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ORIGINAL ARTICLE

Toxicity of the lower gastrointestinal tract and its predictive factors after 72Gy conventionally fractionated 3D conformal radiotherapy of localized prostate cancer

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Summary

Purpose: *To estimate the incidence of acute and late lower gastrointestinal tract toxicity (LGIT) in patients treated with 3D conformal radiotherapy (3DCRT) for localized prostate cancer (PC) and estimate the influence of dosimetric parameters and other possible factors.*

Methods: *Ninety-four patients with localized PC treated with 3DCRT, with an estimated risk of lymph node involvement ≤15%, according to the Roach formula, were evaluated in this study. All patients received a total dose of 72Gy in 36 fractions. Acute and late lower gastrointestinal tract (LGIT) toxicity were graded according to the EORTC radiation morbidity scoring scale. Characteristics such as alcohol intake, gastrointestinal (GI) co-morbidities, hemorrhoids, previous abdominal or pelvic surgery (PAPS), diabetes mellitus (DM), the use of antiaggregants, and dosimetric parameters, were analyzed as possible predictive factors of radiation (RT) toxicity.*

Results: *Grade ≥1 acute LGIT toxicity during 3DCRT developed in 41 of 94 patients (43.6%). At univariate logistic regression analysis (UVA) using the baseline model, alcohol consumption (p=0.068), hemorrhoids (p=0.004), GI co-morbidities (p=0.018), PAPS (p=0.033), V60 (p=0.070), V65 (p=0.046) and V70 (P=0.056) were significant predictive factors for any grade of acute LGIT toxicity. Predictive factors of grade ≥1 acute toxicity in the multivariate logistic regression analysis (MVA) were current hemorrhoids (p=0.007), and the GI co-morbidities (p=0.025). Late grade 1 LGIT toxicity occurred in 17 (18.1%) patients. Late grade ≥2 LGIT toxicity as a maximum toxicity score occurred in 9 (9.57%) patients during a median follow-up of 27 months. Following UVA, hemorrhoids (p=0.001) and use of antiaggregants (p=0.034) were significant predictive factors for any grade of late LGIT toxicity. In the MVA, hemorrhoids were significantly associated with late grade ≥1 LGIT toxicity (p=0.005).*

Conclusion: *Hemorrhoids and GI co-morbidities had a significant impact on the occurrence of acute grade ≥1 LGIT toxicity. Hemorrhoids had significant influence on the development of any grade of late LGIT toxicity*

Key words: *acute toxicity, conformal radiotherapy, late toxicity, lower gastrointestinal tract, prostate cancer*

Introduction

One of the standard curative treatments for localized PC is a radical course of RT. RT is a recognized treatment for PC and high-dose 3DCRT is the recommended standard of care for localized tumors [1]. There is definitely a relationship between dose escalation and response to RT with

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RT-induced morbidity to normal surrounding tissues [2,3]. Intensity modulated RT (IMRT) improves the therapeutic outcome, sparing the normal surrounding tissues and reducing acute and late RT-induced toxicity [4-7]. Hypofractionation with higher-than-standard RT doses (2.5-2.75 Gy/fraction/day) is also used in the treatment of localized PC without increasing late toxicity rate [8].

The total RT dose that can be delivered through conventional conformal techniques is still limited by the tolerance of the surrounding normal tissues, mainly the rectum and bladder [9].

However, due to its anatomic proximity to the rectum, radiation injury to the rectum is a common sequel RT to the prostate. Up to 9% of patients report moderate to severe impairment in quality of life [10] and up to 55% report some type of bowel dysfunction [11]. Clinicians need the ability to estimate the risk of LGIT toxicity prior to treatment and determine factors the modification of which can minimize complications [12]. In addition to the dose-volume effect reported in the literature, other factors that may affect the incidence of acute and late LGIT toxicities such as age, hemorrhoids, GI co-morbidities, diabetes mellitus, use of certain drugs, and genetic markers have been mentioned by several authors [13-18].

Published data strongly supports the presence of an association between acute and late LGIT toxicity following RT for PC [19].

Therefore, we conducted a longitudinal study on 94 patients with localized PC in order to assess the incidence of acute and late LGIT toxicity after 3DCRT at a single institution. Furthermore, we sought to explore which factors are involved in the occurrence of acute and late LGIT toxicity and determine possible correlations between them.

Methods

From September 2009 to September 2013, all consecutive PC patients treated with 3DCRT at the Institute for Oncology and Radiology of Serbia were considered for enrollment in the study. Ninety-four patients who met the following inclusion criteria were enrolled: localized disease stage (T1-2), prostate specific antigen (PSA) level ≤ 20, Gleason score (GS) ≤ 7, Karnofsky index (KI) ≥80, and an estimated risk of lymph node involvement ≤15% according to the Roach formula [20]. Exclusion criteria were: disease stage ≥T3, estimated risk of lymph node involvement >15% according to the Roach formula, the presence of enlarged lymph nodes (N1 stage), the presence of distant metastases (M1 stage), PSA level >20, GS ≥8, KI <80, and previous pelvic irradiation. Administration of neoadjuvant hormonal therapy was not an exclusion criterion in the present study.

Radiotherapy

Each patient underwent CT-simulation in supine position, using an immobilization device for the knees and feet. Patients were instructed to have a comfortably full bladder and empty the rectum during simulation and the whole course of treatment.

Two dose-volume groups were defined according to the estimated risk of seminal vesicle (SV) involvement, according to the Roach formula. The first group was the prostate only (P) if the risk was ≤15%, and the second group was the prostate and seminal vesicle group (P+SV) if the risk was ≥15%. Clinical target volume (CTV) and planning target volume (PTV) were used as standardized nomenclature, according to the International Commission on Radiation Units and Measurements recommendations (ICRU) 50 and ICRU 62 [21,22]. CTV included the whole prostate. CTV1 included the whole prostate with entire seminal vesicle. CTV2 encompassed the same volume as CTV. Margins for PTV and PTV1 were 10 mm around the CTV and CTV1, except the posterior margin which was reduced to 8 mm. Margins for PTV2 were reduced to 5 mm, except the posterior margin which was further reduced to 0 mm. Normal tissue volumes contoured included the bladder, rectum, bilateral femora and skin. The normal tissues were considered as solid organs. The prescribed dose to the ICRU reference volume to cover PTV in the P only group was 72Gy. In the second group the prescribed dose to cover PTV1 was 66Gy and to cover PTV2 it was 6Gy.

Patients were treated using 15-MV X-rays with a 2Gy daily fraction/5 days a week. For the bladder and rectum, dose constraints were ≥65 and ≥60Gy, respectively, given to at least one-third of the organ. These values were taken from Emami et al. as the dose likely to result in a normal tissue complication probability of more than 5% after 5 years of follow-up [23].

Dose volume histograms (DVHs) for the treatment plans were analyzed for each patient.

Verification of the patient setup was performed by electronic portal images. The first-day electronic portal images of orthogonal fields (AP and one side of lateral projection) were obtained and, after that, portal images were done weekly.

Acute and late LGIT morbidity was graded according to the European Organization for the Research and Treatment of Cancer (EORTC) scoring scale [24], slightly modified by Peters and coworkers [25], which is presented in Table 1. The maximal acute and late LGIT toxicity grades were recorded for each patient. Side effects occurring within 120 days from the start of RT were considered as acute radiation morbidity. Late toxicity was scored 120 days after the start of treatment.

Follow-up duration was calculated from the date of 3DCRT completion. Patients were seen in routine

Table 1. Acute and late GI complications according to the RTOG morbidity scale (adaptations with regard to the original RTOG scale *in italic*)

Grade	*Acute GI complications according to the RTOG morbidity scale*
G1	Increased frequency or change in quality of bowel habits not requiring medication / rectal discomfort not requiring analgesics
G2	Diarrhea requiring parasympatholityc drugs /mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics
G3	Diarrhea requiring parenteral support ;severe mucous or blood discharge necessitating sanitary pads; abdominal distension (flat plate radiograph demonstrates distended bowel loops)
G4	Obstruction, fistula, or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Grade	*Late* GI complication according to the RTOG morbidity scale*
G1	Mild diarrhea; mild cramping; bowel movements 2-5 per day; slight rectal discharge or bleeding
G2	Moderate diarrhea; intermittent, severe cramping; bowel movements >5 per day; *Moderate* excessive, rectal discharge; intermittent, *frequent* bleeding →*single laser treatment and/or transfusion*
G3	*Watery diarrhea*; obstruction requiring surgery; bleeding requiring surgery *or ≥2 laser treatments and/or transfusions*
G4	Necrosis; perforation; fistula *Abdominal pain or tenesmus requiring tube decompression or bowel diversion*

*****The difference between Grade 1 and Grade 2 GI pain, mucosal loss, or bleeding is most easily made, when Grade 2 is defined as morbidity requiring specific medication: Grade 1= stool softener, diet modification, occasional (≤2/week) non-narcotic drug, occasional antidiarrheal agent (2/week), occasional use of incontinence pads (1-2 days/week); Grade 2 = regular (>2/week) use of (non)-narcotic drugs for pain, regular(>2/week) antidiarrheals, steroid suppositories, 1 laser

follow-up visits every 3-4 months for the first 2 years, and every 6 months during years 2-5. At each follow-up visit physical examination, additional examinations (e.g. imaging, endoscopy), PSA determination and assessment of specific genitourinary and gastrointestinal morbidity were carried out.

Statistics

The primary analysis involved descriptive summary statistics for estimating the distribution of demographic and the clinical characteristics of the study participants. Differences in the occurrence of symptoms of acute and late LGIT toxicity regarding different investigated clinical parameters were assessed using the x^2 test. Spearman's rank correlation coefficient was employed in order to assess the relationships between individual characteristics of PC patients and the development of any grade of acute or late LGIT toxicity. A p value of less than 0.05 was considered statistically significant.

Independent predictors of acute LGIT toxicity in patients with localized prostate cancer, who underwent 72 Gy of conventionally fractionated 3DCRT, were identified using a series of logistic regression models based on heterogeneous factors with potential confounding effects. All potential covariates (including demographic and clinical factors, as well as dosimetric parameters) were first analyzed in an unadjusted UVA model with occurrence of any grade of acute LGIT toxicity as dependent variable. Subsequently, MVA was performed to test whether possible predictors remained significant. The adjusted model included all covariates that appeared to be associated ($p<0.1$) with the endpoint in the preceding analysis.

Cox proportional hazards regression model was used to determine the independent effect of the covariates on the development of late LGIT toxicity. In the calculation of predictors of late toxicity, the time period in the Cox model has been considered as the total period of follow-up (for participants who did not experience late toxicity) or the time until the appearance of late toxicity symptoms. The results of the regression analyses are presented in the form of hazard ratio (HR). All covariates were first analyzed by UVA in a Cox baseline model. Baseline model includes: age, dose-volume group, hormonal therapy, Dmax and V72. Furthermore, all covariates that appeared to be associated ($p<0.05$) with the endpoint in the baseline analysis were further entered in the MVA Cox proportional hazards regression analysis.

Results

Analysis of dosimetric parameters (Table 2) and individual and clinical characteristics of the study cohort and the toxicity scores are presented in Table 3. Median age was 71 years (range 56-81). Occasional or regular alcohol consumption

Table 2. Dosimetric parameters

Parameters	
Mean prostate volume ±SD (cm^3)	58.2±22.5
Mean rectal volume ±SD (cm^3)	93.4±41.8
Mean PTV^ volume ±SD (cm^3)	210.8±62.1
Median Dmean*, Gy (range)	55.5 (IR 8.2) (36.5 – 66.5)
Median Dmax**, Gy (range)	72.0 (IR 0.5) (71.3 – 74.2)
Median V50***, % (range)	71.6 (IR 21.9) (28.7 – 100.0)
Median V60, % (range)	45.0 (IR 23.5) (13.4 – 87.6)
Median V65, % (range)	33.7 (IR 17.9) (9.6 – 70.8)
Median V70, % (range)	13.9 (IR 9.0) (3.0 – 41.5)
Median V72, % (range)	0.046 (IR 1.7) (range 0 – 16.3)

PTV^ volume=P+SV+margin 10mm in all directions except 8mm posteriorly, *Dmean=mean dose to the rectum, **Dmax=maximal dose to the rectum, ***Vxx=the percentage of the rectal volume that received ≥ xxGy, IR=Interquartile range

Table 3. Clinical, tumor and treatment characteristics

Characteristics	
Number of patients	94
Median age (range), years	71 (56-81)
Lifestyle factors	
Alcohol consumption	
None	48 (valid % 59.3)
Occasionally	30 (valid % 37.0)
Regular	3 (valid % 3.70)
Patients with missing information, N (%)	13 (13.8)
Comorbidities, N (%)	
Hemorrhoids	23 (24.5)
Gastrointestinal co-morbidity	7 (7.40)
Prior abdominal or pelvic surgery (PAPS)	32 (34.0)
Dyslipidemia	21 (22.3)
Diabetes mellitus (non-insulin dependent)	13 (13.8)
Medication intake, N (%)	
Use of antiaggregants	41 (43.6)
Tumor characteristics	
Mean PSA±SD, ng /ml	9.884±3.186
Gleason score, N (%)	
≤6	68 (72.3)
7	26 (27.7)
Risk categories, N (%)	
Low risk	53 (56.4)
Intermediate risk	41 (43.6)
TNM stage, N (%)	
I stage (T1N0M0)	50 (53.2)
II stage (T2N0M0)	44 (46.8)
Treatment characteristics	
Hormonal therapy, N (%)	16 (17.0)
Dose volume group (RT)	
Group I (Prostate only)	47 (50.0)
Group II (Prostate+seminal vesicles), N (%)	47 (50.0)

was registered in 33/81 patients. However, data on alcohol intake were missing in 13 patients. GI co-morbidities had 7 (7.4%) patients: diverticulitis 2 patients, perianal fissures 2, polyps of sigmoid colon 1, irritable colon 1 and ulcerative colitis 1 patient. Three of these patients also had chronic gastric ulcers and another 2 gallbladder with chronic inflammation. Previous PAPS included gastric surgery in 3 (3.19%) patients, cholecystectomy in 11 (11.70%), repair of inguinal hernia

in 13 (13.83%), appendectomy in 6 (6.38%), and other abdominal surgery in 6 (6.38%) patients. Thirteen of 94 patients with DM had non-insulin dependent disease.

The median follow-up was 27 months (range 6-54).

Acute toxicity

Forty-one of 94 patients (43.6%) developed ≥1 grade toxicity i.e 25 patients (26.6%) developed grade 1 and 16 (17.0%) grade 2 acute LGIT toxicity during 3DCRT. None of the patients developed grade 3 or 4 acute toxicity symptoms.

No significant difference was seen between the two dose-volume groups for any grade of acute LGIT toxicity (x^2=0.043, p=0.835). Also, no statistically significant correlation between PTV1 volume and frequency of acute toxicity was noticed (ρ=-0.1042, p=0.724).

At UVA using the baseline model, alcohol consumption (p=0.068), hemorrhoids (p=0.004), GI co-morbidities (p=0.018), PAPS (p=0.033), V60 (p=0.070), V65 (p=0.046), and V70 (p=0.056), were significant predictive factors for any grade of acute LGIT toxicity (Table 4). At MVA only hemorrhoids (OR: 0.023, p=0.007) and GI co-morbidities (OR: 26.181, p=0.025) remained statistically significant factors for the prediction of acute LGIT toxicity.

Late toxicity

After a median follow up of 27 months (range 6-54), 17 (18.1%) patients had symptoms of grade 1 late toxicity, 7 (7.4%) had grade 2 and 2 (2.1%) patients had grade 3 as a maximum toxicity score occurring during follow-up.

When comparing both dose-volume groups for late LGIT toxicity, no significant difference was noticed for overall toxicity scores (x^2=0.949, p=0.330). There was no statistically significant correlation between PTV1 volume and frequency of late toxicity (ρ=0.127, p=0.283).

Following logistic regression analysis, hemorrhoids and use of antiaggregants were significant predictive factors (Table 5). Acute LGIT was not a significant predictive factor (p=0.257, OR: 0.52) for late LGIT.

In the MVA, only hemorrhoids (p=0.005, OR: 6.531) were significantly associated with late LGIT toxicity.

Discussion

Prediction of radiation morbidity after external beam radiotherapy (EBRT) is very important and may help in the decision on treatment modality for localized PC. Evaluation of LGIT toxicity after EBRT is very interesting because its incidence is very low after prostatectomy and brachytherapy.

Conformal RT techniques, such as 3DCRT and IMRT, allow for dose escalation to the prostate to >70Gy, while reducing the radiation to normal tissues and the related side effects, primarily to the rectum [26-28].

It is known that RT dosimetric factors, such

Table 4. Logistic regression models of predictors for acute grade ≥1 GI toxicity

Variables	*Unadjusted models*			*Adjusted model*		
	p value	*SE*	*OR*	*p value*	*SE*	*OR*
Alcohol consumption	0.068	0.610	0.329			
Hemorrhoids	0.004	0.947	15.164	0.007	1.396	0.023
GI co-morbidity	0.018	1.182	16.521	0.025	1.459	26.181
PAPS	0.033	0.557	3.279			
V60	0.070	0.029	0.949			
V65	0.046	0.034	0.934			
V70	0.056	0.062	0.888			

SE:standard error, OR:odds ratio, PAPS:previous abdominal or pelvic surgery. V60: the percentage of the rectal volume that received ≥ 60 Gy. V65: the percentage of the rectal volume that received ≥ 65 Gy. V70: the percentage of the rectal volume that received ≥ 70 Gy

Table 5. Cox proportional hazards model analyses for late grade ≥1 GI toxicity

Variables	*Unadjusted models*	*Adjusted model*				
	p value	*SE*	*HR*	*p value*	*SE*	*HR*
Hemorrhoids	0.001	0.644	0.117	0.005	0.661	6.535
Antiaggregants	0.034	0.613	0.273			

SE: standard error, HR: hazard ratio

as total dose, dose per fraction, volume irradiated, irradiation site and dose inhomogeneity, influence the development of late radiation toxicity [23,29]. There is increasing evidence to support the role of dosimetric variables in the development of late rectal toxicity after radical RT to the prostate [30,31].

Other factors may also predispose patients to the development of late toxicity: additional treatment (e.g. systemic treatment, surgery), patient characteristics (age, smoking history, BMI, co-morbid conditions such as DM, hypertension, etc [32]. Variation between individuals in late LGIT toxicity may be in part due to genetic variations [17].

However, there is currently limited conclusive evidence to determine which patient and other treatment related factors influence the development of late RT toxicity.

Vavassory et al. [33] conducted a prospective multicenter study to evaluate the acute LGIT toxicity during PC high dose 3DCRT. Median ICRU dose was 74Gy (range 70-81.6). Out of 1132 enrolled patients 1120 were evaluable for toxicity. Of these patients, 375 (33.39%), 265 (23.69%) and 28 (2.49%) had grade 1, 2 and 3 acute LGIT toxicity, respectively, according to RTOG toxicity criteria. The mean rectal dose was the most predictive parameter (p=0.0004, OR: 1.035) for grade 2 or worse toxicity, and the use of anticoagulant/antiaggregants (p=0.02, OR:0.063) and hormonal therapy (p=0.04, OR:0.65) were protective. According to the moderate/severe injury scores on the self-assessed questionnaire, several clinical and dose-volume parameters were independently predictive for particular symptoms: greater mean rectal dose was associated with a greater risk of bleeding, hemorrhoids were associated with a greater risk of tenesmus and bleeding, DM was highly associated with diarrhea, and use of antihypertensives was a protective factor against diarrhea. Larger irradiated volumes were associated with frequency, tenesmus, and incontinence and bleeding. V60Gy was related to increased stool frequency and V70 to increased severe incontinence [33].

Correlation between clinical variables/dose-volume histogram constrains and LGIT acute toxicity was investigated by multivariate logistic analyses and published by Valdagni et al. [34]. MVA results were used to create nomograms predicting the symptoms of acute LGIT syndrome. Mean rectal dose was a strong predictor of grade 2-3 RTOG/EORTC acute LGIT toxicity (p=0.0004, OR: 1.035), together with hemorrhoids (p=0.02, OR: 1.51), use of anticoagulant/antiaggregants (p=0.02, OR: 0.63) and androgen deprivation (p=0.04, OR: 0.65). DM (p=0.34, OR: 1.28) and pelvic node irradiation (p=0.11, OR: 1.56) were significant variables to adjust toxicity prediction. V60 (p=0.002, OR: 1.02) was related to bleeding and V70 (p=0.033, OR: 1.029) to severe fecal incontinence.

The first evaluation of late LGIT toxicity during the AIROPROS 01-02 study was performed after 506 patients had completed a 24-month questionnaire [35]. PAPS was significantly correlated with frequency, tenesmus and pain (p=0.05, OR: 3.3), fecal incontinence (p=0.02, OR: 4.4), grade 2-3 rectal bleeding (p=0.06, OR: 2.5) and grade 3 rectal bleeding (p= 0.02, OR: 4.2). DM was associated with grade 2-3 rectal bleeding (p=0.2, OR: 2.5), SV irradiation with grade 3 bleeding (p=0.11, OR: 5.5) and anticoagulant/antiaggregants with frequency, tenesmus and pain (p=0.15, OR: 2.1). V70 was correlated with grade ≥2 and grade 3 (they didn't have grade 4 toxicity), bleeding (p=0.03, OR: 1.025 and p=0.13, OR: 1.037), respectively. V40 was associated with fecal incontinence (p=0.035, OR: 1.037). When 718 patients from this study filled their 36-month questionnaire, the authors performed a new analysis [36]. Based on these results nomograms were created for the prediction of late rectal syndrome. New parameters significant for the prediction of late rectal bleeding ≥2 grade were V75 and acute GI ≥2 grade toxicity.

Peeters et al. have shown an association of PAPS with rectal bleeding and proctitis [25].

Neoadjuvant androgen deprivation therapy has been shown to decrease the incidence of acute rectal toxicity due to the resulting decrease in prostate size [25,33].

Several authors have reported increased late rectal bleeding [37] and increased late LGIT and genitourinary morbidity in patients with DM [38]. Kalakota and al. found only a significant association with late genitourinary (GU) toxicity but not with late GI toxicity. In addition, androgen deprivation therapy use, age ≥70 years, and anticoagulation were associated with grade 2 or greater GI toxicity, and grade 3 or greater GI toxicity, according to the same investigation [16].

Barnett et al. found that increasing age at baseline was associated with a greater risk of developing rectal bleeding [39], whereas others have shown no such an association [40].

A recent study found that late rectal toxicity significantly correlated with GI co-morbidities, such as hemorrhoids, diverticulitis and colonic polyps, but no correlation with dose-volume pa-

rameters was found [41].

The length of follow-up time can also influence the observed rates of late rectal toxicity. The majority of late GI side effects (≥2 grade) occurred within 9-60 months after RT, with a peak at 24 months, lasting for less than 36 months in 90% of the patients, and had a prevalence of 1-2% 5 years after RT. The decline in the prevalence rate after 24 months and the stable incidence rate after 60 months clearly demonstrated the recovery from GI side effects [42].

In the present investigation, 25 (26.5%) and 16 (17%) patients had grade 1 and 2 acute LGIT toxicity respectively and no patient developed grade 3 or 4 toxicity. When considering age, hormonal therapy and dose volume group in the baseline model together with Dmax and V72, and UVA for acute grade ≥1 LGIT toxicity showed that hemorrhoids, GI co-morbidities, PAPS, V60, V65, V70 and alcohol consumption were significantly associated with acute LGIT toxicity. MVA for acute grade ≥1 LGIT toxicity has shown that only hemorrhoids and GI co-morbidities remained statistically significant. When late toxicity was analyzed after a median follow-up of 27 months, 17 (18%), 7 (7.4%) and 2 (2.1%) patients developed late grade 1, 2 and 3 LGIT toxicity respectively, according to the late RTOG/EORTC scoring scale. UVA Cox proportional hazards analysis showed that hemorrhoids and use of antiaggregants were associated with the occurrence of grade ≥1 late toxicity. After MVA Cox proportional hazards analysis hemorrhoids remained a statistically significant parameter for the occurrence of late LGIT toxicity.

This study did not show a significant correlation between PAPS and DM and the development of late LGIT symptoms.

Due to the retrospective nature of analysis, we didn't use self-assessment questionnaires and so we couldn't assess the correlation of clinical and dosimetric parameters with the occurrence of each symptom separately.

Our preliminary results showed acceptable acute and late LGIT toxicity. Clinical parameters such as hemorrhoids and gastrointestinal co-morbidities were more significant predictive factors than dosimetry in the prediction LGIT toxicity. Surprisingly, alcohol consumption may have some beneficial influence on the occurrence of acute ≥1grade LGIT toxicity. Alcohol consumption is often not well quantified, particularly in cancers beyond the upper aerodigestive tract, but would, probably, be a subject of further clinical studies.

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Conflict of interests

The authors declare no confict of interests.

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