doi:10.4149/neo_2017_421

Ultrahypofractionated CyberKnife™ based stereotactic radiotherapy versus conventional radiotherapy in patients with prostate cancer – acute toxicity evaluation in two phase II prospective studies

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Our purpose was to compare the acute toxicity of ultrahypofractionated CyberKnife™ based stereotactic radiotherapy (SBRT Arm) and conventional radiotherapy (EBRT Arm) in prostate cancer patients. Two-hundred-sixteen men with prostate cancer were enrolled in our prospective studies. One-hundred and nine were irradiated using CyberKnife to total dose of 36,25 Gy in 5 fractions. One-hundred and seven were irradiated conventionally to total dose of 76 Gy in 38 fractions. Mean age of patients was 69. Acute genitourinary (GU) and gastrointestinal (GI) adverse-events were collected. The maximal acute toxicity EORTC/RTOG score was assumed. A total of 41%, 44%, 12% and 3% of patients presented grade 0, 1, 2 and 3 acute genitourinary toxicity in SBRT arm, respectively. A total of 21%, 33%, 43% and 3% of patients demonstrated acute grade 0, 1, 2 and 3 genitourinary toxicity in EBRT arm. A significant difference between number of patients with grade 2 GU toxicity was observed (p-0.000) and between patients without any toxicity (p-0.0017).

A significant difference in frequency of acute GI toxicity between both groups was observed, too. 71% vs. 44% had no toxicity (p-0.0001), and 3% vs. 18% (p-0.0004) presented grade 2 GI toxicity in SBRT and EBRT arms respectively.

The acute toxicity rates of fractionated stereotactic radiotherapy is lower compared to conventional irradiation.

Key words: CyberKnife, prostate cancer, acute toxicity

Efficacy of conventional external-beam radiotherapy in prostate cancer patients was confirmed in many studies [1-3]. It is also safe with acceptable side-effects. Moreover it is as effective as prostatectomy [4]. Technological progress, particularly in imaging and image-guidance, but also low alpha/beta ratios for prostate cancer [5-10] led to ultrahypofractionation. Although feasibility studies and phase II trials showed that it is also safe and efficient [11-20], there are no data comparing these two schedules of fractionation directly.

If low alpha/beta ratio (<2 Gy) for prostate cancer is considered, ultrahypofractionated schedule may demonstrate similar or higher equivalent dose comparing to conventional radiotherapy. Moreover early responding tissues (alpha/beta ratio ~10 Gy) receive lower equivalent dose which may lead to lower than conventional incidence of acute toxicity. Our radiobiological hypotheses are summarized in Table 1.

Due to lack of such studies we decided to compare early side-effects of conventional external beam radiotherapy (EBRT) with that of robotic ultrahypofractionation CyberKnife (SBRT).

Patients and methods

Two prospective II phase trials were conducted in our center. One focused on toxicity of conventional irradiation and the other due to toxicity of ultrahypofractionated radiotherapy. The evaluation of toxicity was performed using identical RTOG/EORTC acute toxicity protocols by the same group of physicians.

We designed comparison of patients treated with both schedules. Minimum of 100 patients for each arm were assumed. The NCCN prostate cancer risk classification was used. We enrolled 216 men with prostate cancer aged 49-85 (mean 69). The characteristic of patients is presented in Table 2.

Conventional arm. One-hundred and seven men was treated with Conventional Arm (EBRT). Routine evaluation was done prior to radiotherapy. It included digital rectal examination, abdominal and pelvic CT or ultrasound, chest radiograph and bone scan. Patients were immobilized in supine position with thermoplastic mask. Planning CT was performed 1.5-2h after last urination. Total dose of 76 Gy in 2 Gy fractions was prescribed. PTV included CTV (i.e. whole

Table 1. NTD (Normalized Total Dose) and BED (Biological Effective Dose) evaluation for acute, late toxicity and for prostate cancer due to different schedules of fractionation.

	Tumor alfa/beta 1,5 Gy	*Late toxicity alfa/beta* 3 Gy	Acute toxicity *alfa/beta* 10 Gy
$NTD_{7,25\ Gy}$	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

Table 2. Characteristic of groups.

Clinical Parameters	**SBRT Arm Number (%), n = 109**	**EBRT Arm Number (%), n = 107**
Age		
Mean	70	69
Range	54-83	49-85
≤ 60	10 (9)	9 (8)
61-70	51 (53)	53 (50)
71-80	46 (36)	44 (41)
>80	2 (2)	1 (1)
T stage		
T1c	45 (42)	56 (52)
T2a	10 (9)	29 (27)
T2b	36 (33)	17 (16)
T2c	17 (16)	3 (3)
T3	0	2 (2)
Gleason Score		
<7	105 (96)	78 (73)
7	4 (4)	39 (27)
Pretreatment maximal PSA (ng/dl)		
<10	90 (83)	55 (51)
10-20	16 (15)	51 (48)
>20	1 (1)	1 (1)
No data	2 (1)	0
Risk groups NCCN		
Low	50 (46)	32 (30)
Intermediate	58 (53)	73 (68)
High	1 (1)*	2 (2)
Neoadiuvant ADT		
Yes	63 (58)	86 (80)
No	46 (42)	21 (20)
Comorbidity		
Diabetes	15 (14)	13 (12)
Hypertention/ Cardiovascular diseases	63 (58)	67 (63)
Asthma/ Respiratory system diseases	5 (5)	bd
Hematological diseases	1 (1)	bd
No diseases reported	41 (38)	40 (37)

*PSA level above 20 in the day of start of radiotherapy

prostate plus base of seminal vesicles (1,5 cm)) with 7-10 mm margin. Dynamic techniques such as IMRT or VMAT were planned. 2D-2D KV IGRT was done, daily. In subgroup of 52% of patients additionally one fiducial marker (GoldAnchor™) was implanted into the prostate under TRUS. At the rest of 48% of patients verification of position was based on bony structures.

Ultrahypofractionated arm. One-hundred nine patients were treated in robotic ultrahypofractionation CyberKnife arm (SBRT). Low and intermediate NCCN risk groups of patients were included into the study. Routine evaluation as in CA was done. Patients were immobilized with vacuum matress in supine position. Three golden markers (Gold Anchor™) were implanted into the prostate gland under TRUS guidance. Planning was done on CT/MRI fusion. Prostate gland and proximal part of seminal vesicles (1.5 cm) were included into clinical target volume (CTV). To obtain PTV three millimeters rectal margin and five millimeters margins in other directions were added. Total dose of 36,25 Gy in five fractions in two weeks was prescribed. Patient position was verified with dedicated kVs system. Also fiducial tracking was performed during irradiation. The dose constraints for target and OAR`s for both schedules are presented in Table 3.

Follow-up. Conventional arm patients were examined once-a-week during treatment and on the last fraction day. SBRT patients were evaluated on the end of treatment or more often if necessary. All patients were followed after one month and then every 3 months from last fraction of irradiation. Acute genitourinary (GU) and gastrointestinal (GI) adverse-events were collected. The maximal acute toxicity EORTC/RTOG score was assumed.

Statistic. The comparison of toxicity between groups was performed with $\chi 2$ test. Results were statistically significant if p-value was below 0.05.

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

Organ	EBRT	SBRT
Maximum plan dose	81.3 Gy	43.5 Gy
PTV	72.2 – 81.3 Gy	34.4 – 43.5 Gy
Rectum	V_{40} – 60% V_{50} – 50% V_{60} – 35% V_{70} -15%	V_{18} – 50 % V_{29} – 20 % $V_{32.6}$ – 10 % $V_{36.25}$ – 5 %
Bladder	V_{40} – 65% V_{50} – 55% V_{60} – 40% V_{70} – 20%	V_{18} – 55 % V_{29} – 25 % $V_{32.6}$ – 15 % $V_{36.25}$ – 10%
Femoral heads	V_{50} – 45%	V_{25} – 45 %
Urethra	Point dose 80Gy	Maximal dose 43.5 Gy

Table 4. The incidence of maximal acute Genitourinary (GU) toxicity

Grade of GU toxicity	SBRT	EBRT	p-value	EBRT Marker (–)	EBRT Marker (+)	p-value
Grade 0	45 (41%)	23 (21%)	0.0017	11 (22%)	12 (21%)	0.9
Grade 1	48 (44%)	35 (33%)	0.1	17 (33%)	18 (33%)	1
Grade 2	13 (12%)	46 (43%)	0	20 (39%)	26 (46%)	0.46
Grade 3	3 (3%)	3 (3%)	1	3 (6%)	0	0.066
Grade 4	0	0	-	0	0	-

Table 5. The incidence of maximal acute Gastrointestinal (GI) toxicity

Grade of GI toxicity	SBRT	EBRT	p-value	EBRT Marker (–)	EBRT Marker (+)	p-value
Grade 0	77 (71%)	47 (44%)	0.0001	18 (35%)	29 (52%)	0.08
Grade 1	28 (26%)	40 (37%)	0.08	23 (45%)	17 (30%)	0.11
Grade 2	4 (3%)	19 (18%)	0.0004	9 (18%)	10 (18%)	1
Grade 3	0	1 (1%)	0.3	1 (2%)	0	0.29
Grade 4	0	0	-	0	0	-

Results

Both of the two methods of treatment were well tolerated. There wasn't incidence of grade IV acute genitourinary and rectal toxicity. The grade 3 GU toxicity was incidental in both groups (3%). The GI toxicity wasn't observed in SBRT arm and was low in EBRT arm (1%).

The significant difference between groups was noted due to 0 and 2 Grade GU and GI toxicity. The G2 GU toxicity was almost 4 times higher than in SBRT arm. The similar observation due to GI toxicity was noted. The number of patients without any GU or GI toxicity was significantly higher in SBRT arm (41% vs. 21% for GU, (p=0.002) and 71% vs. 44% for GI (p=0.0001) respectively). There was not significant difference between patients with or without implanted marker in conventional arm.

The comparison of acute GU and GI toxicity is presented in Tables 4 and 5.

Discussion

Hypofractionation in treatment of patients with prostate cancer is not an invention of XXI century. Some of studies were conducted in 90`s and even in 60`s [21, 22, 23]. The dose response analyses suggested that alpha/beta for prostate cancer is low (1.2 – 3.5 Gy) [5-10]. Many data showed that it might be lower than 2 Gy. This led to schedules with higher dose per fraction (i.e. hypofractionated), but lower than conventional total dose. Even though hypofractionation should theoretically yield lower toxicity rates with high efficacy, it did not find wide interest in the past.

Fast technological development and clinical availability of state-of-the-art radiotherapy devices made hypofractionation more feasible. It is mostly due to introduction of precise image-guided dynamic techniques and/or stereotactic body irradiation.

The reported toxicity in vast majority of new era studies on hypofractionation is quite low. Rene et al. reported lack of acute toxicity in more than 50% of patients and persistant late toxicity at 2% and 1,5% respectively for GU and GI [24]. Similary Martin reported at 90 patients acute G2 toxicity 11% for GI and 25% for GU using fiducial based IGRT [25]. Although Soete reported higher rate of acute G1 and G2 toxicity than in earlier treated conventional group the symptoms disappeared after 2 months after RT. There werent G3 and G4 acute toxicity in both groups [26].

There are some phase III studies among mild hipofractionation publicated recently. Lukka et al. randomised 936 men between conventional and hypofractinated arm. The acute toxicity was sliglty highier for hypofractionation. Although the total dose was quite low of 66 Gy in conventional arm. Late toxicity of 3% was similar in both groups [27]. Yeoh et al. reported significantly highier GI toxicity one month after radiotherapy at hypofractionated arm. GI and GU toxicity persisted after 60 months didnt differ beetwen arms. Again in this study the total dose in conventional arm was only 64 Gy [28, 29].In the light of present data this dose is unaceptable today.

Pollack et al. compared efficacy and toxicy between 76 Gy conventional group and 70.2 Gy (2.7 Gy per fraction) and didn't observed significant diffrence in acute toxicity beetwen arms [30]. In publicated update there were no statistically significant differences in late toxicity between the arms; however, in subgroup analysis, patients with compromised urinary function before enrollment had significantly worse urinary function after hypofractionation [31].

Similarly Arcangeli et al. didn't observed significant diffrence in acute and late toxicity between patients treated conventionally with 80 Gy (2 Gy per fraction) to those irradiated using 62 Gy (3,1 Gy per fraction) [32]. Deamley et al. in three arms study confirmed that there is no difference in toxicity in 2 years observation beetween conventional treatment and hipofracionated arms [33]. Similarly no difference due to acute toxicity. Hypofractionation at 3.15 Gy per fraction to 63 Gy within 5 weeks was well tolerated. The GI and GU physician-rated acute toxicity both developed earlier but recovered faster using hypofractionation [34].

There are data on ultrahypofractionation from I/II phase trials available [11-20]. The vast majority of results are from United States. The high precision of such irradiation allowed to gain very good outcomes even with reduced margins. Toxicity rates are reported as quite low with acute GI and GU toxicity between 5-20% and <5% for Grade 2 and 3, respectively. Grade 4 adverse-events were not observed.

Recently publicated data by King among 1,100 patients pooled into analysis from eight prospective trialas showed excellent 5 years biochemical control for low and intermiediate risk groups 99% and 93% respectively [35]. Although the majority of studies are focused on long term results and late toxicity there is still unaviable any data of directly comparison with conventional treatment due to acute or late toxicity. In our opinion such analysis is highly reasonable. All focused only on late toxicity while severe acute toxicity could be the reason of consenquentive late effects or even breaks, delay or not complete the treatment.

Based on radiobiological considerations we didnt expect higher acute toxicity of hypofractionated radiotherapy than conventional treatment. Due to smaller total dose expected acute toxicity should be lower. These consideration was confirmed in our study. In both arms G3 or higher acute toxicity didn`t exceed 3%. What is interesting there was large difference between arms due to acute toxicity G 0 and 2. In patients treated with CK there were much more patients without any toxicity and small number with G2 toxicity. Probably there are three main reasons of such results: Firstly smaller prescribed total dose, secondary smaller CTV to PTV margins in CK arm and the last using of continuous positioning verification (tracking).

The weak point of all radiotherapy schedules given in a very short time is the possibility of development of acute toxicity shortly after the completion of radiotherapy (CHART) [36]. Such toxicity may resolve in a couple of days, before the first follow-up visit, which in a typical clinical practice may lead to the underestimation of a real incidence of acute toxicity. We cannot exclude that fact, however because of a strictly scheduled follow-up performed by the same team the risk of such underestimation was in our opinion diminished considerably. Therefore, we conclude the lower acute toxicity of robotic ultrahypofractionation was indeed present. However, the incidence of acute toxicity in a conventionally fractionated arm is rather high when compared to other modern series [37]. But, on the other hand it seems comparable to other studies utilizing IMRT+IGRT especially when Grade 2 GU toxicity is taken into consideration (41-50%) [38-40]. The incidence of GI toxicity is more variable with a rate of 11% [39], 13% [38] or 30% [40]. It seems that the amount of a spared rectal volume is of importance. We think that apart from dosimetric issues, the differences between the results of those studies may be attributable for instance to physician attitude towards drug prescription or slight modifications of RTOG toxicity scale.

There wasn`t difference in toxicity between patients in conventional arm irradiated with or without marker. In our opinion it is result the of identical CTV to PTV margins in both subgroups. Probably the narrowed margins in group with fidutial marker could decrease the toxicity of treatment.

In conclusion acute toxicity of CyberKnife based hypofractionated radiotherapy is lower than in conventional treatment.

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