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Endorectal contact radiation boosting: making the case for dose AND volume reporting

Abstract

Introduction:

The various rectal endoluminal radiation techniques all have steep, but different, dose gradients. In rectal contact brachytherapy (CXB) doses are typically prescribed and reported to the applicator surface and not to the gross tumor volume (GTV), clinical target volume (CTV) or organs at risk (OAR), which is crucial to understand tumor response and toxicity rates. To quantify the above-described problem, we performed a dose modeling study using a fixed prescription dose at the surface of the applicator and varied tumor response scenarios.

Methods: endorectal ultrasound-based 3D-volume-models of rectal tumors and the rectal wall were used to simulate the delivered dose to GTV, CTV and the rectal wall layers, assuming treatment with Maastro HDR contact applicator for rectal cancer with a fixed prescription dose to the applicator surface (equivalent to 3 x 30 Gy CXB) and various response scenarios.

Results: An identical prescribed dose to the surface of the applicator resulted in a broad range of doses delivered to the GTV, CTV and the uninvolved intestinal wall. For example, the equieffective dose in 2 Gy per fraction (EQD2) D90% of the GTV varied between 63 and 231 Gy, whereas the EQD2 D2cc of the rectal wall varied between 97 and 165 Gy.

Conclusion: Doses prescribed at the surface are not representative of the dose received by the tumor and the bowel wall. This stresses the relevance of dose reporting and prescription to GTV and CTV volumes and OAR in order to gain insight between delivered dose, local control and toxicity and to optimize treatment protocols.

Introduction

In rectal cancer, radiotherapy, often combined with chemotherapy, can be applied before surgery to reduce the chance of locoregional recurrence. With current standard radiation doses, about 10-20% of all patients with locally advanced cancer will develop a clincal complete (cCR) response after neo-adjuvant (chemo)radiotherapy [1].

One approach to increase the rate of cCR while still preserving rectal function is to add an endoluminal radiation boost. Both contact X-ray brachytherapy (CXB) and high dose rate (HDR) brachytherapy have been reported for this purpose. Endoluminal irradiation is a very attractive boost option, as a more selective volume can be irradiated compared to external beam radiotherapy (EBRT). Various non-randomized series have shown that endoluminal boosting results in high cCR rates of 60-78% in selected patients [2-4]. The randomized phase III OPERA trial (NCT02505750) currently investigates the efficacy of an endoluminal boost using contact X-ray radiotherapy compared to an external beam boost after neoadjuvant chemo-radiotherapy in terms of organ preservation.

Although the reported cCR rates in selected patients are high, there is clearly room for improvement. About 15% of the patients who develop a cCR after an endoluminal boost will develop a local regrowth [2, 3]. Moreover, long-term toxicity, including rectal bleeding, is seen in up to 78% of all patients [3, 5].

In other treatment fields, such as prostate and gynecological brachytherapy, progress has been made that has led to a better understanding of the relationship between dose-volume parameters and tumor control probability (TCP) and normal tissue complication probability (NTCP) [6-9]. For rectal endoluminal radiation techniques, such data are seldom reported. In rectal CXB, for example, dose is prescribed and reported at the applicator surface. Because of the steep dose gradient, the doses received by the tumor and normal tissues are expected to vary significantly depending on tumor thickness and distance from the applicator surface. As a consequence, these reported doses at the applicator surface provide only limited insight into the relationship between delivered dose and TCP or NTCP.

To quantify this problem, we performed a dose modeling study using a fixed dose prescribed to the surface of the applicator and several potential clinical scenarios with varying tumor thickness

and response patterns. The modeling exercise provides data on the actual doses that would be delivered to the tumor and bowel wall substructures.

Materials and methods

3D tumor and intestinal wall models

In order to create 3 dimensional (3D) volume models representing the rectal cancer and the various intestinal wall layers at the moment of the endorectal radiation boost, 3D endorectal ultrasound images of the rectum were used. Seven patients with rectal cancer ((y)cT1N0), undergoing transrectal ultrasonography as part of their standard clinical workup before potential transanal endoscopic microsurgery (TEM), were asked to provide informed consent for re-use of their ultrasound images (Laurentius Ziekenhuis Roermond, protocol approved by Maastro Institutional Review Board). The acquired ultrasound images were de-identified and stored.

Tumor thickness perpendicular to the rectal wall, tumor diameter parallel to the rectal wall and thickness of the various rectal wall layers were measured in these 7 datasets. Based on these measurements, 2 different 3D models, representing a “thick” and a “thin” (y)cT1N0 tumor, were created. In order to assess the dose to potential microscopic tumor spread, an isotropic CTV margin of 5.5 mm was incorporated in the model around the GTV[10]. According to analysis by Verrijssen et al., a CTV margin of 5.5 mm should be sufficient to encompass all microscopic tumor extension in 95% of the patients.

Dose calculations

For dose calculations, a 3D dose distribution of the prototype of the Maastro HDR applicator was used [11]. This dose distribution was obtained using Monte Carlo simulations of photon transport, for a region of 60 x 60 x 38 mm^3 with a voxel size of 0.5 x 0.5 x 0.5 mm^3. The dose distribution of the Maastro applicator is similar to that of CXB using the Papillon 50 device with a 22 mm applicator (Ariane Medical Systems, Derbyshire, UK), though the former has a slightly steeper dose falloff [11]. For treatments using the Papillon 50, usually an applicator surface dose of 30 Gy is prescribed, resulting in 23.1 Gy at 2 mm depth [12]. As the Maastro applicator does not have a uniform dose distribution directly at the surface, in order to simulate a treatment comparable to CXB using the Papillon 50 device, the 3D dose distribution was normalized to give 23.1 Gy at 2 mm

depth[11]. This 23.1 Gy at 2 mm depth is henceforth referred to as the 30 Gy Papillon 50 surface dose equivalent (PSDE).

Simulations of a 3-fraction treatment course of 3 x 30 Gy PSDE were performed in MATLAB (version 2018b, MathWorks Inc., Natick, MA, USA) by creating a mask of the GTV, CTV, and different rectal layers (see Figure 1 for a schematic representation). Tissue composition was considered to be equivalent to water. For all simulations, the center of the surface of the tumor was positioned in the center of the high-dose region.

For both the "thin" and "thick" tumor models, 3D dose maps were created for 3 potential response scenarios: 1) no tumor response after 3 fractions; 2) complete macroscopic response after 2 fractions; 3) partial response after 3 fractions. For the scenarios with a complete macroscopic response, both non-concentric and concentric shrinkage were simulated (Figure 2), assuming that at fraction 2 tumor size was reduced by 50% in either the depth direction only or in all directions, and that at fraction 3 only microscopic tumor was left at the surface. In addition, for this last fraction with no visible tumor left, two scenarios were simulated: recovery of layers, in which the mucosa and submucosa recover, and layer collapse, in which the mucosa and submucosa do not recover and the muscularis and adventitia move towards the surface.
The partial response scenario assumed a 25% reduction of the original tumor dimensions after each fraction. Again, both a non-concentric and concentric shrinkage scenario was used.

Dose reporting

The following dose and volume characteristics were extracted for the GTV and CTV for each fraction: the minimum dose and the highest dose level that covered 90% of the volume of the GTV and CTV (D90). Minimum doses were preferably reported as Dmin 0.03cc. In case of a GTV volume < 0.03cc, Dmin was reported. For the GTV, also the highest dose level that covered 50% of the GTV (D50) and the mean dose (Dmean) were extracted.
For the various intestinal wall layers as well as the total intestinal wall structure, the minimum dose to the sub-volumes that receive the highest dose were calculated for the following sub-volumes: 2cc (D2cc), 1cc (D1cc) and 0.1cc (D0.1cc) (see figure 1b-d for schematic representation). These volumes were chosen as they are commonly used in dose reporting for prostate and gynecological brachytherapy. Their relevance in rectal contact therapy, however,

are unclear. The cumulative equieffective dose in fractions of 2 Gy (EQD2) was calculated for each fraction with an α/β of 10 Gy for the tumor and 3 Gy for the rectal layers [7]. Cumulative doses were calculated by adding the dose volume histogram (DVH) parameter values of the various fractions [7].

Dose adaptation strategies, a proof of concept

Potential different dose escalation strategies for poor (partially) responding tumors were compared. 1) Including a 4th fraction of 20 Gy PSDE, or 2) escalating the dose during the 3rd fraction with a dose that would result in a similar cumulative EQD_2 to the GTV as 1).

These scenarios were evaluated for one of the previously explained partial response scenarios: a tumor with 10 mm invasion depth and the assumption that after fractions 1, 2 and 3 tumor depth is reduced by 25% of the original depth per fraction in case of non-concentric shrinkage. In case of concentric tumor shrinkage, a per fraction reduction of 25% of the original size in both tumor depth and surface diameter was used. Doses to the GTV, CTV and bowel wall were modeled.

Results

3D tumor and intestinal wall models

Based on the measurements in the 7 patients, tumor thickness at start of treatment for the ”thick” tumor model was set at 10 mm. For the “thin” tumor model, it was set at 5 mm. For both tumors, a circular surface with a diameter of 2 cm was chosen, as this is a tumor diameter that would be treatable by CXB or Maastro applicator HDR radiotherapy. Little variation in thickness of the various intestinal wall layers was observed between the 7 datasets. Mean thicknesses of the intestinal wall layers were used and rounded to nearest 0.5 mm to create the 3D model, see Table 1.

Dose delivery to the tumor based on tumor thickness and response scenario

Modeled cumulative doses for the no response and complete response scenarios can be found in Table 1A. Modeled cumulative doses for the partial response scenario can be found in Table S1.

Depending on tumor thickness, large differences in modeled minimal delivered doses to 90% of the GTV were observed. A single fraction of a 30 Gy PSDE resulted in a GTV D90 of 11.6 Gy (21 Gy EQD2), and a GTV Dmin 0.03 cc of 9.8 Gy (16.3 Gy EQD2) in case of a tumor thickness of 10

mm. For a tumor thickness of 5 mm, the GTV D90 and Dmin 0.03cc doses were 18.6 Gy (44.4 Gy EQD2) and 16.8 Gy (37.6 Gy EQD2)

The cumulative dose over the three fractions varied significantly over the scenarios as well. The highest cumulative dose to the GTV was seen in the scenario with a good response in a thin tumor (D90 231.2 Gy EQD2). The lowest GTV D90 was found in a thick tumor without shrinkage between the fractions (63.0 Gy EQD2).

When considering the CTV, cumulative doses varied between a D90 29.6 Gy EQD2 in a thick tumor without shrinkage, and 84.4 Gy EQD2 in a thin tumor with concentric shrinkage.

Differences in GTV/CTV and bowel wall dose were predominantly determined by initial tumor thickness and magnitude of tumor response during treatment. The effect of concentric shrinkage vs non-concentric shrinkage was very limited for the GTV D90, but not for the CTV D90, as in concentric shrinkage the CTV areas outside of the GTV started moving into the high dose area.

Dose delivery to the intestinal wall based on tumor thickness and response scenario

Modeled dose delivery to the intestinal wall and its separate layers can be found in Table 1B (this regards “recovery of bowel wall layers scenario”, for both this scenario and “the layer collapse scenario” see table S2) .

Doses to the bowel wall varied significantly between the different scenarios as the presence of tumor tissue shielded part of the normal tissues. The highest D2cc of the bowel wall was seen in the thin tumors showing good response and concentric shrinkage (EQD2 D2cc 164.6 Gy), and the lowest was seen in thick tumors without shrinkage (EQD2 D2cc 96.5 Gy). Recovery of layers versus layer collapse did not or only minimally affect D2cc doses in the total bowel wall and its separate layers. In case of layer collapse, higher EQD2 D1cc and D0.1cc to the muscularis and adventitia were observed.

Future analyses will have to show whether the volume parameters used in this modelling study are of clinical relevance. As of the small treatment volume, a large part of the 2cc and 1cc volume of the intestinal wall layers was located outside of the application area. At the first fraction the following volumes were located directly underneath the applicator: mucosa 0.26 cc; submucosa 0.41 cc; muscularis 1.13 cc; adventitia 1.47 cc. Moreover, the following volumes were located within 1 cm of the applicator: mucosa 1.64 cc; submucosa 2.48 cc; muscularis 3.21 cc; adventitia 4.29 cc.

Dose escalation strategies

We describe an interesting parallel between the dose to the bowel wall and the dose to the GTV. Lower GTV doses seem to result in lower doses to the bowel wall as well. This observation created an interesting window of opportunity to model dose escalation in poor responding tumors. In this context, we took a closer look at what should be the preferred dose escalation strategy in case of incomplete response at the 3rd fraction. In the modeled scenarios giving a 4th fraction of 20 Gy PSDE resulted in a more favorable dose to the bowel wall than giving a higher dose the 3rd fraction (non-concentric tumor shrinkage: EQD2 D2cc 133 vs. 148 Gy; concentric tumor shrinkage: EQD2 D2cc 164 vs. 186 Gy). Interestingly, in this non-concentric scenario, the EQD2 D2cc to the bowel wall of a 4th fraction treatment to a poor responding tumor ended up lower than the EQD2 D2cc to the bowel wall in good responding tumors that received 3 fractions of 30 Gy PSDE without any form of dose escalation (Table 2).

Discussion

In rectal contact therapy, as the dose is prescribed to the surface of the applicator, the actual dose received by the GTV or CTV remains elusive. Here, for the first time, a mathematical reconstruction was performed to estimate doses to the GTV/CTV and rectal wall while prescribing a PSDE of 3 x 30 Gy to the applicator surface. We found that this prescription technique may result in a broad range of doses received by the GTV, CTV and rectal wall.

In order to understand and calculate dose delivery to a target volume, both dose and volume characteristics need to be provided. To date such characteristics are either inconsistently reported or not reported at all [13].

Standardization of treatment reporting is a prerequisite for the collection of high-quality data regarding this subject. This is important, first of all to improve the quality of the reported treatment data, secondly to allow comparison between treatment series, and eventually to improve the treatment itself based on multicenter TCP and NTCP data models. For most other

brachytherapy applications, such as prostate and gynecological brachytherapy, such guidelines have already been implemented [7, 9].

As expected, our modelling data show that poor responding tumors receive the lowest GTV doses, and good responding tumors the highest. This is because a shrinking tumor GTV moves closer to the applicator surface into the higher dose areas. As a direct result of this, our calculations uncover a paradoxical situation, which we designate as the 'Catch-22' of endorectal radiation boosting. With a traditional equal dose prescription at the applicator surface, a poor responding tumor with potentially relatively low radiosensitivity, by definition needing a higher dose to result in a complete remission than a well responding tumor, will unavoidably receive a lower dose to the tumor, although the accompanying lower dose to the OAR would leave room for dose escalation. On the other hand, well responding tumors with relatively high radiosensitivity are more likely to receive more dose than likely needed, which could result in avoidable toxicity. Either way, the result tends to end up unfavorable. The only way out of the Catch-22 situation is to move towards dose prescriptions to the CTV or GTV and/or dose constraints to the bowel wall, possibly combined with an adaptive treatment approach. The development of such methodology, which requires both imaging and dose reconstruction methodology, is currently a research priority within our group. Endorectal ultrasound may be a promising imaging approach, due to the fact that it is easily available, cheap, and gives good anatomical information on the tumor infiltration depth, as well as on the different bowel layers. This information could be used for either advanced treatment planning or the selection of a standard treatment plan based on the invasion depth of the tumor/the thickness of the target volume. We believe that in the future the collective experts should define what would be the preferred strategy. It is important to note that before such methodology can be applied uniformly, consensus on the definition of the target volume should be reached first.

The same holds for dose reporting. In order to be able to establish dose-response relationships, it is essential that a minimal set of treatment and target volume characteristics is being reported. Ideally, the various teams that are applying endoluminal rectal radiotherapy will be able to define common guidelines for both target volume definition as well as for dose reporting. Which and how many items should be minimally reported in order to enable adequate dose reconstruction without inducing a realistic reporting burden should be discussed extensively while designing these guidelines. The results of this study indicate that some tumor and response parameters are

more relevant than others. The parameters with the strongest effect on the dose received by the GTV are the initial tumor thickness and the change in tumor thickness between fractions. Concentric vs non-concentric shrinkage, on the other hand, did not greatly affect the dose received by the GTV, although it had some impact on CTV dose, making it less relevant as a reference parameter for dose reporting than the evolution of tumor thickness.

3 x 30 Gy PSDE is a standard clinical treatment schedule for contact therapy, and this treatment is typically delivered after induction EBRT with a total dose of approximately 50 Gy EQD2. As we modeled, radiation doses to the tumor varied between 63 and 231 Gy in the used scenarios depending on tumor thickness and response pattern. These doses are in stark contrast to the boost doses delivered by EBRT in earlier experimental study protocols. For example, the recent RECTAL-BOOST study attempted an EBRT dose escalation of 15 Gy in 5 fractions resulting in an additional 16.3 Gy EQD2 boost following a 50 Gy EQD2 chemoradiotherapy schedule [14]. Within the INTERACT study, a 12.4 Gy EQD2 boost was delivered using a simultaneous integrated boost technique on top of the classical 44.2 Gy EQD2 EBRT schedule concurrent with capecitabine [15]. The results of this modeling study, therefore, underline the superiority of the dose escalation potential of contact treatment compared to EBRT in patients who are eligible for contact therapy.

Rectal toxicity is the main side effect of endoluminal radiation boosting. To date, there are no dose-response models for rectal toxicity available for use in endoluminal contact boosting, nor is it known which DVH parameter would be most suitable to build such model and to be reported. In order to gain insight into the radiation doses that are delivered to the rectal wall in this treatment, we modeled the dose to the bowel wall and its various layers. For reporting we choose DVH parameters that are commonly being used in other types of pelvic brachytherapy. Theoretically, the different substructures may have different radiation tolerances. Here, especially the submucosal substructure deserves special attention. This anatomical substructure contains the vascular plexus. Since bleeding is consistently one of the most prominent side effects reported following contact treatment, it is reasonable to assume that doses to this structure will predict toxicity. From treatment data for brachytherapy for prostate and gynecological cancer, it is known that the D2cc to the rectal wall is related to toxicity, including bleeding [16]. In this work, however, due to the small treatment volume, very little variation in D2cc of the submucosal substructure was found over the different scenarios evaluated (i.e. 12.6 to 16.7 Gy), which

hampers predictive potential of this parameter within NTCP modeling. In contrast, doses to smaller volumes, like D1cc (39.1 to 75.3 Gy), show much larger variation between the different scenarios and may be more relevant in this respect. Reconstructing delivered doses to the different bowel layers and correlating these to observed toxicity will be necessary to evaluate their potential as predictors of toxicity. Considering the small treatment volume, D2cc and D1cc-based rectal wall substructure parameters appear to be of no practical value in rectal contact radiation boosting as a major part of the volume is not located in the applicator area. D2cc and D1cc parameters not expected to be discriminative in rectal contact radiation boosting for these subvolumes. DVH parameters base on smaller volumes are likely more promising.

As mentioned above, poor responding tumors are likely to receive lowered tumor dose when dose was prescribed at the applicator surface. Moreover, we observed that the D2cc to the bowel wall is significantly lower in poor responding tumors, which may leave room for tumor dose escalation. Hence, to illustrate the potential of individualized dose prescription, we explored the effect of various dose escalation strategies in poor responders. In the specific scenarios evaluated, applying a fourth fraction appears to be the preferred option over a dose escalation in the third fraction as it results in lower EQD2 doses to the intestinal wall while delivering a similar GTV dose.
It is interesting to note that this 20 Gy PSDE dose escalation over a standard 3 x 30 Gy PSDE schedule in this specific poor responding tumor scenario resulted in a similar intestinal wall D2cc as a standard 3 x 30 Gy PSDE without dose escalation in our good responding tumor scenario. Considering these bowel wall data, there might indeed be some room for dose escalation in poor responding tumors. However, considering EQD2 doses to the rectal wall, dose escalation to similar D90 doses to the GTV as in complete responders may be a bridge too far (modelled EQD2 D2cc > 200 Gy, data not shown).

In previous work, we tried to determine the extent of microscopic tumor outside of the visible tumor remnant in tumors previously treated with chemoradiotherapy [10]. In this analysis, we found that 80% of tumors did not show microscopic intramural spread (MIS). To cover all MIS in 95% of tumors, an additional margin for the CTV of 5.5 mm was needed, however. In the current work, we evaluated the dose to this CTV volume according to the different response scenarios. The results indicate that the response pattern - concentric vs non-concentric - could have some impact on the doses received by the CTV. The impact, however, was modest. It is interesting to see that

even in the worst-case scenarios (no tumor response), the doses to the CTV, even though not completely covered by the applicator surface, remained substantial, as EQD2 adjusted D90 CTV boost doses remained 29.6 Gy or higher.

This study has some shortcomings. First of all, we used the concept of EQD2 to describe the total biological effect of the cumulative delivered radiation dose, taking into account the modulating effects of dose per fraction of the different scenarios as described by the Linear Quadratic (LQ) model. At a very high dose per fraction, however, the LQ model might no longer accurately describe biological effects. Some previous attempts have been made to extend the LQ model to high doses per fraction, leading to the inclusion of correction factors in the LQ model [17-20]. These models have not been widely adopted yet, however. Besides, in an analysis by Guckenberger et al., it was shown that the LQ formalism continued to model tumor response adequately in a clinical data set of non-small cell lung cancer patients containing single fraction doses up to 33 Gy [21]. They also demonstrated that the models containing correction factors for high dose per fraction failed to improve response modeling over the classical LQ formalism.
Secondly, the novel insights provided in this work are developed on theoretical modeling only. Its clinical relevance still needs to be confirmed. To do this we need clinical datasets from patients treated with contact therapy, which provide dose-volume parameters and enable calculation of TCP and NTCP. Such is expected to improve treatments by enabling individualized dose prescription with the most optimal tradeoff between dose to the target (GTV/CTV, treatment efficacy) and dose to the rectal wall (OAR, treatment toxicity).

Conclusion

The results of this modeling study show that the doses prescribed to the surface of the applicator are not representative of the dose received by the tumor and the bowel wall. The results, therefore, stress the relevance of dose prescription and reporting to GTV/CTV volumes and OAR in order to gain insight into the relationship between delivered dose, local control and toxicity. Differences in GTV/CTV and bowel wall dose were predominantly determined by initial tumor thickness and magnitude of tumor response during treatment.

Disclosures:

E. Van Limbergen, M. Bellazzo F. Verhaegen and M. Berbee have filed a patent application for the Maastro HDR rectal applicator. The patent has been licensed to a commercial partner. The above mentioned authors receive royalties.

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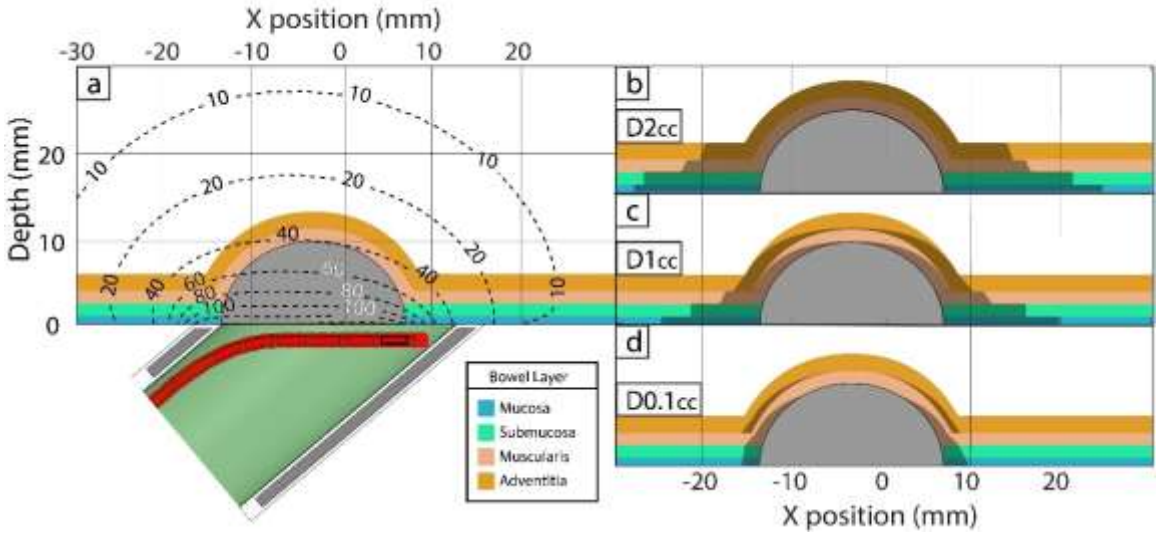
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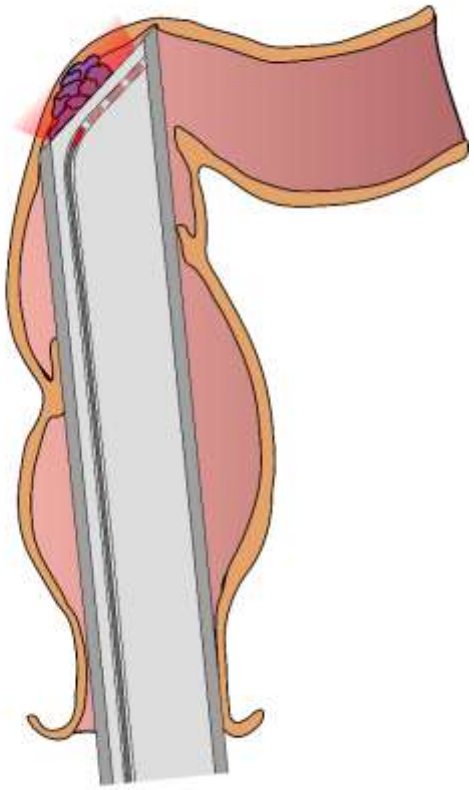
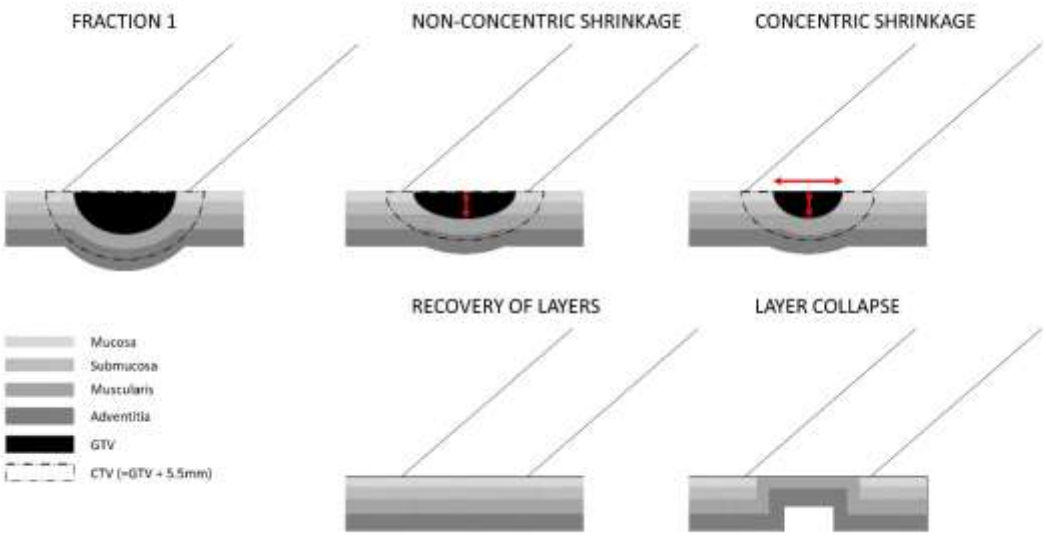


Figure 1: A) Schematic representation of the applicator, tumor (gray), intestinal wall layers and isodose lines; B) schematic representation of the 2cc volume of each instestinal wall layer that receives the highest dose (D2cc); C) schematic representation of the 1cc volume of each instestinal wall layer that receives the highest dose (D1cc); D) schematic representation of the 0.1cc volume of each instestinal wall layer that receives the highest dose (D0.1cc)
E) Schematic representation of the applicator positioned in the rectum.



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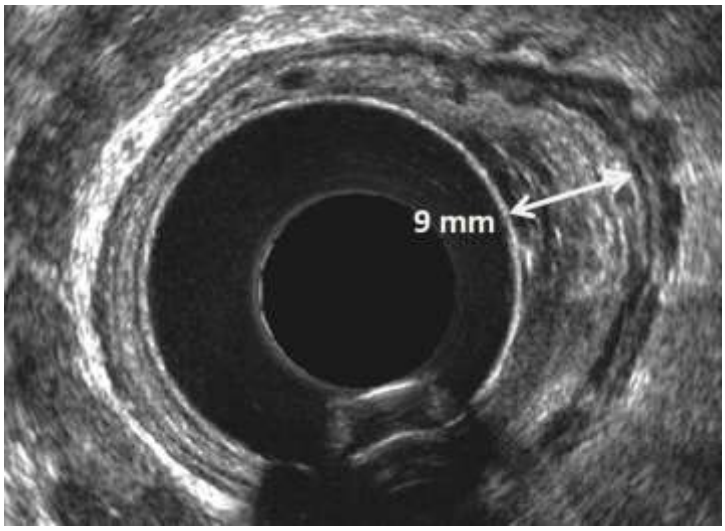
440 Figure 2: Overview of the different response scenarios modeled, describing the concepts of non-
441 concentric shrinkage, concentric shrinkage, recovery of layers and layer collapse. In the collapse
442 of layer scenario, the deeper layers were modeled as moving towards the probe surface as a
443 result of the applicator probe being pressed against the elastic bowel wall.

444

A



B

Bowel layer	Associated thickness (range of measurements) (mm)
Mucosa	1 (0.4-1)
Submucosa	1.5 (0.9-3)
Muscularis	1.5 (0.8-2.2)
Adventitia	2 (0.7-3)

Figure 3: A) Example of an endorectal ultrasound image with a tumor thickness of 9 mm; B) Overview of the thickness of the different bowel wall layers as used in the model.

A

	Thick (10 mm) tumor		
	No response	*Non-concentric shrinkage*	*Concentric shrinkage*
	EQD2 (physical dose) (Gy)		
GTV: $D_{min,0.3cc}$	49 (30)	168 (60)	176 (61)
GTV: $D_{90\%}$	63 (35)	179 (63)	181 (63)
GTV: $D_{50\%}$	134 (56)	232 (76)	232 (76)
GTV: D_{mean}	149 (60)	237 (77)	235 (77)
CTV: $D_{min,0.3cc}$	22 (17)	59 (31)	63 (33)
CTV: $D_{90\%}$	30 (21)	70 (34)	71 (36)
	Thin (5 mm) tumor		
	No response	*Non-concentric shrinkage*	*Concentric shrinkage*
	EQD2 (physical dose) (Gy)		
GTV: $D_{min,0.3cc}$	113 (51)	216 (73)	225 (74)
GTV: $D_{90\%}$	133 (56)	231 (76)	231 (76)
GTV: $D_{50\%}$	219 (75)	231 (86)	282 (86)
GTV: D_{mean}	221 (75)	282 (86)	278 (86)
CTV: $D_{min,0.3cc}$	32 (22)	62 (32)	74 (37)
CTV: $D_{90\%}$	47 (29)	78 (39)	84 (41)

B

	Thick (10 mm) tumor								
	No response			*Non-concentric shrinkage*			*Concentric shrinkage*		
	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$
Recovery of layers									
Mucosa EQD2	5	17	435	6	22	526	6	25	615
Submucosa EQD2	13	39	311	15	60	377	16	72	428
Muscularis EQD2	28	82	200	23	85	245	23	85	262
Adventitia EQD2	44	66	116	38	84	154	38	84	166
All Layers EQD2	96	150	452	137	218	539	152	252	621
	Thin (5 mm) tumor								
	No response			*Non-concentric shrinkage*			*Concentric shrinkage*		
	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$
Recovery of layers									
Mucosa EQD2	5	17	436	6	22	529	6	25	615
Submucosa EQD2	13	41	329	16	65	400	17	75	435
Muscularis EQD2	21	90	232	21	86	279	21	86	279
Adventitia EQD2	35	93	149	34	92	182	34	92	182
All Layers EQD2	125	181	457	155	246	546	165	269	622

Table 1: A) Overview of radiation doses to GTV and CTV in case of no tumor response or complete response; B) Overview of radiation to the rectal wall and its various layers in case of no tumor response or a complete response. This regards the “recovery of bowel wall layers scenario”, for both this scenario and “the layer collapse scenario” see table S2

	4th fraction of 20 Gy PSDE						Dose escalalation in 3rd fraction*					
	Non-concentric shrinkage			*Concentric shrinkage*			*Non-concentric shrinkage*			*Concentric shrinkage*		
Tumor												
GTV Dmin 0.3cc EQD2 (physical dose)	112 (55)			144 (63)			109 (47)			125 (50)		
GTV D90% EQD2 (physical dose)	132 (62)			134 (62)			132 (53)			134 (53)		
CTV Dmin 0.3cc EQD2 (physical dose)	34 (25)			45 (30)			35 (23)			43 (26)		
CTV D90% EQD2 (physical dose)	49 (32)			58 (36)			50 (29)			57 (32)		
Rectal wall	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$
Mucosa EQD2	6	20	505	7	27	709	6	21	579	7	29	827
Submucosa EQD2	15	49	378	18	74	482	16	52	426	19	81	559
Muscularis EQD2	28	103	262	28	104	295	30	116	289	30	117	336
Adventitia EQD2	45	94	162	45	97	184	50	107	178	49	110	209
All Layers EQD2	133	200	528	164	270	715	148	221	605	186	308	833

* in the "dose escalation in 3rd fraction" scenario, escalation is done to a similar cumulative D90 GTV dose as in the corresponding 4th fraction scenario.

Table 2: Dose escalation scenarios in poor responding tumor using either a 4th fraction of 20 Gy (PSDE) or a 3-fraction scenario in which the dose is escalated to a similar cumulative D90 GTV as in the 4th fraction scenario. Doses in Gy.

	Thick (10 mm) tumor		Thin (5 mm) tumor	
	Non-concentric shrinkage	*Concentric shrinkage*	*Non-concentric shrinkage*	*Concentric shrinkage*
	EQD2 (physical dose) (Gy)		*EQD2 (physical dose) (Gy)*	
GTV: $D_{min,0.3cc}$	78 (40)	88 (42)	153 (62)	163 (62)
GTV: $D_{90\%}$	95 (45)	97 (45)	173 (65)	174 (65)
GTV: $D_{50\%}$	174 (65)	175 (65)	250 (81)	174 (81)
GTV: D_{mean}	183 (67)	182 (67)	250 (81)	245 (80)
CTV: $D_{min,0.3cc}$	28 (20)	32 (22)	32 (22)	50 (30)
CTV: $D_{90\%}$	38 (25)	43 (27)	54 (31)	65 (50)

Table S1: Overview of radiation doses (Gy) to GTV and CTV in the partial response scenarios

	Thick (10 mm) tumor								
	No response			*Non-concentric shrinkage*			*Concentric shrinkage*		
	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$
Recovery of layers									
Mucosa EQD2	5	17	435	6	22	526	6	25	615
Submucosa EQD2	13	39	311	15	60	377	16	72	428
Muscularis EQD2	28	82	200	23	85	245	23	85	262
Adventitia EQD2	44	66	116	38	84	154	38	84	166
All Layers EQD2	96	150	452	137	218	539	152	252	621
Layer collaps									
Mucosa EQD2				5	17	436	6	20	525
Submucosa EQD2				13	40	315	14	52	366
Muscularis EQD2				25	100	375	25	100	392
Adventitia EQD2				40	92	228	40	92	240
All Layers EQD2				137	218	539	152	252	621

	Thin (5 mm) tumor								
	No response			*Non-concentric shrinkage*			*Concentric shrinkage*		
	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$	D_{2cc}	D_{1cc}	$D_{0.1cc}$
Recovery of layers									
Mucosa EQD2	5	17	436	6	22	529	6	25	615
Submucosa EQD2	13	41	329	16	65	400	17	75	435
Muscularis EQD2	21	90	232	21	86	279	21	86	279
Adventitia EQD2	35	93	149	34	92	182	34	92	182
All Layers EQD2	125	181	457	155	246	546	165	269	622
Layer collaps									
Mucosa EQD2				5	17	438	6	20	525
Submucosa EQD2				13	44	339	14	55	374
Muscularis EQD2				23	101	409	23	101	409
Adventitia EQD2				37	100	256	37	100	256
All Layers EQD2				155	246	546	165	269	622

Table S2: Overview of radiation to the rectal wall and its various layers in case of no tumor response or a complete response for both the “recovery of bowel wall layers scenario” and the “the layer collapse scenario”.