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Review Article

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Hypofractionated External Beam Irradiation with Single HDR Iridium 192 Boost in the Treatment of intermediate and High Risk Prostate Cancer Patients Initial acute and late side effects

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Abstract

Purpose: *Dose escalation has been shown to improve biochemical outcome in the treatment of prostate cancer. The use of precision radiotherapy whether using IMRT, proton's or other appropriate means have been utilized in an effort to reduce side effects while engaging in dose escalation. However, it is well known that best way to ensure precision delivery of radiation is with the use of brachytherapy. In prostate cancer the use of HDR brachytherapy exploits the low α/β ratios. We sought to evaluate our combination of moderate hypofractionated external beam irradiation with a single HDR boost in terms of acute/late toxicity in patients with intermediate and high risk prostate cancer.*

Method: *69 patients whose age range from 49 to 83 (med = 69 y.o.) years old were offered treatment utilizing the combination of moderate hypofractionated external beam irradiation and single HDR boost. The external beam irradiation consists of 17 fractions of 250 cGy per fraction, which using BED evaluation most closely approximated our previous more conventionally delivered external beam (23 fractions/200 cGy per fraction) irradiation in this setting. All patients were treated with either 3D conformal or IMRT; within 2 weeks of completion of external beam irradiation a single 1500 cGy iridium 192 implant was delivered. Our dose constraints have been previously published but our stated goal was to delivered 98% of the dose to the prostate treatment volume identified by ultrasound. 29 patients received ADT at the discretion of the treating Urology team. Follow up has been maintained on all patients and has ranged from 11 to 53 months (median 37 months).*

Results: *Assessment of acute / late toxicity was assessed using the RTOG/EORTC criteria. Overall 36/69 (52%) developed ACUTE GI toxicity. 49% developed Gr I/II while two patients developed Gr III. 14.5% reported late GI toxicity, all were GR I / II. Without surprise 98% reported acute GU toxicity. Of these 67/69 had Gr I/II with a single patient reporting GR III. However, after 6 months only 8 (11.5%) had persistent GR I/II issues. An additional patient went on to develop GR III toxicity.*

Conclusion: *While further follow up will be required before definitive statements can be made regarding the oncologic effectiveness of this treatment combination, the early toxicity profiles are very encouraging. We continue to offer this treatment regimen for select intermediate/high risk prostate cancer patients.*

Introduction

Prostate cancer continues to be one of the leading cancer diagnosis in the US, behind only breast and lung cancer. It diagnosis has declined recently because of decreased use of PSA screening, based on newer guidelines, which are controversial [1, 2].

However once a diagnosis is made a patient must decide how to move forward. If the cancer appears localized, then there are multiple ways to approach its treatment. These may include surgery, various radiation techniques (external beam, brachytherapy and/or proton), cryotherapy, high frequency ultrasound ablation, androgen deprivation therapy (ADT), active observation.

When radiation is considered there ae several factors that need to be addressed prior to making recommendations. For example, is a patient at risk for lymph node involvement or not? We are still developing how to integrate newer modality imaging into the decision making process. However, there are guidelines, such as the NCCN, that help to guide these decisions [3-6].

For patients that have NCCN defined intermediate/high risk disease, most often external beam irradiation or some combination of external beam and brachytherapy is utilized. There have been trials that have looked at dose escalation in various fashions and they mostly report similar improved biochemical progression free survival (bPFS) when compared to traditional dose sequences [7-10]. The toxicity profiles are also very similar.

In an effort to reduce overall treatment time and to also take advantage of the reported lower alpha/beta ratio there have been series that have utilized moderately hypo fractionated radiation external beam irradiation using 250-300 cGy per treatment to total doses of about 70 Gy [11, 12]. In these published trials there does not appear to be any inferiority when compared to more traditional daily dose schedules with very similar toxicity [13-15].

Another way in which the low a/b ratio can be taken advantage of is with HDR brachytherapy. There are numerous series in early localized prostate cancer that have similar and in some cases improved bPFS with HDR alone [16-19]. However, there are fewer series that have evaluated the combination of either traditional or moderately hypofractionated external beam irradiation with either single or multiple fraction HDR. In these series the addition of brachytherapy has resulted in excellent bPFS and acceptable GI/GU toxicity [20-26].

We report on our experience with moderately hypo fractionated external beam irradiation (250 cGy/treatment x 17) in conjunction with a single HDR boost treatment of 15 Gy and report on our acute and late GI and GU toxicity.

Methods and Materials

69 patients, ages 49 to 83 (med = 69 years old) with intermediate or high risk prostate cancer, as defined by the NCCN (Appendix 1), received treatment that consisted of combined hypo fractionated external beam radiation with single HDR boost. Approval from our IRB was obtained to retrospectively review their records. We reviewed initial tumor information that included but were not limited to Gleason score, perineural involvement, extracapsular extension, number of cores positive and % involvement in positive cores along with age, sex, race and co morbidity factors such as diabetes, hypertension and previous abdominal surgery. External beam radiation treatment, HDR parameters, pre and post treatments PSA and toxicity scores based on RTOG/EORTC system along with radiographic evaluations were also reviewed (Appendix II).

Pre Treatment Assessment

Once a patient was diagnosed, they presented to the department of radiation oncology for consultation. Based on patient characteristics patients were offered either external beam radiation alone or combined external beam radiation with single HDR boost. Reasons for rejecting HDR included but were not limited to work related issues, caretaker responsibilities, fear of anesthesia and issues to weightlifting limits post brachytherapy.

If a patient desired HDR they underwent evaluation with transrectal US to determine if their prostate volume was acceptable for treatment, namely that our template could accommodate the gland size. We also limited our volume to no more than 60 cc's. For patients who did not fulfill these parameters they were offered hormone cytoreductive treatment. There was no patient who underwent cytoreductive therapy who failed eventually to meet size inclusion.

Beginning in 2018 we introduced the use of prostate/rectal spacer technology with use of Space OAR Hydrogel (Augmentix Inc., Bedford MA). This was recommended for all patients in whom there was less than 2.5 mm interface between the prostate /rectum. 7 patients had placement of Space OAR prior to simulation.

External Beam Irradiation

Each patient had simulation using CT based imaging. All patients were treated using 3DC/IMRT and had a planned dose of 4250 cGy using 250 cGy/fx. The treatment field comprised of the traditional pelvic nodes for prostate cancer as described in the RTOG pelvic node consensus.

HDR Boost

Approximately 10 days after completion of external beam radiation patients had single HDR application. All patients had general anesthesia and both the radiation oncologist and Urologist were present for needle placement and decisions regarding volume size, which was especially important for apex delineation which we believe is critical for correct dose deposition. Treatment planning was completed using Oncentra Prostate (Elekta AB, Stockholm, Sweden). Real time US images and use of contrast material via the Foley catheter assisted in identification of bladder prostate base and apex, rectum and urethra.

We had certain dose restrictions allowed for the urethra (V115 < 1%) and rectum (V75 < 1%). Our dose recommendations were Prostate V100 > 98% and Prostate V125 < 55%. Cystoscopy was performed on each patient prior to final planning to ensure there was no catheter violation of either the urethra or bladder mucosa. We sought to see some limited "tenting" of bladder mucosa, and this was based on the radiation oncologist experience as there are no definitive values for this aspect of the implantation. The cystoscopy also allowed the urologist to determine which patients would be discharged with the Foley catheter in place with removal scheduled for next day. Following treatment completion, the

catheters were removed by the radiation oncologist and the patient was recovered. No patient required hospitalization after HDR application.

Follow Up

All patients were followed every 3 months in first year, every 4 months in year 2 and every 6 months until year 5 post treatment when the follow up went to a yearly basis. At each follow up whether it be through the radiation oncology section or urology section, patients had PSA drawn and had evaluation with AUA symptom score system in addition to quality of life evaluation and SHIM (Sexual Health In Men). Toxicity scores were assigned based on RTOG/EORTC scoring system. Follow up has ranged from 11 to 53 mos (med = 37 mos)

Results

Patient and treatment characteristics are found in Table 2. Using NCCN criteria 2 patients were considered favorable intermediate, 38 were unfavorable intermediate and 29 were considered High/ Very high risks.

All patients received whole pelvis irradiation using RTOG atlas guidelines for lymph node coverage. External beam consisted of 17 fractions of 250 cGy/fraction. Using an α/β of 1.5 this resulted in BED of 113.33 Gy and EQD2 of 48.57 Gy. This closely approximated our traditional dose scheme of 23 x 200 cGy which resulted in BED of 107.33 and EQD2 of 46 Gy. HDR was completed using real time dosimetry utilizing TRUS. Results are shown in Table 3. We strived to ensure that V100 prostate > 98% with V125 < 55%. We set urethral dose as V115 < 1% and rectal dose V75 being < 1%. Cystoscopy was performed on each patient to ensure that there were no urethral bladder mucosal violations.

Acute and late GI/GU toxicity were assessed using RTOG/EORTC toxicity criteria. Toxicity profile is found in Table 1. As expected most patients were noted to have Gr I/II GU toxicity (67/69). A single patient was noted to have Gr III acute toxicity. This patient was noted to have renal calculi in the bladder at time of cystoscopy / implant. Late GU Gr I/II toxicity was noted in 11.5% (8/69) with 2 patients recording Gr III GU toxicity (2.8%). 37.5% of patients were noted to have acute Gr I/II GU toxicity. Of note due to our prone set up technique 30/69 (43.5%) report issue with constipation requiring stool softener therapy. Late GI Fr I/II issue were reported in 14.5%. There were no reported ≥ Gr III late GI toxicities.

Table 1: Acute and Late GI/GU Toxicity

	Gr 1	Gr II	>GR III
GI Acute	23.1% (16/69)	14.4% (18/69)	2.8% (2/69)
GI Late	11.5% (8/69)	2.8% (2/69)	0
GU Acute	68.1% (47/69)	28.9% (20/69)	1.4% (1/69)
GU Late	7.2% (5/69)	4.3% (3/69)	2.8% (2/69)

Discussion

Treatment of prostate cancer has many entrants: surgery, ADT, radiation therapy, cryotherapy and surgery along with active observation. It is therefore not surprising that there are various reports using these modalities showing excellent biochemical disease free survival (bDFS) especially in low risk disease [27-35]. There have also been reports on dose escalation using external beam techniques in both in the institutional and cooperative group setting. In these settings we are able to critically evaluate GI/ GU toxicity profile, both acute and late, along with any potential biochemical/local control benefit.

The Dutch trial randomized 664 patients with T1b – T4 prostate cancer. The long term biochemical and local failure rates were significantly lower in the 78 Gy arm ($P<0.05$), Umezawa R. et al reported on 289 patients with high risk prostate cancer were randomized to receive 66, 72 or 78 Gy with ADT [36]. With a median follow up of 77.3 months the 4 year PSA relapse free survival was 72.7, 81.6 and 90.3% for the treatment groups Beckendorf et al reported on the GETUG 06 randomized trial in which 306 men were randomized to either 70 or 80 Gy [7]. With a median follow up of 61 months the 5 yr biochemical relapse rate was 30 and 23.5% ($P= .09$). However, they also reported a slightly higher toxicity profile with GR II or greater GI toxicity while GU toxicity was slightly worse ($P = .046$) with 80 Gy [10]. These are but a few of the series that have shown improved local control with acceptable GI/GU toxicity. However, there is the report by Lee et al in which they found no tumor benefit to dose escalation but did find significant worst > GRII proctitis ($P< 0.01$) [37].

The use of moderately hypo fractionated external beam radiation and Ultra hypo fractionated stereotactic radiation have also been assessed. In the review of moderate hypo fractionated radiation there have been several randomized trials that have shown non inferiority with toxicity profiles that are compatible to traditional radiation sequences [9, 38, 39]. deVries et al recently updated the PhIII HYPRO Trial in which 820 men with intermediate/high risk T1-T4 prostate cancer randomized to conventional (78 Gy/39 fractions) or hypofractionated (64.6 Gy/19 fractions) irradiation. With median follow up of 89 months the hypofractionated treatment arm did not result in inferior tumor control [40-44]. However, they did report statistically higher rates of rectal bleeding, mucoid discharge and fecal incontinence.

Others have not found similar levels of toxicity. Pollack et al randomized 303 men with favorable to high risk prostate cancer to conventionally dosed IMRT (76 Gy/38 fractions) or hypofractionated IMRT (70.2 Gy/26 fractions). There were no statistical differences in late toxicity, however in subgroup analysis patients with pretreatment compromised urinary function had significantly worse urinary function after hypofractionation [39].

Dearnaley et al also offer similar acute/late GI/GU toxicity profiles from the CHHiP Trial. The estimated 5 year cumulative greater than Gr II GI and GU toxicity was 13.7 and 9.1% for convention treatment (74 Gy in 37 fractions) compared with 11.9 and 11.7% for highest hypofraction sequence (60 Gy in 20 fractions). They also offer a comprehensive review of other hypofraction series toxicity profiles [40].

There have been several series that have compared surgery, external beam irradiation +/- brachytherapy and brachytherapy alone [40-42]. From these series it appears that use of brachytherapy either alone or in combination with external beam radiation results in higher bCFS than surgery, with different toxicity profiles.

Recently there have been several series that have reported on

moderate hypo fractionated radiation combined with single fraction HDR. The series from Toronto, reported on over 500 patients who received 37.5 Gy with single fraction HDR boost of 15 Gy. With median follow up of 5.2 years' freedom from biochemical relapse was 91% overall. Shahid updated this series toxicity profile. Late GR I, II and >GR III GI toxicity were reported as 45,19 and 0%. For late GU toxicity the results were 29, 59 and 4% [44].

Joseph et al, from Manchester, reported their experience with a similar external beam dose but using a single fraction of 12.5 Gy for the HDR boost. With median follow of 65 months the 5 year biochemical DFS was 80.5%. They reported IPSS scores peaked 6 weeks after treatment (med = 9) LENT-SOMA bladder/bowel mean scores at baseline were 0.84 and again peaked at 6 weeks (mean = 0.37). EPIC urinary scores returned to baseline at 6 months while bowel median scores returned to baseline after 24 months [45]. Lauche et al treated 87 patients with 37.5 Gy with 15 Gy boost. 28% of patients also received ADT. At 18 months 66% had a PSA < 1.0, 46 had PSA levels <0.5. Only 2 patients had a Gr I GI toxicity at 4 months, there were no Gr II toxicities reported [46].

Conclusion

This series, while it will need more maturation, continues to build the narrative that moderately hypo fractionated external beam radiation combined with single fraction HDR boost results in acceptabletoxicity profiles that are similar to other published series. We continue to advocate it use in our patients and will continue to monitor our patients in follow up for bDFS and toxicity. We have also instituted a neurocognitive trial for those patients who receive ADT as there has been preliminary data suggesting ADT not only can impact cardiovascular health but result in decline in neurocognitive abilities of patients.

Table 2 Patient Characteristics

Patient n = 69

Age	**47 – 83 (med = 69)**	
Race		
AA	43	
White	24	
Other	2	
Gleason		
3/3	1	
3/4	11	
4/3	31	
4/4	14	
4/5	12	
Pre-treatment PSA	At diagnosis	AT LAST FOLLOW UP
< 10	42	≤ 2.0; n = 64
10 – 20	14	2.1 - 4.0 n = 5
21 – 24	6	
>40	7	
Pre-treatment parameters At diagnosis	At last F/U	
median AUA = 5	med AUA = 3	
median QOL = 2	med QOL = 1	
median SHIM = 11	med SHIM = 14	

Table 3: Implant Characteristics

Prostate volume	16 – 56 cc (med = 27.5 cc)
Catheter number	12 – 24 (med = 18)
V100 prostate	97.15 – 99,54 % (med = 99%)
V125 prostate	45 – 63% (med = 55%)
V115 urethra	0 – 2.38% (med = 0.3%)
V75 rectal	0 – 1.24% (med = 0, only 2 patients with rectal dose > 1%)

Appendix I

Risk stratification schema for localized prostate cancer, according to the National Comprehensive Cancer Network (NCCN)

Risk group	Clinical / pathologic features
Very low	● T1c AND ● Gleason score ≤ 6/grade group 1 AND ● PSA <10 ng/mL AND ● Fewer than 3 prostate biopsy fragments/cores positive, ≤ 50% cancer in each fragment/core AND ● PSA density < 0.15 ng/L/g
Low	● T1 to T2a AND ● Gleason score ≤ 6/grade group 1 AND ● PSA < 10 ng/mL
Favorable Intermediate	●T2b to T2c OR ● Gleason score 3+4 = 7 / grade group 2 OR ● PSA 10 to 20 ng/mL And ● Percentage of positive biopsy cores < 50%
Unfavorable Intermediate	● T2b to T2c OR ● Gleason score 3+4 = 7/grade group or Gleason score 4+3 = 7/grade group 3 OR ● PSA 10 to 20 ng/mL
High	● T3a OR ● Gleason score 8/grade group 4 or Gleason score 4+5 = 9/ grade group 5 OR ● PSA > 20 ng/mL
Very high	● T3b to T4 OR ● Primary Gleason pattern 5 OR ● >4 cores with Gleason score 8 to 10/grade group 4 or 5

Risk stratification schema for localized prostate cancer, according to the National Comprehensive Cancer Network (NCCN) PSA: prostate-specific antigen.

Adapted from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Prostate Cancer. Version 4.2018. Graphic 118962 Version 2.0

Appendix 2 RTOG/EORTC Toxicity Scores

Acute Toxicity	Grade I	Grade II	Grade III	Grade IV
Genitourinary	Frequency of urination or nocturia twice pretreatment habit/ dysuria urgency not requiring medication	Frequency with urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g. Pyridium)	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration. Or necrosis
Upper GI	Anorexia with ≤ 5% weight loss from pretreatment baseline/ nausea not requiring antiemetics/abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with ≤ 15% weight loss from pretreatment baseline/ nausea and/or vomiting requiring antiemetics/ abdominal pain requiring analgesics	Anorexia with > 15% weight loss from pretreatment baseline or requiring NG tube or parenteral support. Nausea and/or vomiting requiring tube or parenteral support/ abdominal pain, severe despite medication/ hematemesis or melena/ abdominal distertion (flat plate radiograph distended bowel loops)	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion
Lower GI / Pelvis	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g. Lomotil) / mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bower loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or

Late Toxicity	Grade 1	Grade II	Grade III	Grade IV
Bladder	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency & dysuria severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity <100 cc); severe hemorrhagic cystitis
Small/Large Intestine	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and coli; bowel movement >5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis / perforation fistula

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