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Acute toxicity of curative radiotherapy for intermediate- and high-risk localised prostate cancer in the EORTC trial 22991

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ABSTRACT

Introduction: This trial randomly assessed short-term adjuvant hormonal therapy added to radiotherapy (RT) for intermediate- and high-risk (UICC 1997 cT2a or cT1b-c with high PSA or Gleason score) localised prostate cancer. We report acute toxicity (CTCAE v2) assessed weekly during RT in relation to radiation parameters.

Patients and methods: Centres selected the RT dose (70, 74 or 78 Gy) and RT technique. Statistical significance is at 0.05.

Results: Of 791 patients, 652 received 3D-CRT (70 Gy: 195, 74 Gy: 376, 78 Gy: 81) and 139 received IMRT (74 Gy: 28, 78 Gy: 111). During RT, grade 3 gastrointestinal (GI) and genitourinary (GU) toxicities were reported by7 (0.8%) and 50 (6.3%) patients, respectively. No grade 4 was reported. The risk of grade $\geqslant 2$ GI toxicity increased significantly with increasing D50%-rectum ($p = 0.004$) and that of grade $\geqslant 2$ GU toxicity correlated only to Dmax-bladder ($p = 0.051$). 3D-RT technique, increasing total dose and V95% >400 cc increased D50% and Dmax. One month after RT, only 14 patients (1.8%) reported grade 3 toxicity. AST did not seem to influence the risk of GU or GI acute toxicity.

Conclusion: RT up to 78 Gy was well tolerated. Dmax-bladder and D50%-rectum influenced the risk of grade $\geqslant 2$ GU toxicity and GI toxicity, respectively. Both were lower with IMRT but remained high for an irradiated RT volume > 400 cc for 3D-RT and for a dose of 78 Gy. Hormonal treatment did not influence acute toxicity.

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1. Introduction

The EORTC 22991 phase III trial randomised patients with intermediate- and high-risk localised prostate cancer between three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) alone and 3D-CRT/IMRT combined with 6 months of androgen suppression therapy (AST). It completed recruitment in April 2008 and the final results should become available after 2010.

An extensive quality assurance in radiotherapy (QART) programme was implemented in this trial. These procedures were reported previously and consisted in: a 'Facility Questionnaire' (assessing the overall technology level of the participating Radiation Oncology departments[1]); an external reference dosimetry audit of the radiation beams to assess the accuracy of the basic dosimetry; a dummy run (consisting of a contouring and planning exercise to detect systematic errors and protocol ambiguities as early as possible) and an individual case review (in order to evaluate the overall compliance to the protocol with special emphasis on the compliance to the general (ICRU) and trial-specific treatment specifications).[2]

In addition to the above-mentioned QART programme, further details regarding specific RT-QA parameters were collected for each patient, and during the radiotherapy a weekly assessment of acute toxicity was done.

We report the acute radiation-related toxicity and an exploratory assessment of the impact of radiation parameters, especially QART parameters relating to the organs at risk (bladder and rectum), on the risk of acute toxicity, in both RT arm and RT and hormonal treatment arm

2. Patients and methods

Patients eligible for the study were $\leqslant$80 years old with WHO Performance status 0–2 and serum PSA $\leqslant$50 ng/ml (12.5× Upper Limit of Normal) who presented with histologically proven carcinoma of the prostate staged either cT1b-c, N0, M0 (1997 UICC TNM Classification) with PSA $\geqslant$ 10 ng/ml and/or Gleason score $\geqslant$7 or cT2a, N0, M0 independently from PSA level or Gleason score. Pelvic lymph nodes were assessed by CT-scan or laparoscopic surgery. Previous pelvic irradiation or radical prostatectomy and previous hormonal therapy were not allowed. All patients gave written informed consent according to ICH/GCP and national and local regulations. The protocol was reviewed and approved by the Ethics Committee for each institution. The study is registered with ClinicalTrials.gov (number NCT00021450).

3. Radiotherapy protocol

3D-CRT/IMRT were to be delivered in 2 Gy daily fractions, 5 days per week. Each institution selected upfront one total radiation dose (70, 74 or 78 Gy) to treat all its patients and was allowed to increase the dose level once during the course of the trial. Field size reduction was set at 46 Gy and at 70 Gy. All doses were specified at the ICRU reference point. The dose homogeneity for each planned tumour volume (PTV) had to be within 95% and 107% of the prescribed dose.[3] Treatment planning was CT-based. Patient immobilisation could be used depending on the participating centre's policy.

The organs at risk (OAR) were defined as follows: the bladder was defined by the outer wall, delineated on each slice, from the dome to the base; the rectum was defined by the external wall from the recto-sigmoid junction to the anus and the femoral heads had to be delineated from the top of the hip joint to the smaller trochanter. Each centre had to follow its own policy concerning bladder filling. Some centres, asked their patients to keep their bladder full during the CT planning and the treatment to reduce the amount of bladder wall irradiated. Other centres asked the patients to have an 'empty' bladder to improve the reproducibility of the prostate position. Rectal filling was also according to each institution's policy. Compliance to the protocol required fulfilment of the following constraints: (1) rectum: Dmax: 74 Gy (Dmax $\leqslant$ 74 Gy), this constraint remained however optional as some centres treated the prostate up to 78 Gy; not more than 25% of the rectum should receive more than 72 Gy (D25% $\leqslant$72 Gy) and not more than 50% of the rectum should receive more than 60 Gy (D50% $\leqslant$60 Gy). (2) Bladder: Dmax to the bladder: 78 Gy (Dmax $\leqslant$78 Gy); not more than 50% of the bladder should receive more than 60 Gy (D50% $\leqslant$60 Gy) and not more than 20% of the bladder should receive more than 65 Gy (D20% $\leqslant$65 Gy). Further details on the RT protocol were extensively described previously.[2]

3.1. *Quality assurance form (QAF)*

A specific QAF was completed for every patient to collect the following details: (1) regarding the total PTV: the total dose at the ICRU reference point and the volume of the 95% isodose; for all PTVs: the maximal dose (Dmax), the percentage receiving 95% of the prescribed dose (V95%) and the dose delivered to 90% of the volume (D90%); (2) regarding the rectum: the Dmax, the dose delivered to 50%, 25% and 5% of the rectal volume (D50%, D25% and D5% respectively), the percentage of the rectal volume receiving $\geqslant$60 Gy (V60 Gy) and receiving $\geqslant$72 Gy (V72 Gy); (3) for the bladder: the Dmax; D50%; D20%; V65 Gy; V72 Gy and (4) for the femoral heads: the Dmax and the V50 Gy.

3.2. *Acute reactions evaluation form*

Patients were closely monitored and the highest grade of toxicity was scored on a weekly basis using CTCAE version 2.[4] Besides the WHO/ECOG performance status the following CTCAE items were scored: diarrhoea; rectal bleeding; dysuria; urinary frequency/urgency; urinary retention; haematuria; radiation dermatitis; pain due to radiation; fatigue and other toxicities. After the first interim analysis of the toxicity in March 2005, the following items were added: urinary incontinence, erectile impotence, libido, hot flushes, gynaecomastia and proctitis. Every effort was made to retrospectively collect the information regarding these items for all patients.

In order to limit the number of items and to avoid small numbers we grouped under 'all GI toxicities' the reported diarrhoea, rectal bleeding and proctitis. Likewise 'all GU toxicities' groups reported dysuria, frequency, incontinence and urinary retention.

4. Statistical methods

The analysis was conducted in the 'per protocol population' defined as all randomised patients who were eligible, received irradiation to a minimum of 66 Gy and for whom toxicity and quality assurance parameters were available. The impact of the total prescribed dose, the V95% and the technique used (IMRT versus 3D-CRT) on the QART parameters of the OAR was assessed by general linear models.

To study the impact of dosimetric parameters on the frequency of grade $\geqslant 2$ toxicity (considered clinically burdensome), we used logistic regression models and chi-square tests. To allow non-linear effects, the dosimetric parameters were transformed into 5-level ordinal variables, corresponding to the approximate percentiles of their distribution: for V95%, the percentiles were 150 cm^3, 200 cm^3, 300 cm^3 and 400 cm^3. For the rectum the cut-off points for Dmax were 73 Gy, 74 Gy, 75 Gy and 77 Gy; for D50%: 44 Gy, 51 Gy, 58 Gy and 63 Gy, for D25%: 62 Gy, 67 Gy, 69 Gy and 71 Gy; for D5%: 71 Gy, 72 Gy, 73 Gy and 74 Gy, for V60 Gy: 27%, 37%, 46% and 57% and for V72 Gy: 1%, 6%, 12% and 18%. For the bladder, the cut-off points for Dmax were 73 Gy, 74 Gy, 76 Gy and 78 Gy; for D50% 31 Gy, 41 Gy, 56 Gy and 66 Gy; for D20% 57 Gy, 67 Gy, 70 Gy and 73 Gy; for V65 Gy, 15%, 23%, 37% and 52% and for V72 Gy 2%, 6%, 13% and 24%.

Table 1 – Patients' characteristics.

	(N = 791)
Age (years)	
Median (range)	70 (43–80)
WHO performance status	
0	694 (87.7)
1	95 (12.0)
2	2 (0.3)
Clinical T category (UICC TNM 1997)	
T1b	25 (3.2)
T1c	362 (45.8)
T2(a)	404 (51.0)
Gleason score	
2–6	388 (49.0)
7	324 (41.0)
8–10	79 (10.0)

To analyse treatment toxicity in patients with pre-existing symptoms, toxicity grades were considered only if they represented a worsening compared to baseline. Kaplan–Meier estimates of the time to occurrence of toxicity grade >1 were compared by Wald test stratified by the treatment regimen. Statistical significance was claimed at the 0.05 level.

5. Results

Eight hundred and nineteen patients from 37 centres were randomised in the EORTC trial 22991 between September 2001 and April 2008. Of them, 791 (96.6%) were included in the present analysis (Table 1). Three patients who stopped the treatment prematurely were excluded: 2 died suddenly unrelated to cancer or treatment (total dose delivered 40 and 48 Gy) and one stopped after 52 Gy because of septicaemia. Another 25 patients were excluded because radiotherapy was not documented (12 patients), acute toxicity was not documented (2 patients), quality assurance data were missing (10 patients) or the patient had metastatic disease (1 patient).

Table 2 summarises the main pre-existing signs and symptoms in the total population of 791 patients. Around one-third of the treated patients presented mild (grade 1–2) urinary urgency and around 5% presented mild urinary incontinence. Around one percent presented with a pre-existing proctitis.

5.1. *Effect of androgen suppression therapy (AST)) on acute GI and GU toxicities*

To assess the possible impact of AST on the acute toxicity analysis, we first compared the rate of acute GI and GU toxicities between the two randomised treatment arms. There was no statistically significant difference in acute GI toxicity (Logrank test: $p = 0.502$) nor in acute GU toxicity (Logrank test: $p = 0.650$) (Fig. 1). Therefore the treatment groups were pooled in all further analyses.

5.2. *Radiotherapy*

Of the 791 patients, 652 (82.4%) were treated with a 3D-CRT technique, 77 with step-and-shoot IMRT and 62 with dynamic arcing IMRT. Three centres treated upfront their patients with IMRT; ten centres treated their patients with IMRT at the end

Table 2 – Pre-existing urinary and rectal signs and symptoms.

CTCAE version 2.0	RT regimen					Total (N = 791)
	70 Gy (N = 195) N (%)	74 Gy (N = 376) N (%)	78 Gy (N = 81) N (%)	74 Gy IMRT (N = 28) N (%)	78 Gy IMRT (N = 111) N (%)	N (%)
Urinary incontinence						
Grade 1	10 (5.1)	17 (4.5)	1 (1.2)	1 (3.6)	7 (6.3)	36 (4.6)
Grade 2	2 (1.0)	1 (0.3)	1 (1.2)	0 (0.0)	0 (0.0)	4 (0.5)
Urinary frequency/urgency						
Grade 1	71 (36.4)	95 (25.3)	12 (14.8)	8 (28.6)	43 (38.7)	229 (29.0)
Grade 2	8 (4.1)	8 (2.1)	6 (7.4)	2 (7.1)	5 (4.5)	29 (3.7)
Grade 3	1 (0.5)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.9)	3 (0.4)
Proctitis						
Grade 1	3 (1.5)	3 (0.8)	0 (0.0)	0 (0.0)	3 (2.7)	9 (1.1)

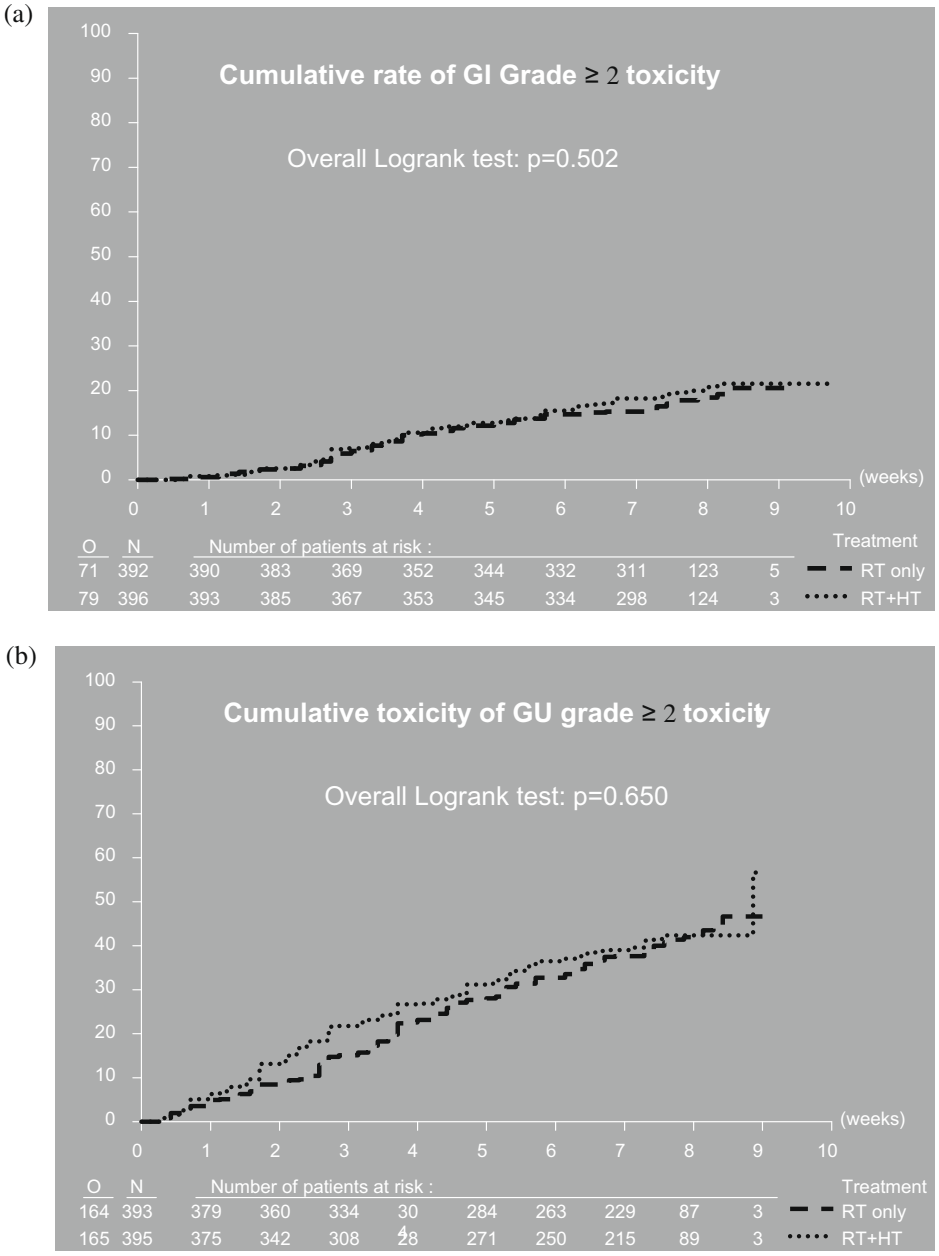

Fig. 1 – Cumulative rate of (a) gastrointestinal toxicity grade ⩾2, and (b) genitourinary toxicity grade ⩾2, by randomisation arm.

of the study. In the 3D-CRT group, 195 patients (29.9%) were treated with a total prescribed dose of 70 Gy; 376 (57.7%) received 74 Gy and 81 (12.4%) received 78 Gy. Of the 37 centres, 6 used the possibility to increase the prescribed total dose once (3 centres from 70 Gy to 74 Gy and 3 centres from 74 Gy to 78 Gy). In the IMRT group, 28 (20.1%) were treated to a total dose of 74 Gy and 111 (79.9%) to a total dose of 78 Gy. Table 3 summarises the RT delivery by RT regimen.

Irradiation was prematurely stopped in 4 (0.5%) patients. Acute toxicity was the indicated reason in two (0.24%) of these four patients who both received 70 Gy instead of 74 Gy and presented Grade 3 urinary frequency. The decision to prematurely interrupt the treatment in the two remaining patients was taken because of dosimetric considerations on organs at risk. The first received 70 Gy when 74 Gy was initially planned as the dose to the femoral head reached 45 Gy. The second was also stopped at 70 Gy (78 Gy initially planned) because of an intestinal loop located in the cavum douglasi.

5.3. *Acute toxicity*

The most severe acute toxicity reported during the treatment is summarised in Table 4. The treatment was overall well tolerated. Only few grade 3 toxicities were reported: 6 patients with diarrhoea (0.7%), one patient with rectal bleeding (0.1%) and one patient with proctitis; 14 patients with dysuria (1.7%), 38

Table 3 – Radiotherapy (RT) parameters.

	70 Gy (N = 195)	74 Gy (N = 376)	78 Gy (N = 81)	74 Gy IMRT (N = 28)	78 Gy IMRT (N = 111)
RT duration (days)					
Median	51	54	56	56	57
Range	45–64	49–108[a]	49–68	50–64	53–64
Total dose administered (Gy)					
Median	70	74	78	74	78
Range	66–72	73.6–76	70–78.2	70–84[b]	78–78
RT prematurely stopped	1 (0.5)	0 (0.0)	1 (1.2)	3 (10.7)	0 (0.0)
Interruption/stop due to toxicity	1 pt	5 pts	0 pts	3 pts	0 pts

a Treatment was interrupted during 51d due to angina pectoris.
b Patient was upstaged to T2c and treated at 84 Gy.

Table 4 – Worst grade of toxicity reported during RT.

CTCAE version 2.0	70 Gy (N = 195)	74 Gy (N = 376)	78 Gy (N = 81)	74 Gy IMRT (N = 28)	78 Gy IMRT (N = 111)
Genitourinary[a] toxicity					
Grade 0	24 (12.3)	32 (8.5)	7 (8.6)	5 (17.9)	3 (2.7)
Grade 1	91 (46.7)	195 (51.9)	37 (45.7)	13 (46.4)	53 (47.7)
Grade 2	65 (33.3)	131 (34.8)	31 (38.3)	7 (25.0)	46 (41.4)
Grade 3	14 (7.2)	18 (4.8)	6 (7.4)	3 (10.7)	9 (8.1)
Gastrointestinal[b] toxicity					
Grade 0	61 (31.3)	114 (30.3)	34 (42.0)	15 (53.6)	44 (39.6)
Grade 1	89 (45.6)	192 (51.1)	39 (48.1)	11 (39.3)	42 (37.8)
Grade 2	45 (23.1)	67 (17.8)	6 (7.4)	2 (7.1)	23 (20.7)
Grade 3	0 (0.0)	3 (0.8)	2 (2.5)	0 (0.0)	2 (1.8)

a Dysuria, urinary frequency, urinary retention, haematuria and incontinence.
b Diarrhoea, rectal bleeding and proctitis.

patients (4.6%) with urinary frequency, 2 patients (0.2%) with urinary incontinence, 11 patients with urinary retention (1.3%), and one patient with haematuria; and 3 patients (0.4%) with dermatitis and one patient with fatigue. No grade 4 toxicity was reported. Fig. 2a and b show the frequency of 'all GI' and 'all GU' grade $\geqslant 2$ toxicities during each treatment week. Fig. 3 shows the worst reported toxicity by RT regimen.

5.4. *Correlation between the worst acute toxicity grade and the dosimetric parameters of OAR*

In order to determine which QART parameters impact the risk of acute toxicity most, we assessed the correlation between the dosimetric parameters of the rectum (of the bladder, respectively) with the reported GI toxicity (GU toxicity, respectively) by logistic regression models and chi-square tests. This analysis revealed a statistically significant correlation between the risk of all GI toxicities and D50%-rectum. The risk of GI toxicity seems lowest whenever the D50% to rectum is below 44 Gy ($p = 0.004$). There was no statistical correlation with Dmax-rectum ($p = 0.81$), D25%-rectum ($p = 0.09$) or D5%-rectum ($p = 0.10$). For GU toxicity, the analysis revealed that Dmax-bladder is the only variable that approaches statistical significance ($p = 0.051$), whereas D50%-bladder, D20%-bladder, V65%-bladder and V72%-bladder do not ($p > 0.5$ for each). Fig 4 depicts the worst GI toxicity grade in relation to the Dmax-rectum and to the D50%-rectum and the worst reported GU toxicity in relation to the Dmax-bladder.

5.5. *Analysis of the duration and the time to occurrence of acute toxicity*

Since acute toxicity was reported weekly, we also analysed the time to occurrence (from start of RT to toxicity grade $\geqslant 2$) and the duration of the acute toxic episodes (number of weeks with toxicity of grade $\geqslant 2$) as these parameters may have a clinically relevant influence on the patient's quality of life. Neither the time of occurrence nor the duration of GI and GU toxicities differed between the two treatment arms (Fig. 1; other data not shown).

5.6. *QART parameters*

We performed a multivariate general linear model analysis (data not shown) in order to evaluate the impact of the treatment volume (V95%), of the technique (3D-CRT versus IMRT) and of the total prescribed dose on several OAR dose constraints that might influence the risk of acute toxicity (Dmax-rectum; D50%-rectum; D25%-rectum; V60 Gy-rectum; Dmax-bladder).

Dmax-rectum was higher with 3D-RT than with IMRT (+8.3 Gy on average, $P < 0.001$), and increased with increasing total delivered dose ($p < 0.001$) and, for 3D-RT, with increasing volume of the 95% isodose ($p < 0.001$). For 3D-RT, Dmax-rectum increased on average by 0.72 Gy for a 1-Gy increase in total dose to the prostate; for IMRT, the average increase in D-max was 1.25 Gy. With 3D-CRT, Dmax-rectum increased

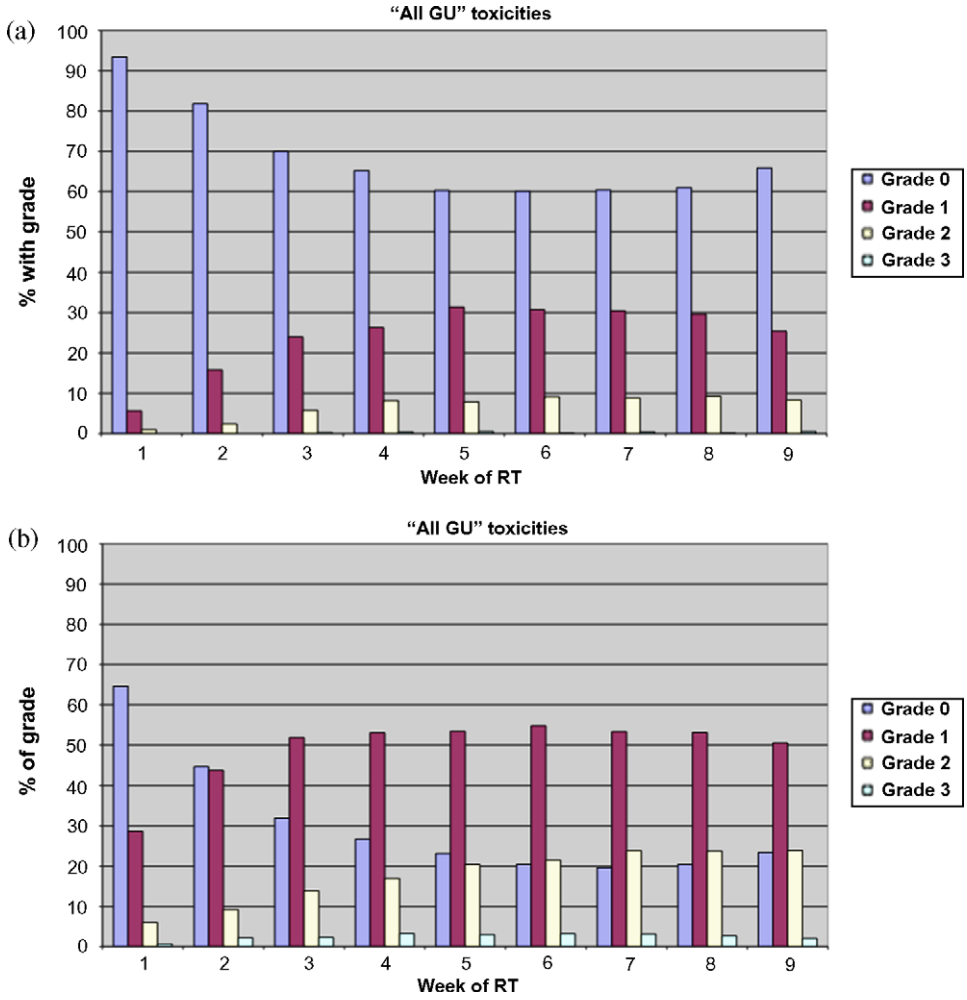

Fig. 2 – Frequency of worst reported (a) gastrointestinal and (b) genitourinary toxicities per treatment week.

significantly whenever the volume covered by the 95% isodose was >300 cm^3 ($p = 0.004$) or >400 cm^3 ($p < 0.001$). D50%-rectum, D25%-rectum and V60 Gy-rectum were not correlated to IMRT or to the total dose. The only significant correlation ($p < 0.0001$) was with the V95%-volume in the patient group treated with 3D-CRT.

Dmax-bladder increased significantly with increasing total dose in both IMRT- and 3D-CRT-treated patients ($P < 0.001$) and with increasing V95% (>400 cm^3, $p = 0.003$ or >300 cm^3, $p = 0.016$) in the 3D-CRT-treated patients but did not differ between techniques ($p = 0.09$). Of note, volumes >300 cm^3 were not reported with IMRT.

The analysis by treatment regimens of the influence of the different QART parameters on the time to occurrence of the first grade $\geqslant 2$ toxicity showed only a statistically significant correlation between the D50%-rectum and the time to a grade $\geqslant 2$ 'all GI toxicity'. The group that presented a significantly earlier onset of grade $\geqslant 2$ toxicity had a D50%-rectum > 63 Gy.

5.7. *Residual grade 3 toxicity at one month after the end of RT*

Overall, only 14 patients (1.8%) had residual grade 3 toxicity one month after RT (5 after RT + AST, 9 after RT alone). The only grade 3 residual GI toxicity was rectal bleeding in 1 patient (RT 74 Gy + AST). As regards to residual GU toxicity, we observed grade 3 dysuria in 6 patients; urinary frequency in 6 patients; haematuria in one patient and urinary retention in 4 patients. Even if the number of these patients is very small, they seem evenly distributed over the different treatment regimens.

6. Discussion

Several randomised dose escalation trials have shown that dose escalation in RT improves the biochemical control in localised prostate cancer.[5–8] Furthermore, new RT techniques, such as IMRT, facilitate an improved dose distribution leading to an increase of the therapeutic index.[9–12] For these reasons, recently there has been renewed interest in RT-related toxicity and in its predictive dosimetric parameters.[11,13–16] The EORTC 22991 trial in intermediate- and high-risk localised prostate cancer offered a unique opportunity to relate different QART parameters to weekly acute toxicity data in a prospective multicentre trial where various treatment techniques and doses were used. It is indeed to our knowledge the only phase III randomised study that evaluated prospectively acute toxicity on a

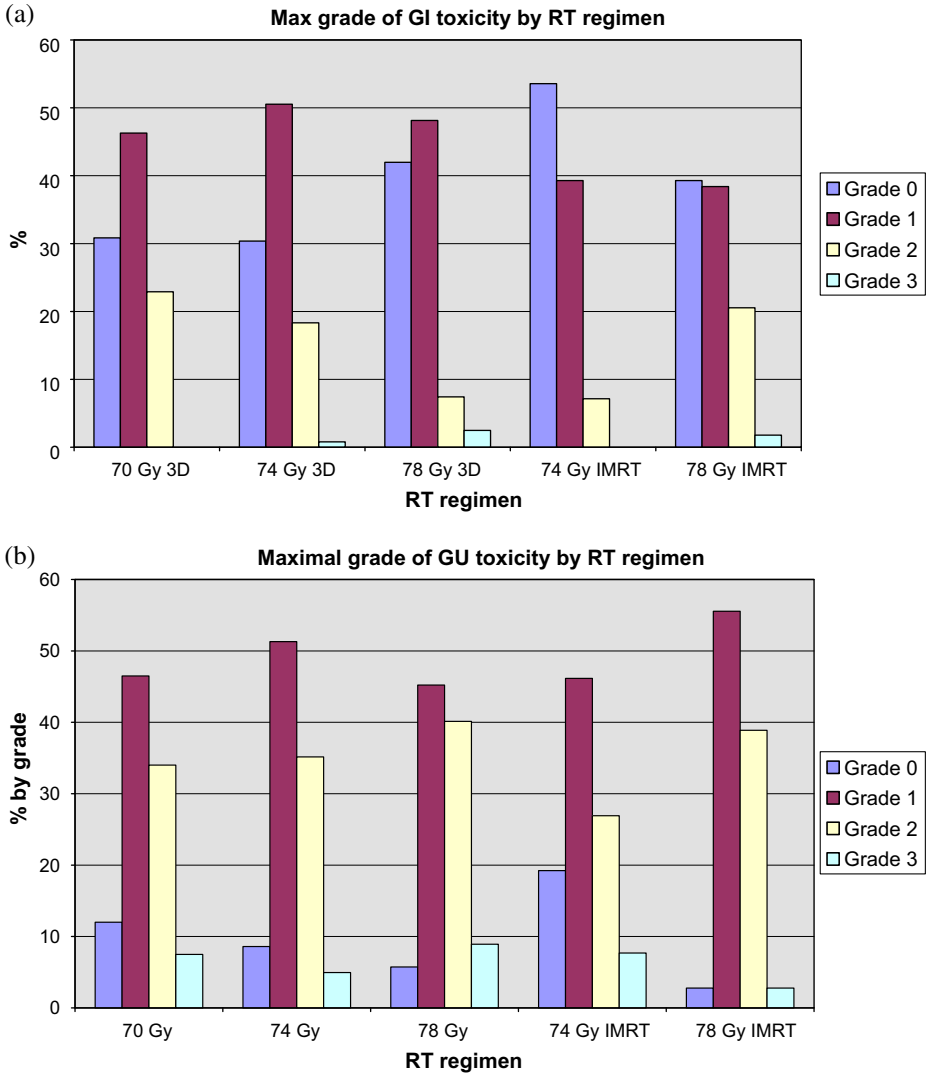

Fig. 3 – Frequency of worst reported (a) gastrointestinal and (b) genitourinary toxicities per RT regimen.

weekly basis. Furthermore the QART programme was elaborate, allowing a detailed analysis of different RT-related parameters regarding the reported acute toxicity.

Different dosimetric parameters and normograms have been described to predict acute and late GI and GU toxicities in prostate radiotherapy.[16–18] In our study we analysed the parameters that were defined in the protocol and had to be reported on the case report forms. We found a statistically significant relationship between the D50% of the rectum and the risk of grade $\geqslant 2$ GI toxicity. The analysis of the urinary toxicity suggested a correlation between the Dmax of the bladder and the risk of grade $\geqslant 2$ GU toxicity.

However, as the study protocol recommended specific dose constraints, as prescribed previously, we could not observe a wide distribution of those parameters.[2] We can therefore not conclude that these factors are not clinically relevant if other dose constraints for OAR are used. We should rather consider D50% rectum and Dmax-bladder as relevant to predict the risk for acute toxicity and therefore we suggest giving more consideration to these parameters in future studies.

The D50% rectum in this study ranged from 20.4 to 70.4 Gy (50% of the patients had D50% rectum between 43.7 and 57.1 Gy). The rate of grade $\geqslant 2$ GI toxicity related to the D50% rectum was: 12.5% if $\leqslant 44$ Gy, 19.6% if 44–58 Gy, 21.3% if 58–63 Gy and 27.5% if >63 Gy. Regarding the onset of the reported toxicity within the same subgroups, there was a significant earlier onset only in the >63 Gy group in comparison with the other groups. It seems therefore reasonable to recommend keeping the D50% rectum below a dose of 44 Gy.

The Dmax-bladder ranged from 54.5 to 83.3 Gy (Q1–Q3: 72.9–76 Gy). The rate of grade $\geqslant 2$ GU toxicity related to Dmax-bladder was: 39.5% if $\leqslant 73$ Gy, 32.3% if 73–74 Gy, 41.7% if 74–76 Gy, 45.1% if 76–78 Gy group and 52.3% if >78 Gy. It seems therefore reasonable to advice keeping the Dmax-bladder under 74 Gy.

Overall, acute toxicity remained low with approximately 1% of grade 3 GI toxicity and 6.2% of grade 3 GU toxicity, without any grade 4 toxicity. Grade $\geqslant 2$ GU toxicity varied between 40% for the 70 Gy group and 35% to 49% in the different dose-escalated groups. Grade $\geqslant 2$ GI toxicity varied between 7% and 23% between the different groups (same percentage (23%)

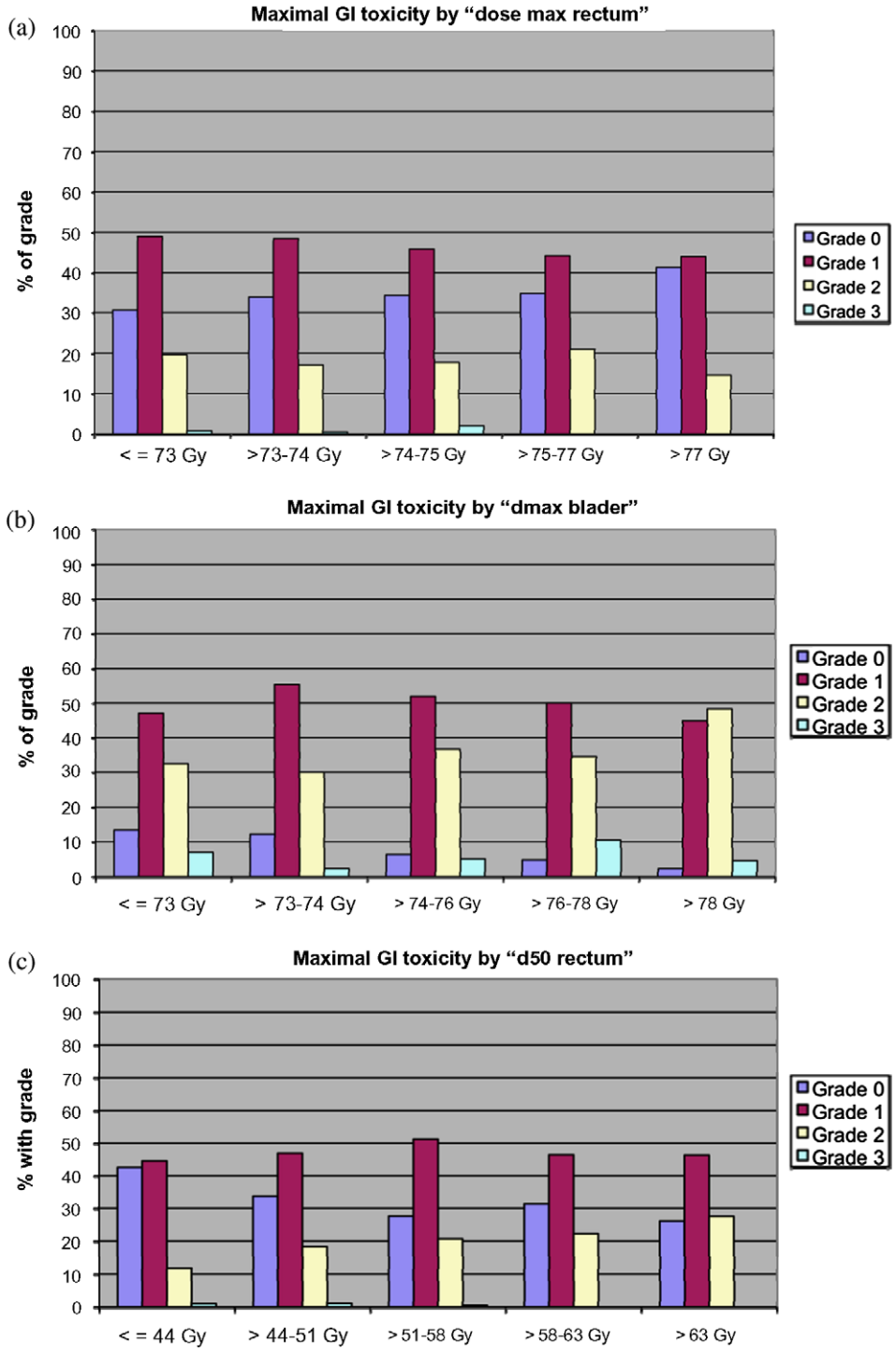

Fig. 4 – Maximal toxicity by different QART parameters. (a) Gastrointestinal toxicity by maximum dose to rectum (b) maximal genitourinary toxicity by Dmax to Bladder and (c) maximum gastrointestinal toxicity by D50% rectum.

between 3-D CRT with 70 Gy and IMRT with 78 Gy group). Other groups reported acute toxicity in dose escalation trials for prostate cancer: the NKI trial reported 669 patients and compared 68 and 78 Gy with grade $\geqslant 2$ GU and GI toxicities of, respectively, 53% and 55% in the standard treatment arm and 47% and 51% in the escalated group.[19] The GETUG trial[20] compared 70 and 80 Gy and showed grade $\geqslant 2$ GU and GI toxicities of, respectively, 45% and 56% in the standard treatment arm and of 46% and 57% in the escalated group. The MRC RT01 study[21] compared 64 Gy and 74 Gy and showed Grade $\geqslant 2$ GU and GI toxicities of, respectively, 38% and 30% in the standard treatment arm and of 39% and 33% in the escalated group.

Our early toxicity data remain below most reported acute toxicity reports in dose escalation studies for prostate cancer. This might be explained by the extensive QA programme that

we coupled to this prospective clinical trial. We could also demonstrate, in this multicentre setting, that the use of IMRT enables the delivery of higher RT doses to the treatment volume without compromising dose constraints to OAR. Therefore, it seems feasible to pursue studies in prostate cancer using escalated doses. However the results of this toxicity analysis have to be considered within its correct frame, being directed to acute toxicity only. Even if some authors state that late rectal toxicity is closely related to acute toxicity and that acute GU toxicity predicts the risk for late GU toxicity, a further detailed analysis of late toxicity will have to be performed to confirm these findings.[18,22]

Conflict of interest statement

None declared.

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