initiation, at treatment completion, 2 weeks after RT completion, and finally at 4 months post RT.

Treatment results

Fig. 2 depicts the workflow of one online-ART session.

The online-ART procedure lasted on average 23.8 min (range: 20.6–26.9 min), from the start of CBCT acquisition to the end of the RT delivery. Most of this time was allocated to the online editing of OARs and CTV (average: 8.9 min, Fig. 2). For the CTV daily delineation, we modified the volume generated by the ETHOS as proposed in our methodology, extending from the top of the most cranial radiopaque markers to bottom of the most caudal one. The tumour had the same tissue density as the surrounding colon wall, therefore, making its precise visualization impossible on the CBCT (Fig. 1C).

For all sessions, the radiation oncologist chose the daily adapted plan instead of the non-adapted plan. When comparing dosimetric data between both plans for each session, OARs sparing and target volumes coverage were better with the adapted plan (Fig. 1D, Table 1).

For the interfraction motion, the average mDTA and HD95 between the planning-CTV and the CTV delineated on the first CBCT of each session (CTV1) were 6.1 +/- 2.5 mm and 14.7 +/- 4.6 mm respectively. The intrafraction motion was quantify by using the average mDTA and HD95 between the CTV1 and the union of the CTV delineated on all the CBCTs from the same session. These values reached 1.9 +/- 0.6 mm and 8.3 +/- 2.3 mm, respectively (Table 2). The interfraction motion was greater than intrafraction motion. The average intrafraction displacement (ΔCoM) of the markers was found to be 7.0 mm (range: 3.5 – 12.4 mm), mostly in the antero-posterior axis. Our PTV margin was sufficient to encompass all these intrafraction variations of the tumoral colon wall. At the time of the second CBCT acquisition, online evaluation of the intrafraction motion was made by the physician. No replannig was required due to intrafraction extend of the CTV outside the PTV at this time.

Table 1
Dosimetric comparison between the non-adapted and daily-adapted plans for each individual session. Organs at risk constraints for which values did not exceed 10% of the objective were not reported. Δ: Difference, CTV: Clinical target volume, PTV: Planning target volume, SD: Standard deviation.

	Non-adapted (mean +/− SD)	Adapted (mean +/− SD)	Δ
Organs at risk constraint			
Small bowel D0.1 cc	5.6 +/− 0.1 Gy	5.3 +/− 0 Gy	− 0,3 Gy
Small bowel D5 cc	5.3 +/− 0.1 Gy	5.1 +/− 0 Gy	− 0,2 Gy
Sigmoid colon D0.1 cc	5.3 +/− 0.1 Gy	5.2 +/− 0.1 Gy	− 0,1 Gy
Sigmoid colon V5 Gy	5.8 +/− 2.5 cc	6.8 +/− 4.8 cc	+ 1,1 cc
Skin D0.1 cc	4.9 +/− 0.1 Gy	5.0 +/− 0.1 Gy	+ 0,1 Gy
Target volumes coverage			
PTV D95 %	81.5 +/− 13.9 %	99.8 +/− 0.2 %	+ 18,4 %
CTV D98 %	99.1 +/− 2.3 %	99.6 +/− 0.5 %	+ 0,5 %

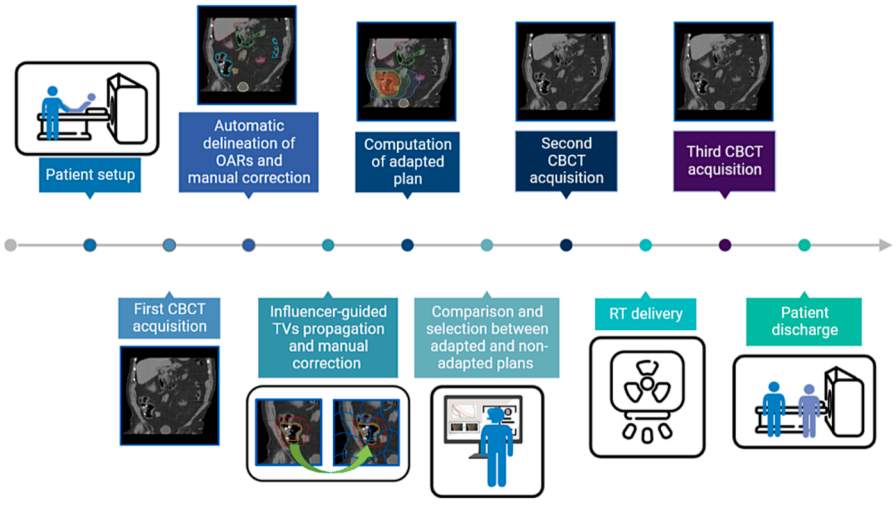
Regarding patient's tolerance to the treatment, the patient never complained about the treatment duration nor declared any discomfort.

At the RT initiation, a grade 2 rectal bleeding was reported by the patient. At the RT end, the rectal bleeding had stopped (grade 0), and no further RT-induced toxicity was reported. After treatment completion, the rectal bleeding never occurred again, and no RT-induced toxicity was reported.

Four months post RT, a colonoscopy showed a major tumour response (>50%) but biopsies demonstrated the persistence of adenocarcinoma cells.

Discussion

Although the majority of adaptive treatments happen for pelvic RT



Online-ART task	Mean (minutes)	Range (minutes)
Manual correction of OARs and TVs	8.9	7.1 – 10.3
Computation of adapted plan	2.3	2.1 – 2.5
Selection of the plan	2.6	2.3 – 3.2
Second CBCT acquisition	0.9	0.7 – 1.2
RT delivery	6.3	5.8 – 7.0
Third CBCT acquisition and patient discharge	2.6	1.1 – 6.0
Total session duration	**23.8**	**20.6 – 26.9**

Fig. 2. Workflow of a CBCT-guided online-ART session with duration of the different steps. ART: Adaptive radiotherapy, CBCT: Cone-beam computed tomography, OARs: Organs at risk, RT: Radiotherapy, TVs: Target volumes.

Table 2
For interfraction assessment, mDTA and HD95 were measured between the planning-CTV and the CTV delineated on the first CBCT of the online-ART session. The total CTV value was obtained by comparing the planning-CTV and the union volume of all CTV delineated on each first CBCT of all sessions. For intrafraction variation measurement, the same metrics were reported between the CTV delineated on the first CBCT of the online-ART session and the union of the CTV delineated on each of the three CBCTs of the session. CBCT: Cone-beam computed tomography, CTV: Clinical target volume, HD95: 95% Hausdorff distance, mDTA: Mean distance-to-agreement, SD: Standard deviation.

Interfraction variation			Intrafraction variation		
	CTV mDTA (mm)	CTV HD95 (mm)		CTV mDTA (mm)	CTV HD95 (mm)
Session 1	5.7	12.8	Session 1	2.5	9.9
Session 2	4.2	13.7	Session 2	2.5	10.0
Session 3	9.2	18.2	Session 3	1.9	7.0
Session 4	8.2	20.3	Session 4	1.1	4.9
Session 5	3.3	8.6	Session 5	1.7	9.6
Total CTV	6.5	17.0	Mean +/− SD	+/- 0.6	8.3 +/− 2.3

treatments due to large and stochastic variations in anatomy, ETHOS has been used for other tumour locations, such as pancreatic and lower oesophagus cancers [11,12]. To our knowledge, this is the first case of online-ART treatment for a colon cancer. This case demonstrates that online-ART for colon tumours is feasible in clinical practice. Indeed, the patient experienced neither discomfort nor adverse events from the RT treatment and deemed the treatment duration acceptable. The time from CBCT reconstruction to plan acceptance (13.9 min on average) was mostly allocated to the manual correction of automatically delineated OARs and CTV during the online-ART procedure (8.9 min on average, Fig. 2). This is consistent with reports by Schiff et al., who assessed the online-ART feasibility in upper-abdominal and pancreatic tumours [13,14]. In their in-silico studies, the mean duration was 22.6 min for upper abdominal locations (11.4 min dedicated to OAR delineation) and 36.3 min (24.0 min dedicated to OAR delineation) for pancreatic tumours [13,14].

Colon cancer RT is scarcely performed in clinical practice. In the intergroup protocol 0130, patients with locally advanced colon cancer who received RT and chemotherapy combination in an adjuvant setting had a 5-year overall survival probability of 58%, compared to 62% for the patients treated with chemotherapy alone ($p > 0.50$) [2]. Furthermore, patients in the RT group had more grade ≥ 3 adverse events ($p = 0.04$). However, as in other studies evaluating RT in colon cancer, the intergroup protocol 0130 did not use modern RT techniques such as intensity-modulated radiation therapy or systematic CBCT-based IGRT, not even mentioning online-ART [2,15].

By using daily delineation and planning to consider the patient's anatomical variations, online-ART could be a solution to deal with the interfraction deformation of the whole colonic wall (used to delineate the CTV) and the other abdominal organs such as the small bowel and sigmoid colon. However, it does not compensate for intrafraction variations, which remains the greatest source of uncertainty in online-ART. Also, colon RT must deal with the lack of visibility of the tumour and inter- and intra-fraction variations of the abdominal organs. Previous reports suggest the use of radio-opaque markers to guide IGRT [2,8]. Magnetic resonance-guided RT could provide an attractive alternative given the direct visualisation of the tumour it allows, making it possible to avoid radio-opaque markers, as is already the case for ART of rectal cancers [16].

Since our analysis is based on a single patient, further confirmations and longer follow-ups are needed in larger studies to determine whether online-ART for localised colon cancer could be an alternative when surgery is contraindicated in a radical setting. Although the tumour response is incomplete, a significant partial response and symptomatic control were achieved in this case. Based on these promising results, online-ART is an attractive technique for symptom palliation or tumour control and should be considered in future trials in colon cancer.

Conclusion

We present the first case of exclusive online-ART for a localised colon cancer. This technique was feasible and led to better target volume coverage and OAR sparing compared to a non-adaptive strategy. The unpredictability of the interfraction variation of the abdominal organs can be mitigated by online-ART. The insertion of radio-opaque markers is required to guide daily CTV delineation throughout the online-ART procedure due to the lack of visibility of the tumour on CBCT. There are still concerns about stochastic intrafraction variations. This should encourage larger-scale analyses to get a population-based quantification that may be integrated into PTV margin.

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Data Availability Statement for this Work

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Informed Patient Consent

The authors confirm that written informed consent has been obtained from the involved patient and he has given approval for this information to be published in this case report.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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