Moderate hypofractionated external beam radiotherapy alone for intermediate risk prostate cancer: long term outcomes

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Introduction: *To report long term toxicity and efficacy of patients with intermediate risk prostate cancer treated with moderate hypofractionated radiotherapy (HypoRT).*
Materials and methods: *We studied the first consecutive 100 men with intermediate risk (stage T2b-T2c, or PSA = 10-20 ug/L, or Gleason score = 7) adenocarcinoma of the prostate treated between October 2002 and May 2010 in our institution with moderate HypoRT. Patients were treated using three-dimensional conformal HypoRT to a dose of 66 Gy in 22 daily fractions prescribed to the isocenter. Androgen suppression was not given to any patient. A uniform 7 mm margin was created around the prostate for the planning target volume. Daily ultrasound was used to guide the radiotherapy. Common Terminology Criteria for Adverse Events, version 3.0, was used to prospectively score toxicity. Biochemical failure was defined as the nadir PSA level plus 2 ng/m.*
Results: *After a median follow up time of 80 months (range: 7-152), the 8 year actuarial freedom from biochemical relapse survival rate was 90%. The 8 year cancer specific survival and overall survival rates were 96% and 84%, respectively. Only 2 patients died from prostate cancer. The worst grade ≥ 2 late genitourinary (GU) or gastrointestinal (GI) toxicities ever documented were 19% and 20%, respectively. At the last follow up the incidence of grade ≥ 2 late GI or GU toxicity was of only 2% and 3%, respectively. No grade 4 or 5 late toxicity was seen.*
Conclusion: *Our long term experience with HypoRT delivering 66 Gy/22 fractions prescribed to the isocenter using three-dimensional conformal radiotherapy shows excellent tumor control with acceptable toxicity.*

Key Words: intermediate risk prostate cancer, hypofractionated radiotherapy

Introduction

Radiotherapy is a well-accepted alternative for curative treatment of localized prostate cancer.[1] For the intermediate risk group, radiation treatment has been delivered in many ways including external beam radiation therapy (EBRT) alone, brachytherapy alone, the combination of both, or any of the three previous alternatives in combination with androgen deprivation. The most effective of all these radiation treatments remains undefined.

Moderate hypofractionated radiotherapy (HypoRT) has been increasingly used in the treatment of prostate cancer since the concept of low alpha/beta ratio for prostate cancer was introduced around 15 years ago.[2] The α/β parameter is an indication of the cell sensitivity to alterations in fraction size. In general, rapidly proliferating cells (such as tumor cells) are not very sensitive to fraction size (high α/β) while slowly proliferating cells (such as normal tissues) are very sensitive to fraction size (low α/β). Unlike most tumors, the α/β ratio for prostate cancer has been consistently estimated around 1.5-3 Gy which is below the estimated α/β ratio for the pelvic organs at risk, particularly the rectum. Theoretically, that

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difference favors the use of HypoRT in prostate cancer. In HypoRT, fewer, larger daily fractions are thought to have the potential to either improve the therapeutic ratio or give similar outcomes compared to conventionally fractionated radiotherapy, with the important additional benefit of shortening the overall treatment time.[3] A radiation treatment without hormones that provides good tumor control with acceptable toxicity and is delivered in a shorter period of time becomes a practical and attractive treatment option for intermediate risk prostate cancer patients. We previously reported preliminary results of patients with intermediate risk prostate cancer treated with HypoRT alone at our institution.[4] We now present the long term outcomes of a larger cohort of patients.

Materials and methods

We reviewed the first 100 men with intermediate risk, histologically proven adenocarcinoma of the prostate, never exposed to any hormonal treatment prior to or during radiotherapy, and who were treated with HypoRT at our institution between October 2002 and May 2010. The definition of intermediate risk disease was: clinical stage T2b-T2c, or pre-treatment PSA = 10-20 µg/L, or Gleason score = 7.[5] Pre-treatment evaluation consisted of medical history and physical examination including digital rectal examination and PSA values were obtained for all patients. Computed tomography of the pelvis/abdomen and/or bone scans were performed prior to treatment at the discretion of the treating physician.

All patients received the same radiation treatment as previously reported.[6] In summary, radiotherapy was delivered using a three-dimensional conformal plan consisting of five 18-MV photon beams to a dose of 66 Gy in 22 daily fractions of 3 Gy prescribed at the isocenter. A planning CT scan (5 mm slice thickness) was performed in the supine position in all patients. Patients were advised to have a comfortably full bladder and an empty rectum at the time of CT simulation. An urethrogram was performed in all patients to assist in defining the prostatic apex. The prostate, seminal vesicles, whole rectum (contoured from the anus to the sigmoid junction), whole bladder, femoral heads and penile bulb were contoured in all patients. The clinical target volume (CTV) was the whole prostate gland. A maximum of 10 mm of seminal vesicles could be included in the fields at the discretion of the treating radiation oncologist. The planning target volume (PTV) consisted of the CTV plus a uniform 7 mm margin in all directions. There were no pre-defined limiting dosimetric constraints for organs at risk. Daily pre-treatment image guiding localization of the prostate gland was performed using transabdominal ultrasound (''BAT'' system, Nomos Corporation, Sewickly, PA, USA).[7]

Follow up always included PSA blood tests and were performed every 4-6 months in the first 5 years and then annually. Gastrointestinal (GI) and genitourinary (GU) toxicity were prospectively assessed and graded according to version 3 of the Common Terminology Criteria for Adverse Events (CTCAE)[8] in every patient at each follow up visit. Patients developing any rectal bleeding requiring one or more Argon plasma coagulation through colonoscopy were always considered as having grade 3 late rectal toxicity. The worst-grade toxicity documented at any time was considered as the final late toxicity. Biochemical failure was defined according to Phoenix criteria (PSA nadir + 2 µg/L). Overall, cancer specific and biochemical relapse-free survival rates were calculated by the actuarial method of Kaplan–Meier. Statistical analyses were performed using Graph Pad Prism version 4.0 for Macintosh (GraphPad Software, San Diego, CA, USA). The institutional ethics committee provided approval for this review.

Results

Table 1 summarizes the characteristics of the patients. All of them completed the treatment without interruption. The median PSA was 8.67 µg/L (range: 1.17-18.64), with 65% of the patients having Gleason score of 7. Clinically, 42% had stage T2.

TABLE 1. **Patient characteristics**

Characteristic	**% of patients**
Median age (range)	
71 years (51-83)	
Tumor stage	
T1	55
T2	42
Tx	3
Gleason score	
6	35
7 (3+4)	52
7 (4+3)	13
Serum PSA, µg/L	
< 10	57
10- < 15	36
15-20	7

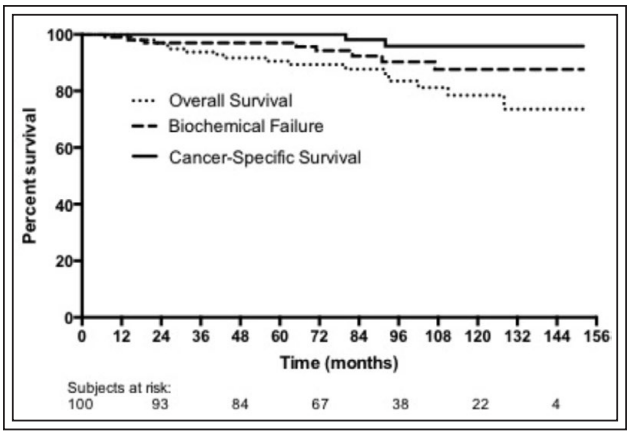

Figure 1. Actuarial survival curves and subjects at risk.

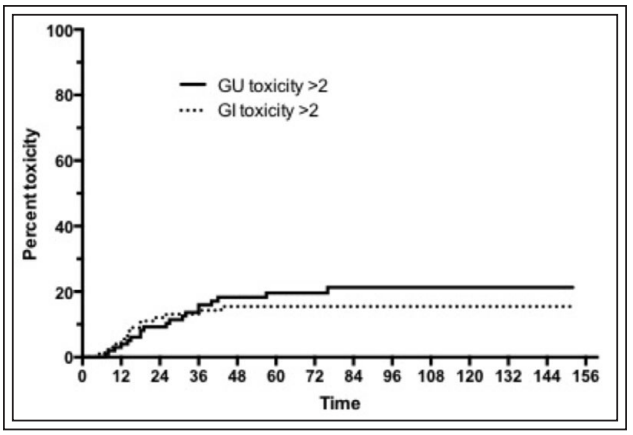

Figure 2. Actuarial distribution of late genitourinary (GU) and gastrointestinal (GI) toxicity grade ≥ 2 over time.

After a median follow up time of 80 months (range: 7-152), 8 patients developed biochemical failure at a median time of 68 months (range: 4-108). At the time of this analysis (August 2015), 16 patients had died with only 2 deaths related to prostate cancer at 80 and 92 months post treatment. The remaining causes of death include other cancers (GBM, mesothelioma, lymphoma, head and neck, rectum and stomach), vascular disease, pneumonia and one case of suicide.

The 5 year and 8 year actuarial biochemical freedom from relapse (bNED) survival rates were 96% and 90%, respectively. The 5 year and 8 year cancer specific survival (CSS) rates were 100% and 96%, respectively, whereas the 5 year and 8 year overall survival (OS) rates were 91% and 84%, respectively, Figure 1.

The late GU and GI toxicity rates are summarized in Table 2. Our actuarial distributions of late GU and GI toxicity grade ≥ 2 over time are shown in Figure 2. The worst grade ≥ 2 late GU or GI toxicities ever documented were 19% and 20%, respectively. Most toxicity resolved during follow up visits, and at the last follow up the incidence of grade ≥ 2 late GI or GU toxicity was of only 2% and 3% for each group, respectively. No grade 4 or 5 late toxicity was seen.

Discussion

The daily dose for conventionally fractionated radiotherapy in prostate cancer is between 1.8 Gy and 2 Gy. In moderate HypoRT the daily dose ranges between 2.5 Gy and 4 Gy. We report the long term results of patients with intermediate risk prostate cancer treated with HypoRT to a dose of 66 Gy in 22 fractions of 3 Gy. It is important to emphasize that those patients were treated with three-dimensional planning, the dose was prescribed to the isocenter and there were no predefined limiting dosimetric constraints for the organs at risk. The NCCN guidelines[5] were used for the definition of intermediate risk prostate cancer in this group of patients as described initially, meaning that patients clinically staged as T2c were also included in our cohort as intermediate risk prostate cancer.

With a median follow up of 80 months, our results compare favorably to other experiences,[9-12] as summarized in Table 3. There is a paucity of publications reporting long term outcomes in intermediate risk prostate cancer patients, as defined by the NCCN guidelines, treated with escalated doses of radiotherapy. Not infrequently, studies designed for

TABLE 2. **Percentage of patients related to grade of late genitourinary (GU) and gastrointestinal (GI) toxicity as seen at the last follow up and the highest grade seen at any time during follow up**

Toxicity	GU toxicity				GI toxicity			
	Gr 0	Gr 1	Gr 2	Gr 3	Gr 0	Gr 1	Gr 2	Gr 3
Highest	43	38	16	3	60	20	12	8
Last follow up	77	20	3	0	88	10	2	0

Gr = grade

TABLE 3. **Results for 8 year biochemical freedom from relapse (bNED), cancer specific survival (CSS) and overall survival (OS) rates of intermediate risk prostate cancer patients treated with different regimens of escalated dose radiotherapy and with follow up longer than 70 months**

	Hormonal therapy	Follow up (months)	bNED (%)	CSS (%)	OS (%)
RTOG 0019[9]	yes	98	82	98	81
RTOG 0126[10]	no	84	77	97	80
PCS 3 trial[11]	yes/no	75	77	97	75
CALGB[12] (7 year)	yes	73	81	n/a	87
McGill (current)	no	80	90	96	84

"intermediate risk" prostate cancer patients include different risk stratifications making comparison of results difficult. For instance, the RTOG 9910 trial, at the time of protocol development, was designed for patients with intermediate risk prostate cancer, but included patients of all risk groups as currently defined, allowing patients with PSA up to 100 µg/L, Gleason score from 2 to 10 and clinically staged T1b to T4.[13]

Table 3 compares our series with other published results with long term follow up that used escalated doses of different radiotherapy regimens and that included only intermediate risk prostate cancer patients, as per the NCCN definition. Lawton et al[9] reported long term results of the RTOG 0019 study that included only intermediate risk patients. They were treated with a combination of conventionally fractionated EBRT to a dose of 45 Gy in 5 weeks followed by a LDR brachytherapy boost (dose of 108 Gy). Importantly, 27% of them also received androgen suppression therapy (AST). The 8 year estimate of freedom from biochemical failure (bNED) was 82%. The 8 year OS and CSS rates were 81% and 98%, respectively. Hurwitz et al[12] reported the results of a similar CALGB study that included only intermediate risk patients who also received EBRT followed by brachytherapy boost and AST with an estimate 7 year bNED of 81% and an OS of 87%. Those results are similar to ours in spite of the use of a longer course of EBRT, a component of an invasive radiotherapy approach and the addition of hormonal treatment.

More recently, Michalski et al presented the results of the RTOG 0126 study that included only intermediate risk patients (but with a PSA upper limit limited to 15 ng/mL). Patients on the escalated arm of the trial received 79.2 Gy in 44 fractions (almost 9 weeks of EBRT) without hormones. The 8 year estimate bNED was 77%, with an OS of 80% and CSS of 97%.[10] This regimen was also a monotherapy, but given with standard fractionation making the duration of treatment twice as longer when compared to our regime of HypoRT.

The role of AST in the treatment of intermediate risk prostate cancer with escalated dose radiotherapy is unclear. The recently reported Quebec PCS III trial[11] included only intermediate risk prostate cancer patients, as defined in our study, and randomized patients to: 1) 70 Gy with standard fractionation of 2 Gy per fraction and 6 months of AST; 2) 76 Gy with standard fractionation of 2 Gy per fraction and 6 months of AST; and 3) 76 Gy with standard fractionation of 2 Gy per day but without any hormonal treatment. With a median follow up time of 75 months, the study showed a statistically better bNED for the two arms receiving AST, although there was no statistical difference in overall survival among the 3 arms (8 year OS estimate of 75%).[11] The role of AST in this group of patients is being further studied by the recently closed RTOG 0815 study which randomized patients to receive or not AST, both arms receiving escalated dose radiotherapy. HypoRT was not allowed in this study.

The definitive role of HypoRT for intermediate risk prostate cancer patients will probably be answered by the Canadian Prostate Fractionated Irradiation Trial (PROFIT Trial). This already closed study included more than 1200 intermediate risk prostate cancer patients (defined the same way as in our present study), and compared the hypofractionated regimen of 60 Gy in 20 fractions planned with IMRT, with the standard fractionation regimen of 78 Gy in 39 fractions.[14] Results should be forthcoming in the near future.

The potential for late toxicity has been a major concern for the use of hypofractionated radiotherapy regimens in patients with prostate cancer. With that

TABLE 4. **Percentage of the worst late gastrointestinal (GI) and genitourinary (GU) toxicity grade > 2 of prostate cancer patients treated with escalated radiation doses either with standard or hypofractionated external beam radiation therapy**

Author	Standard fractionation		Hypofractionation	
	GI toxicity (%)	GU toxicity (%)	GI toxicity (%)	GU toxicity (%)
Kuban 2008[17]	26	13		
Zietman 2010[18]	24	29		
Dearnaley 2007[19]	33	11		
Peeters 2005[20]	30	30		
Michalski 2015[10]	22	15		
Pollack 2013[21]			18	21.5
Arcangelli 2012[22]			17	14
McGill (current)			20	19

in mind, we prospectively scored GU and GI late toxicities in each follow up visit of our patients. The use of the CTC version 3 scoring table for adverse events applied in this study may not be an appropriate choice for comparison to other studies considering that this scoring system has been rarely used in published reports of late radiation induced toxicity in prostate cancer and because there are significant differences between the CTVv3 and the often used RTOG/EORTC late toxicity scoring system.[15] For instance, a grade 3 late rectal toxicity by the RTOG/EORTC scale is a severe side effect causing either rectal obstruction or a rectal bleeding so important that requires surgical intervention. We have never observed such severe complication in our cohort. Our rates of 19% for GU and 20% for GI worst grade ≥ 2 late toxicity seeing during follow up do not seem different from other series. An important point is that, at the last follow up, the majority of grade ≥ 2 late toxicity of our patients resolved being presented in only 2%-3% of the cases. Table 4 summarizes data of grade ≥ 2 radiation induced late GI and GU toxicity of prostate cancer patients treated with escalated dose with either standard or hypofractionated radiotherapy regimens. From the table, we appreciate a wide range of reported grade ≥ 2 late GI (17%-33%) and GU (11%-30%) toxicity. This variation suggests that the only optimal way to properly compare late toxicity between different radiotherapy regimens is through prospective randomized phase 3 studies.

There is no prospective randomized trial comparing conventional fractionation versus hypofractionation including only intermediate risk prostate cancer patients. Recently, two large randomized prospective trials reported in abstract form only compared moderate HypoRT versus standard fractionation. The RTOG-0415 trial performed in North America included only low risk prostate cancer patients treated with radiotherapy alone and compared 73.8 Gy in 41 fractions of 1.8 Gy (standard) to 70 Gy in 28 fractions of 2.5 Gy (HypoRT) on a non-inferiority design. At a median follow up of 5.8 years and 1092 patients in the study, outcomes with HypoRT were not inferior to the standard fractionation, including no significant differences in acute and late toxicity.[23] Dearnaley et al presented an update of the CHHiP trial[24] performed in the United Kingdom, in which 3216 patients with prostate cancer and different risk stratification (15% low risk; 73% intermediate risk and 12% high risk) received either standard fractionation of 74 Gy in 37 fractions of 2 Gy, versus HypoRT of 57 Gy in 19 fractions of 3 Gy each versus HypoRT of 60 Gy in 20 fractions of 3 Gy. Hormonal therapy was allowed for high risk disease. After a median follow up of 5.2 years, 57 Gy proved to be inferior to either 74 Gy or 60 Gy in terms of tumor control. However, there was no difference between 74 Gy and 60 Gy both in terms of tumor control or toxicity. These large studies confirm the safety of modern HypoRT in any prostate risk group.

Conclusion

Our long term experience with HypoRT alone in intermediate risk prostate cancer shows good tumor control with acceptable toxicity. With modern radiotherapy, the recent medical literature has shown that moderate hypofractionated radiation treatment

appears to have similar efficacy and toxicity compared to the more protracted conventionally fractionated course of EBRT.[3] It has even been suggested by recent NCCN guidelines as an alternative to conventionally fractionated regimens when clinically indicated.[16] However, until results of mature randomized trials are reported, HypoRT should be used cautiously in this group of patients. □

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