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Acute toxicity of robotic ultrahypofractionated radiotherapy CyberKnife™ in prostate cancer patients

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Our purpose was *t*o evaluate the toxicity of CyberKnife™ based fractionated stereotactic radiotherapy (FSRT) in prostate cancer patients. One-hunred-thirty-two men with low (62) and intermediate (70) prostate cancer were enrolled in our prospective study. Mean age was 69. Total dose of 36,25 Gy in 5 fractions was prescribed. Image guided FSRT was performed on CyberKnife. Minimum follow-up ranged from 3 to 28 months. EORTC/RTOG scale was used to evaluate toxicity. A total of 47%, 10% and 2% of patients presented grade 1, 2 and 3 acute genitourinary toxicity, respectively. In 25% and 3% of patients, respectively, grade 1 and 2 acute gastrointestinal toxicity was observed. No significant association between acute grade ≥ 2 toxicity and clinical factors: age, androgen deprivation therapy or infections were found. Neither CTV nor PTV volumes had significant impact on acute grade ≥ 2 toxicity. Late toxicity was assessed in 104 patients. In 16% and 1% of patients late GU toxicity in grade 1 and 2, respectively, was presented. Late GI toxicity grade 1, 2 and 3 occurred in 8%, 3% and 1% of patients, respectively. The acute toxicity rates of fractionated stereotactic radiotherapy are low. Early data suggest also low late toxicity rates.

Key words: CyberKnife, prostate cancer, toxicity, radiotherapy

Conventional external-beam radiotherapy (EBRT) in prostate cancer patients has became safe and widespread in last two decades. Moreover its efficacy has been proven in several studies [1, 2, 3]. There are publications suggesting low alpha/beta ratios (i.e. 1 – 3 Gy) for prostate cancer, which makes a promising background for hypofractionation [4, 5, 6, 7]. Higher than conventional doses per fraction are used in many centers [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]. Although high doses per fraction can be delivered on classical accelerators, there are even more precise techniques of irradiation [21, 22, 23]. One of these is stereotactic robotic radiotherapy – CyberKnife™ [24,25,26]. High precision of this device allows to provide very conformal dose coverage of the target. This means high dose in the tumor volume and low in the organs-at-risk (OARs). Advantages of CyberKnife allowed to create hypofractionated schedules with doses per fraction exceeding 7 Gy and two-week treatment time. Encouraging results were presented in several studies reporting favorable patients outcomes and good tolerance rates [27, 28, 29, 30, 31, 32, 33]. Hypofractionation schedules used in prostate cancer radiotherapy are summarized in Table 1.

We designed prospective study to evaluate the toxicity and efficacy of hypofractionated stereotactic radiotherapy with CyberKnife™.

Patients and methods

One-hundred thirty-two men with low and intermediate risk prostate cancer were treated with stereotactic hypofractionated radiotherapy using CyberKnife between 2011 and 2013. These were initial, consecutive patients in our institution, when we adopted the Stanford protocol into clinical practice [30]. That approach was an alternative to conventional radiotherapy. Patient chose treatment schedule after discussion with physician. Written consent was required.

The National Comprehensive Cancer Network (NCCN) prostate cancer risk classification was used. Treatment schedule

Abbreviations: FSRT – Fractionated Stereotactic Radiotherapy; CTV – Clinical Target Volume; PTV – Planning Target Volume; NCCN – National Comprehensive Cancer Network; EORTC – European Organisation for Research and Treatment of Cancer; RTOG – Radiation Therapy Oncology Group; WHO – World Health Organization; ICRU – International Commission on Radiation Units and Measurements; ADT – Androgen Deprivation Therapy; CTCAE – Common Terminology Criteria for Adverse Events

provided five fractions of 7.25 Gy every other day to the total dose of 36.25 Gy in ten days. The clinical characteristic of the group is presented in Table 2.

Eligibility criteria. Only patients with performance status WHO 0-1 were enrolled into the study. They had to have biopsy proven localized prostate cancer. Bone and nodal metastases exclusion was based on imaging (i.e. bone scan, CT and/or MRI). No previous pelvic irradiation, no prostatectomy or transurethral electroresection were allowed. Every patient had to undergo golden markers implantation. Ulcerative colitis or Crohn's disease were not contraindicated directly, however these patients needed additional individual risk evaluation. Low risk group was defined as T1-T2a, PSA < 10 ng/ml, Gleason score < 7. Intermediate risk group was defined as T2b-T2c, PSA 10-20 ng/ml, Gleason = 7 (3+4 only), pelvis nodes dissemination risk < 20% (Roach`s formula).

Treatment planning. Three golden markers (Gold Anchor™) were implanted into the prostate gland under TRUS guidance. Ten days later computed tomography and magnetic resonance with fusion were done. Patients were immobilized with vacuum mattress.

Treatment volumes were delineated under International Commission on Radiation Units and Measurements (ICRU) 50 and 62 protocols. Clinical target volume (CTV) included prostate gland and base of seminal vesicles. Planning target volume (PTV) included CTV with 3 mm rectal margin and 5 mm margins in other directions. Neither less than 95% nor more than 120% of total dose was accepted in the PTV. The dose was normalized/prescribed on 84% or higher isodose encompassing the PTV contour. It means the maximum dose in prostate was not higher than 120% of the prescribed dose. The minimum requirement for coverage index was 95%. Organs at risk (OARs) were urethra, rectum, bladder and femoral heads. Constraints for PTV and OAR`s are presented

Table 1. Hypofractionated dose schedules in prostate cancer radiotherapy

Study	Dose per fraction (Gy)	No of fractions	Total dose (Gy)
Arcangeli [8]	3.1	20	62
Kupelian [9]	2.5	28	70
Livsey [10]	3.13	16	50
Lloyd-Davis [11]	6	6	36
Lloyd-Davis [11]	4.6	12	55
Lukka [12]	2.6	20	52.5
Pollack [13]	2.7	26	70.2
Rene [14]	3	22	66
Soete [15]	5	9	45
Yeoh [16]	2.75	20	55
Boike [17]*	9	5	45
Boike [17]*	9.5	5	47.5
Boike [17]*	10	5	50
Jabbari [18]*	9.5	4	38
Madsen [19]*	6.7	5	33.5
Tang [20]*	7	5	35
McBride [26] †	7.25	5	36.25
Aluwini [27] †	9.5	4	38
Friedland [28] †	7	5	35
Freeman [29] †	7.25	5	36.25
King [30] †	7.25	5	36.25
Townsend [31] †	7.25	5	36.25
Bolzicco [32] †	7	5	35
Katz [33] †	7	5	35
Katz [33] †	7.25	5	36.25

*SBRT; †CyberKnife

Table 2. Clinical characteristics of the analyzed group

	Number (%)
Age	69*
53-83	
≤ 60	18 (14)
61-70	59 (45)
71-80	52 (39)
>80	3 (2)
T stage	
T1c	59 (45)
T2a	16 (12)
T2b	40 (30)
T2c	17 (13)
Gleason Score	
<7	127 (96)
7	5 (4)
Pretreatment maximal PSA (ng/dl)	
<10	106 (80)
10-20	24 (18)
No data	2 (2)
Risk groups NCCN	
Low	62 (47)
Intermediate	70 (53)
Neoadiuvant ADT	
Yes	74 (56)
No	58 (44)
Comorbidity†	
Diabetes	17 (13)
Hypertention/ Cardiovascular diseases	76 (57)
Asthma/ Respiratory system diseases	7 (5)
Bladder cancer	1 (1)
Hematological diseases	2 (1)
No diseases reported	52 (39)
Pretreatment symptoms†	
No symptoms	27 (20)
Polyuria	46 (35)
Nocturia	74 (56)
Dysuria/pain	49 (37)
Diarrhoea	1 (1)
Rectal bleeding	1 (1)

*mean

† Some of the patients had more than one comorbidity or more than one symptom.

The total number of symptoms is higher than total number of patients.

in Table 3. The verification of patients' position was based on two kVs dedicated to CyberKnife, which were repeated during the treatment session. This allowed to evaluate displacements in all of the axes including rotation. Fiducial based tracking was performed in all patients.

Statistics. The maximum toxicity was scored. The detailed analysis of the influence of selected factors on acute toxicity was also performed. The $\chi 2$ test was used with Yates` and Fisher`s correction if necessary. The continuous variables were analyzed with logistic regression. Results were statistically significant if p-value was below 0.05.

Follow up. Patients were evaluated during and on the last day of the treatment, one month after and then every three months. PSA level, blood count and urinalysis were monitored and compared to those prior to the treatment. Acute and late toxicities were assessed due to European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) scale.

Results

Median follow-up was 8.5 months (3-28). Most of patients had mild (47%) or no (41%) acute genitourinary (GU) toxicity. Grade 2 acute GU toxicity was reported by 10% of men. Only three patients (2%) had grade 3 acute GU toxicity, and no grade 4 GU toxicity was observed. Grade 1 gastrointestinal (GI) acute toxicities were reported in 25% of patients. Four patients (3%) required drugs, due to diarrhea – grade 2 GI toxicity. No grade 3 or 4 GI toxicities were observed. (Table 4.).

One hundred and four (79%) patients were followed-up over 4 months after radiotherapy (median 9 months, 4.5-28 months), which allowed to asses late toxicity rates. Late GU toxicity grade 1 was observed in 16% of them. One patient (<1%) had grade 2 late GU toxicity (persistent moderate polyuria). Less than 12% of such patients had late GI side-effects. Eight of them had grade 1 late GI toxicity.

Table 3. Dose-volume constraints for PTV and OARs.

Organ	Dose/Volume
Maximum plan dose	43.5 Gy
PTV	34.4 – 43.5 Gy
Rectum	V_{18} – 50 % V_{29} – 20 % $V_{32.6}$ – 10 % $V_{36.25}$ – 5 %
Bladder	V_{18} – 55 % V_{29} – 25 % $V_{32.6}$ – 15 % $V_{36.25}$ – 10%
Femoral heads	V_{25} – 45 %
Urethra	Maximal dose 43.5 Gy

Table 4. The incidence of acute GU and GI toxicity.

Toxicity	GU	GI
Grade 0	54 (41%)	95 (72%)
Grade 1	61 (47%)	33 (25%)
Grade 2	14 (10%)	4 (3%)
Grade 3	3 (2%)	0
Grade 4	0	0

Table 5. The incidence of late GU and GI toxicity (preliminary data).

Toxicity	GU	GI
Grade 0	86 (83%)	92 (88%)
Grade 1	17 (16%)	8 (8%)
Grade 2	1 (<1%)	3 (3%)
Grade 3	0	1 (<1%)
Grade 4	0	0

Table 6. The influence of selected factors on the incidence of Grade ≥2 acute GU toxicity.

		Grade <2	Grade ≥2	p – value
Diabetes				
No	115	103(90%)	12 (10%)	**0.04**
Yes	17	12 (71%)	5 (29%)	
Neoadiuvant HT				
No	58	49 (85%)	9 (15%)	0.27
Yes	74	66 (89%)	8 (11%)	
Pre-treatment urinary infection †				
No	88	78 (89%)	10 (11%)	0.31
Yes	14	12 (86%)	2 (14%)	
Age				
<=60	18	16 (89%)	2 (11%)	0.77
61-70	59	52 (88%)	7 (12%)	
71-80	52	44 (85%)	8 (15%)	
>80	3	3 (100%)	0 (0%)	
CTV*				
<50 cm^3	56	50 (89%)	6 (11%)	0.44
50-100 cm^3	65	55 (85%)	10 (15%)	
>100 cm^3	11	10 (91%)	1 (9%)	
PTV†				
<100 cm^3	63	56 (89%)	7 (11%)	0.46
100-150 cm^3	56	48 (86%)	8 (14%)	
>150 cm^3	13	11 (85%)	2 (15%)	

*range: 17-125 cm^3 (median:54) †range: 39-223 cm^3 (median:103)
† We failed to collect the urinalysis in 22,7% of the patients.

Three patients suffered from grade 2 GI side-effects (severe diarhoea, rectal bleeding, chronic proctitis nonresponding to anti-inflammatory drugs). One patient had grade 3 late GI toxicity (rectal bleeding requiring laser coagulation of teleangectasies) (Table 5.).

The late effects were evaluated using the EORTC/RTOG scale with slight modification of Grade 1 GU toxicity – i.e., small increase in urinary symptoms no more than twice that of pre-tretment was scored as grade 1 toxicity.

Age, neoadiuvant androgen deprivation therapy (ADT) or infections prior to FSRT did not affect acute grade ≥ 2 GU and GI toxicity (Table 6 and 7). Neither CTV nor PTV had significant impact on acute toxicity grade 2 or above. Only patients with diabetes had significantly higher rates of acute grade ≥ 2 GU toxicity. Diabetes had no influence on acute GI toxicity in the analyzed group.

Although, larger PTV significantly influenced any GU toxicity (grade ≥ 1 versus grade 0; p-0.04), it didn't have any significant impact on grade ≥ 2 GU toxicity (Table 8).

Every patient had a decrease in PSA concentration after treatment. Median PSA level below 1 ng/ml was achieved after 1 – 2 months from radiotherapy in ADT group. No ADT patients achieved median PSA level below 2 ng/ml after 4 – 5 months and 1 ng/ml after 14-17 months from FSRT, respectively (Table 9. and Figure 1).

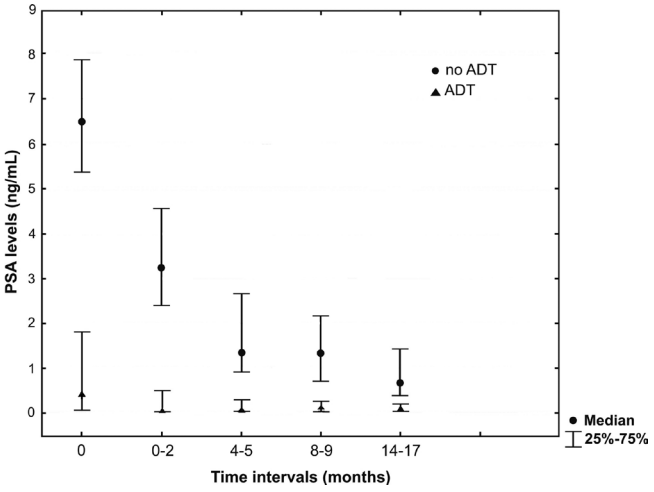

Figure 1. PSA levels as a function of time in ADT and no ADT groups.

Discussion

The outcome of external beam radiotherapy (EBRT) is comparable to radical prostatectomy [1]. It may be regarded as main non-invasive method of treatment in prostate cancer. In conventional EBRT a high total dose above 72 Gy should be used [34]. Total dose should probably exceed 78 – 80 Gy [35]. High total dose in 2 Gy per fraction is safe and efficient, which was published many times over past years. On the other hand, high dose brachytherapy in prostate cancer uses hypofractionation with equal outcomes [36,37,38,39,40]. The

Table 7. The influence of selected factors on the incidence of Grade ≥2 acute GI toxicity.

		Grade <2	Grade ≥2	p – value
Diabetes				
No	115	111 (97%)	4 (3%)	0.98
Yes	17	17 (100%)	0 (0%)	
Neoadiuvant HT				
No	58	56 (97%)	2 (3%)	0.64
Yes	74	72 (97%)	2 (3%)	
Age				
<=60	18	18 (100%)	0 (0%)	0.34
61-70	59	55 (94%)	4 (6%)	
71-80	52	52 (100%)	0 (0%)	
>80	3	3 (100%)	0 (0%)	
CTV*				
<50 cm^3	56	54 (96%)	2 (4%)	0.75
50-100 cm^3	65	63 (97%)	2 (3%)	
>100 cm^3	11	11 (100%)	0 (0%)	
PTV†				
<100 cm^3	63	61 (97%)	2 (3%)	0.79
100-150 cm^3	56	54 (96%)	2 (4%)	
>150 cm^3	13	13 (100%)	0 (0%)	

*range: 17-125 cm^3 (median:54) †range: 39-223 cm^3 (median:103)

Table 8. The influence of CTV and PTV on the incidence of Grade 0, Grade 1 and Grade ≥ 2 acute GU toxicity.

CTV* Grade 0 vs. Grade ≥ 1 p-value				
<50 cm^3	56	28 (50%)	28 (50%)	n/s
50-100 cm^3	65	21 (33%)	44 (67%)	
>100 cm^3	11	4 (37%)	7 (63%)	
PTV†				
<100 cm^3	63	32 (51%)	31 (49%)	0.04
100-150 cm^3	56	18 (32%)	38 (68%)	
>150 cm^3	13	3 (23%)	10 (77%)	
CTV* Grade ≤1 vs. Grade ≥ 2				
<50 cm^3	56	50 (89%)	6 (11%)	n/s
50-100 cm^3	65	55 (85%)	10 (15%)	
>100 cm^3	11	10 (91%)	1 (9%)	
PTV†				
<100 cm^3	63	56 (89%)	7 (11%)	n/s
100-150 cm^3	56	48 (86%)	8 (14%)	
>150 cm^3	13	11 (85%)	2 (15%)	

*range: 17-125 cm^3 (median:54) †range: 39-223 cm^3 (median:103)

Table 9. Levels of PSA at sequence controls according to ADT.

Interval (months)	no ADT group			ADT group		
	PSA level(ng/dl)			PSA level(ng/dl)		
	range	mean	median	range	mean	median
Treatment start	1.6–15.2	6.7	6.5	0-13.5	1.6	0.4
1–2	0.1–9.5	3.6	3.2	0-6.9	0.7	0.06
4–5	0.1–5.2	1.8	1.3	0-3.9	0.4	0.04
8–9	0.1–6.4	1.7	1.3	0-1.7	0.2	0.05
14–17	0.1–6.7	1.3	0.7	0-0.8	0.15	0.09

low alpha/beta ratio in prostate cancer cells makes rationale for hypofractionation. CyberKnife is a useful as a noninvasive and very precise device. It allows to deliver safely very high dose per fraction (i.e. ultra – hypofractionation). High fractional doses lead to higher biological effects for cancers with low alpha/beta ratio due to decreasing a probability of sublethal damage repair in cancer cells [4]. On the other hand it seems to be dangerous for normal tissues with low alpha/beta ratio. Differences in alpha/beta ratios between tumor and OARs (i.e. very low alpha/beta for prostate cancer, higher alpha/beta for late toxicity) result in lower biological doses in normal tissues with biological dose escalation in a tumor (Table 10).

There are encouraging studies on prostate cancer treatment with stereotactic hypofractionated radiotherapy over past few years. Katz et al. reported the largest group of 304 men irradiated to the total dose of 35-36,25 Gy in 5 fractions [33]. Median follow-up was 30 months. Only 4% of patients suffered from grade 2 acute GI or GU toxicities. No grade 3 acute toxicity was observed. Freeman et al. treated 41 patients with the same schedule [29]. They reported 5-year biochemical control of 93%. No GI grade 3 or more late toxicities were observed. One patient had grade 3 late GU side-effects. Acute toxicity was not reported. King et al. reported 100% biochemical control with low acute and late toxicity [30]. Detailed acute toxicity data was not reported, either. The same author published an update, recently [41]. In that study 3% of patients had grade 3 late GU toxicity. No grade 3 or 4 late GI toxicity was observed, and 4-year biochemical control was 94%.

Different schedule study was also reported. Bolzicco et al. treated patients to total dose of 35 Gy in five fractions [32]. Median follow-up was 20 months. Maximal acute toxicities were grade 2, with 11% of patients suffering from grade 2 GU toxicity and 24,5 % from grade 2 GI toxicity, respectively. Townsend study showed more enhanced toxicity with rather large group of patients (8%) experiencing grade 3 acute GU toxicities, however that group was small [31]. Fortunately, the symptoms resolved shortly after radiotherapy within 3 months without enhanced persistent toxicity.

Low rates of acute and late side-effects reported Madsen et al. [19]. Acute grade 3 toxicities had 1% of patients. No grade 3 late toxicities were observed. However biochemical control was only 90% with median follow-up of 3.5 years.

On the contrary, Chen at al. reported higher grade 2 acute GU toxicity [42]. In their series, 35 % of patients suffered from adverse events, but no grade 3 toxicities were notified. Probably this was due to different scale (i.e. Common Terminology Criteria for Adverse Events – CTCAE) used to rate the acute toxicity. Mean prescription volume of PTV of 135 cm^3 and urethra dose constrain 13% higher than ours (i.e. 133%) could have influence on GU toxicity.

Our results are comparable to the majority of studies published in past years (Table 11) [19, 26, 29, 30, 31, 32, 33, 41, 42, 43, 44]. Grade 3 acute toxicity was negligible (2%) and the rate of grade 2 toxicity was very low (10% for GU, 3 % for GI).

There were no significant factors associated with grade ≥ 2 acute toxicity in the analyzed group. Although CTV and PTV did not influence the incidence of adverse events, there are some studies on conventional radiotherapy reporting CTV impact on toxicity [45, 46]. It may be influenced by small number of patients with side effects in our group. Another explanation could be very high precision of CyberKnife. Fiducial tracking made the accurate treatment reproducibility possible and the risk of geographical error was minimal even for larger treated volumes. It also may be the result of dose constrains for bladder and rectum which were equal for all patients. Strict dose constraints in each patient independent from CTV/PTV might lead to lack of correlation between treated volumes and acute toxicities.

Low overall toxicity irrespective of patients' age makes CyberKnife a good option for treatment in elderly ones. Unlike eight week of conventional radiotherapy, patients finished FSRT after 10 days.

Acute toxicity is also important. It may influence the risk of late toxicity, as reported in some series on conventional

Table 10. Normalized Total Dose (NTD) and Biologically Effective Dose (BED) values for prostate cancer and normal tissues (conventional and hypofractionated RT).

	Prostate cancer*	Late toxicity†	Acute toxicity‡
NTD $_{7.25\ Gy}$	90.6 Gy	74.3 Gy	52 Gy
NTD $_{2\ Gy}$	76 Gy	76 Gy	76 Gy
BED $_{7.25\ Gy}$	211.5 Gy	123.8 Gy	62.5 Gy
BED $_{2\ Gy}$	177.3 Gy	126.7 Gy	91.2 Gy

**alfa/beta* = 1.5 Gy; †*alfa/beta* = 3 Gy; ‡ *alfa/beta* = 10 Gy

treatment. [47, 48] Uncontrolled acute toxicity may provide to breaks or termination of treatment. State-of-art radiotherapy schedules should yield not only high efficiency, but also appropriate acute and late tolerance. This is very important, especially when implementing new schedules and technologies in radiotherapy.

Neither phase III randomized trials results with conventional arm nor long term follow-up studies on side-effects, biochemical control and outcome are available. This makes impossible to conclude at present time which approach is superior. Several randomized trials compared hypofractionated radiotherapy to conventional EBRT, but doses per fraction were lower than these used in stereotactic irradiation [8, 49, 50]. However recent studies showed that ultra – hypofractionated stereotactic radiotherapy with CyberKnife has acceptable toxicity rates. It is also at least comparable or even lower than conventional EBRT.

Table 11. Acute and late toxicity and bRFS (biochemical relapse free survival) for fractionated stereotactic radiotherapy in prostate cancer patients.

Study	n	Median follow -up [months]	Fractional dose [Gy]	Total dose [Gy]	Results [bRFS]	Acute toxicity		Late toxicity	
						GU	GI	GU	GI
McBride [26]	43	44	7.5 7.25	37.5 36.25	97.7	GI – 59%* GII – 19%* GIII – 4%* GIV – 0%*	GI – 31%* GII – 7%* GIII – 0%* GIV – 0%*	GI – 17%* GII – 17%* GIII – 1pt* GIV – 0%*	GI – 7%* GII – 7%* GIII – 5%* GIV – 0%*
Freeman [29]	41	60	7-7.25	35-36.25	93%	n/a	n/a	GI – 25% GII – 7% GIII – 2.5% GIV – 0%	GI – 13% GII – 2.5% GIII – 0% GIV – 0%
King [30]	41	33	7.25	36.25	100%	n/a	n/a	GI – 41% GII – 24% GIII – 5% GIV – 0%	GI – 33% GII -15% GIII – 0% GIV – 0%
Townsend [31]	37	n/a	7-7.25	35-36.25	n/a	GI – 57%† GII – 5%† GIII – 8%†	GI – 13.5%† GII – 0%† GIII – 0%†	n/a	n/a
Bolzicco [32]	45	20	7	35	100%	GI – 35.5% GII – 11% GIII – 0% GIV – 0%	GI – 24.4% GII – 24.5% GIII – 0% GIV – 0%	GI – 8.8% GII – 0% GIII – 2.2% GIV – 0%	GI – 0% GII – 2.2% GIII – 0% GIV – 0%
Katz [33]	254	17	7.25	36.25	L- 99%‡ I-100%‡ H -83%‡	GII – 4.7% GIII – 0% GIV – 0%	GII – 3.6% GIII – 0% GIV – 0%	GII – 5.8% GIII – 1 pt GIV – 0%	GII – 2.9% GIII – 0% GIV – 0%
Katz [33]	50	30	7	35	100%	GII – 4% GIII – 0% GIV – 0%	GII – 4% GIII – 0% GIV – 0%	GII – 1 pt GIII – 0% GIV – 0%	GII – 0% GIII – 0% GIV – 0%
King [41]	57	32	7.25	36.25	94%	n/a	n/a	GI – 23 % GII – 5% GIII – 3% GIV – 0%	GI – 14% GII – 2% GIII – 0% GIV – 0%
Chen [42]	100	28	7-7.25	35-36.25	99%	GI – 36%† GII – 35%† GIII – 0%†	GI – 35%† GII – 5%† GIII – 0%†	GI – 26%† GII – 17%† GIII –1%†	GI – 11%† GII – 1%† GIII – 0%†
Oliai [43]	70	27/37	7.5 7.25 7	37.5 36.25 35	L-100%‡ I- 95%‡ H – 77%‡	GI – 56% GII – 19% GIII – 4% GIV – 0%	GI – 17% GII – 4% GIII – 0% GIV – 0%	GI – 44% GII – 29% GIII – 3% GIV – 0%	GI – 10% GII – 9% GIII – 0% GIV – 0%
Bolzicco [44]	100	36	7	35	96%	GII – 12% GIII – 0%	GII – 18% GIII – 0%	GI – 4% GII – 3% GIII – 1% GIV – 0%	GI – 2% GII – 1% GIII – 0% GIV – 0%
Analyzed group	132	9	7.25	36.25	99%	GI – 47% GII – 10% GIII – 2% GIV – 0%	GI – 25% GII – 3% GIII – 0% GIV – 0%	GI – 16%§ GII – <1%§ GIII – 0 %§	GI – 8%§ GII – 3%§ GIII – <1%§

*CTCAEv4; †CTCAEv3; ‡ L, I, H – low, intermediate, high risk; § n – 104

The limitation of this study is a small number of patients. The low incidence of grade 2 and grade 3 toxicity could provide to underestimation of any of the analyzed factors. However, our group is still one of the largest published to date. Our and others data encourage for wider use of ultra-hypofractionation.

In conclusion, the acute toxicity of FSRT is low. Early data suggest also low late toxicity rates. The conventional arm is needed for comparison.

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