Late Toxicity In Patients Irradiated With IGRT For Prostate Adenocarcinoma

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Abstract

Introduction and Objectives. Results after external beam radiotherapy have significantly improved through dose escalation and the use of androgen deprivation therapy (ADT). The purpose of this study was to assess the long-term urinary, bowel, and sexual functions after image guided radiotherapy (IGRT).

Materials and Methods. Our study group included 85 men with localized prostate cancer (clinical classification T1–3 N0 (pN0) M0) treated with external beam radiotherapy guided on intraprostatic fiducial gold markers, between 2012 and 2017. The radiation dose ranged from 74 to 78 Gy (mean dose of 77,9 Gy); 72 men had received ADT for 6 to 36 months. Functional status was assessed at baseline every three months in the first year, and every six months from two to five years.

Results. After five years of follow up, 83% of patients presented with no symptoms of late rectal toxicity. Grade 2 gastrointesitanl (GI) toxicity was present in 12 patients (14,11%). Grade 3 proctitis was reported for two patients (2.4%). Comparing the urinary status before radiotherapy and two and five years after completing radiotherapy, 68%, respectively 61% of patients reported improvement of symptoms. One patient developed urethral stricture seven months after completion of radiotherapy. Erectile function defined as the ability to achieve an erection adequate for intromission was present in 62 patients (73%) before treatment. Out of these, 33 (53%) presented with erectile dysfunction 4 years after the treatment. There were no Grade 4 or fatal toxicity encountered.

Conclusion. In the modern era, treatment consisting of high-dose radiotherapy delivered with advanced radiotherapy techniques (intensity-modulated radiation therapy and image-guided radiation therapy) which significantly improve tumor control, can contribute to reduction of late toxicity.

Keywords: modern radiation therapy, prostate cancer, treatment toxicity

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Introduction and Objectives

External beam irradiation and brachytherapy, commonly used as curative treatments for prostate cancer, benefitted in the recent decades from important technological advances that increase the quality of the administered treatments [1-3]. We now know that dose escalation – by intensity modulated radiotherapy (IMRT), brachytherapy (BT), or a combination of IMRT and BT - allows for improved biological relapse free survival. Although this increased dose is more efficient in tumor control, normal tissues' tolerance limits the radiation dose that can be delivered safely, the rectum, in most of the cases, being the structure that limits the total prescribed dose due to potential side effects [4].

Early toxicity usually persists for up to 90 days after the end of treatment and the symptoms are usually self-limited. Even so, more severe acute toxicity predisposes patients to a higher risk of delayed radiation induced side effects [5]. Late toxicity persists or develops after 90 days from irradiation. The development of chronic proctitis after pelvic irradiation has been reported in 5% to 40% of patients [6]. Rectal bleeding is the most frequent manifestation of late toxicity and it is caused by the formation of neovascularization and telangiectasia [7, 8]. Severe bowel damage can also result in ischemia and fibrosis, which transpose into more severe clinical manifestations, such as fistulas, strictures, loss of anal sphincter compliance, and even rectal perforation. Although only few patients develop bleeding that requires transfusions, their daily activities and quality of life may be severely affected.

The accuracy of treatment in prostate cancer is particularly challenging because of the location of the prostate in the immediate vicinity of the bladder and rectum and its tendency to move depending on the degree of filling of the bladder and rectum and the pelvic muscles tonus. Modern radiotherapy concepts have improved outcomes, even for high-risk patients, with 10-year survival rates of approximately 95% at doses ≥75.6Gy. Modern irradiation techniques allow the fusion of MRI or PET/CT images into the treatment plan for precise definition of target volumes, including implanting radio-opaque fiducial markers in the prostate and daily evaluation of the treatment position with radiographic or CT images with an imaging system mounted on the linear accelerator for higher precision [1,2,3,9,10].

The goal of our study is to evaluate the digestive, urinary toxicity and sexual function in patients who have received image guided intensity modulated irradiation (IGRT) with doses ranging from 74 to 78 Gy in a five year period, between 2012 and 2017.

Materials and Methods

Between October 2012 and October 2017, 117 patients with clinically localized adenocarcinoma of the prostate, stage T1–3 N0 (pN0) M0 according to American Joint Committee on Cancer 2002, were treated with volumetric modulated arc therapy (VMAT) guided on fiducial gold markers – image guided radiotherapy (IGRT). Totally, 31 patients were lost from follow up: deceased (two patients); not willing to receive and to fill in the questionnaires (three patients), could not be contacted (26 patients). Thus, 85 patients could be evaluated for late toxicity.

Fiducial gold markers were implanted at least one week before CT simulation. We used three needles of 20 cm, each containing one gold marker of 1.2/3mm implanted transrectally using the biopsy canal from the endorectal probe under ultrasound guidance. The implants were positioned by the urologist, one in the apex, one in the middle and one in the base of the prostate. For CT planning, patients were positioned and treated in a supine position, with a knee and feet support (Vac-Lok/Dual Leg Positioner Cushion) to transfix the legs and pelvis. An IMRT treatment planning system (Pinnacle 3 TPS, version 9.6, manufactured by Philips Healthcare) was used for all treatment plans. The planning target volume included prostate and the base of seminal vesicles with or without pelvic lymph nodes, with a margin of 4-5 mm (anterior, posterior, laterals and cranio-, caudal) to compensate for pelvic organs movement during each irradiation fraction.

Patients were treated using two or three plans: first plan including prostate, seminal vesicles and lymph nodes – first five weeks, second plan for prostate and base of seminal vesicles - three fractions and the third plan for prostate only – last 9-11 fractions. When irradiating without lymph nodes, we used one plan for 28 fractions including prostate and base of seminal vesicles and the boost plan for prostate only. The prescribed dose was 78 Gy for prostate, 56 Gy for seminal vesicles and 50 Gy for lymph nodes. Dose inhomogeneity in the range of 95–107% in the planning target volume was fulfilled for the majority of patients. A 6 MV linear accelerator (Elekta – Synergy) has been used to deliver radiation. The prescribed dose was delivered in daily fractions of 2 Gy, five days a week.

Hormonal therapy had been given to 72 patients from the intermediate and high risk groups. Luteiniz-

ing hormone-releasing hormone analogue and oral antiandrogens (30 days) were initiated 2 to 3 months before irradiation and continued during the treatment course. Patients from high risk group received adjuvant androgen suppression—luteinizing hormone-releasing hormone analogue for 2- 3 years, while patients from the intermediate risk group for 6 months.

All patients were scheduled to be examined every three months in the first year and every six months from the second year. Late gastrointestinal (GI) and genitourinary (GU) symptoms and erectile function were recorded at each visit, using the Fox Chase modification of the Radiation Therapy Oncology Group (RTOG) and Late Effects Normal Tissue Task Force (LENT) criteria and self-assessment questionnaires approved by the World Health Organization (WHO-QOL-BREF) for post-treatment monitoring of prostate cancer patients: EPIC- Bowel for digestive toxicity, EPIC-Urinary for urinary toxicity and SHIM - Sexual Health Inventory for Men.

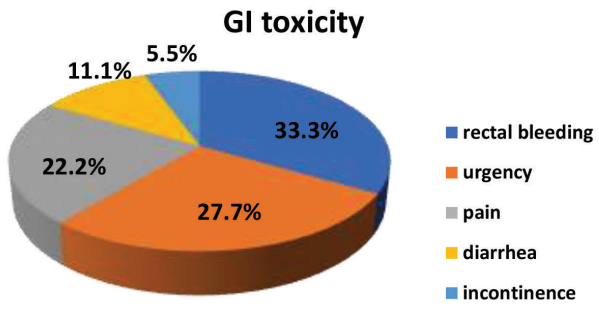


Figure 1. The 5-year actuarial risk of grade 2 and 3 GI toxicity 16.5 %.

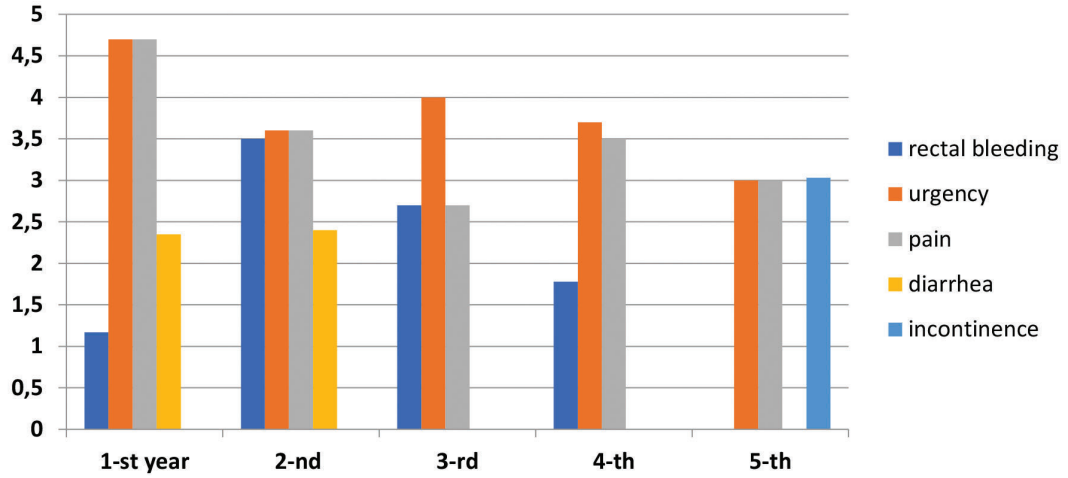


Figure 2. Prevalence and profile of grade 2 and 3 GI toxicity.

Results

Late gastro-intestinal (GI) Toxicity

Between six and 62 months, 83% of patients presented with either no late toxicity or with minimal symptoms (Grade 1 toxicity). Grade 2 GI toxicity, including rectal bleeding, urgency of bowel movements, diarrhea, chronic abdominal pain or rectal incontinence, developed in 12 patients (14,11%). Grade 3 proctitis with associated rectal bleeding, which required red blood cell transfusions or laser Argon photocoagulation as part of the management of this complication was reported for 2 patients (2.4%). There were no Grade 4 or fatal toxicity.

Overall, of the 12 patients with Grade 2–3 late toxicities, six presented this complication in the form of rectal bleeding, five patients with urgency, four patients with abdominal pain, two patients with chronic diarrhea and one patient with fecal incontinence. Endoscopic findings included telangiectasia and friability of the anterior rectal wall mucosa and ulceration. The onset of rectal bleeding was between 6-27 months from completion of radiation therapy with a median time of 19 months. The rate of fecal incontinence was low; the only case was reported 54 months after the completion of radiotherapy.

Late genito-urinary (GU) Toxicity

Twenty-one patients (24%) reported late Grade 1 and 2 GU toxicity. In general, these patients experienced symptoms of chronic urinary frequency and urgency: dysuria and nocturia (22%); pollakiuria (20%), dribbling (9%), incontinence (2%). Comparing the urinary status before radiotherapy and 2 and 5 years after completing radiotherapy 68%, respectively 61 % patients reported improvement of symptoms. One patient developed urethral stricture 7 months after completion of radiotherapy treated by internal optical urethrotomy. No grade 4 GU complications were observed.

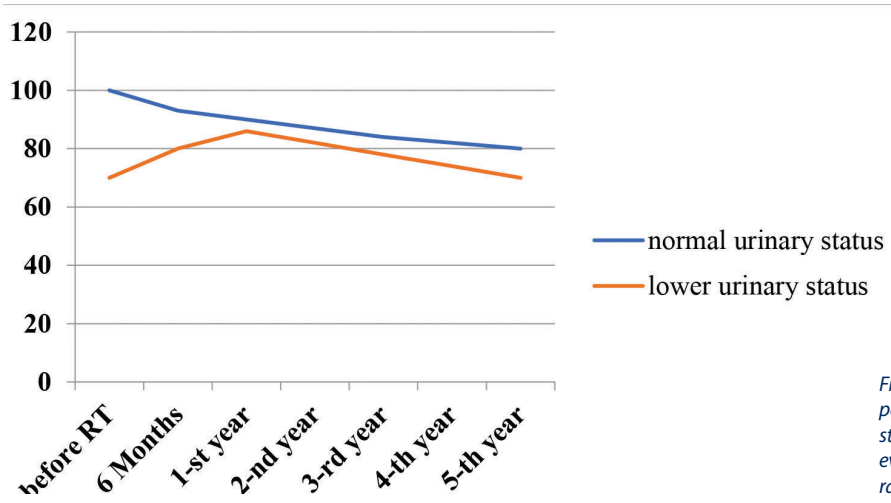


Figure 3. Longitudinal evaluation of patients with initial normal vs. lower urinary status. The baseline status is the urinary evaluation performed 1 week before starting radiotherapy.

Erectile Function

The erectile function, defined as the ability to achieve an erection adequate for sexual intercourse was present in 62 patients (73%) before the treatment start. Out of these patients, 33 (53%) presented with erectile disfunction 4 years after treatment completion. 66% of patients under 70 years of age with definitive RT (without ADT) have maintained their erectile function compared to 14% over 70 years. In the group of patients with RT and short course ADT, 23% of patients under the age of 70 recovered erectile function after treatment completion, while over 70 years only 7%. In the group of patients with RT and long course ADT, 18% of patients under 70 had erectile function and 11% after 70 years, respectively. Age and ADT were predictive factors for preserving erectile function

Discussion

Patients in our assessment group presented with some decline in sexual and urinary function over the duration of the study. At 4 years, the prevalence of erectile dysfunction was 65.8%. Age and ADT were predictive factors for preserving erectile function: nine (64.28%) patients under 70 years of age with RT alone have maintained their erectile function compared to only three (13.63%) patients over 70 years. Nonetheless, only nine (10.58%) patients reported being bothered with respect to sexual symptoms. The possible reasons for this finding include declining sexual interest with age, acceptance of sexual dysfunction over time, or both. Sanda et al.[11] found that 60% of patients who had undergone radiotherapy had poor-quality erections 2 years after treatment completion. Furthermore, 7% of those who had undergone radiotherapy had urinary incontinence[11]. Various investigators have reported similar short and medium-term declines in diverse populations within different health care systems [12-16]. The causes of these declines probably include both advancing age and additional cancer treatments. Indeed, many patients without prostate cancer have age-related urinary and sexual dysfunction. Litwin [17] who administered the University of California Los Angeles Prostate Cancer Index (UCLA-PCI) to a population of 598 men (median age of 73 years) without prostate cancer, found that 50% were unable to achieve an erection sufficient for intercourse and 32% were unable to achieve an erection sufficient for any sexual activity. Urinary incontinence was reported in 31% of men, with at least weekly urinary incontinence reported in 18%.

In patients with localized prostate cancer, the target volume for radiation therapy included prostate and seminal vesicles (mostly the base, less often the entire seminal vesicles). The area of clinically relevant dose always covers a portion of the rectum and it may cover a segment of the sigmoid bowel [18]. Curative effect of radiation therapy on prostate cancer and the development of rectal toxicity are dose dependent. Modern methods of radiation therapy are able to precisely conform the dose distribution to the 3D tumor shape. Therefore, it is possible to safely deliver doses in the range of 75–80 Gy, provided that the dose constraints for rectum and bladder are not exceeded [19-23].

Analysis of the time-course of late rectal toxicity showed that its incidence in our patients seems comparable with the ones published by other researchers, who reported plateau on the toxicity risk curve starting between 2 and 5 years after treatment [21,22,24]; prevalence of rectal symptoms in our study declined over

time from 11.7% at 1 year to 3.5% at 4.5 years for grade 2 symptoms and from 2.35% at 1 year to 0% at 4.5 years for grade 3 symptoms. Among rectal symptoms - rectal bleeding in our patients was 22.2% with grade 2 and 11.1% with grade 3 toxicity, respectively. Zelefsky et al. [21] from the Memorial Sloan-Kettering Cancer Center published the long-term data on late toxicity in patients treated with doses ranging from 66 to 81 Gy. They reported the manifestation of GI toxicity by means of rectal bleeding in >90% of affected patients. It is noteworthy that the incidence of grade 3 fecal incontinence was very low in our group of patients - persistent use of incontinence pads was necessary in only one patient out of 85 (1.17%).

Rectal bleeding was determinant for prevalence fluctuation. Rectal bleeding culminated at 1.5–2 years and subsequently declined. At least two factors are related to the decreasing prevalence of hemorrhagic radiation proctopathy after a maximum at 1–2 years. First, spontaneous regression of radiation mucosal changes, including multiple telangiectasis, has been observed during repeated sigmoidoscopy [25]. Second, local treatment of rectal bleeding is quite successful, especially with argon plasma coagulation [26]. Thus, patients who had rectal bleeding at 3 years were not the same patients with rectal bleeding at 1 year. Regarding abdominal pain and urgency, the same patients reported these symptoms at 1 and 3 years. Prevalence of fecal incontinence after radiation therapy showed evidence of progressive worsening of the anorectal function. Yeoh et al. [27] found a decline in rectal compliance and thickening of the external anal sphincter in patients after radiotherapy. Altered morphology of the sphincter may be associated with radiation-induced swelling and fibrosis of the surrounding connective tissue. The risk of fecal incontinence is connected to the radiation dose. It's been shown that patients with severe incontinence had higher minimum dose administered to the anal canal compared to continent patients or those with slight incontinence [28]. In our analysis, the low incontinence rate may be due to the small dose of irradiation in the anal canal, which was achievable by precise positioning using intraprostatic fiducial markers and daily verification with portal imaging.

Conclusion

Disease-specific health-related outcomes regarding quality of life are essential components of decision making for any man with prostate cancer [29-31]. Thus, in the modern era, treatment consisting of high-dose radiotherapy delivered with advanced radiotherapy techniques (intensity-modulated radiation therapy and image-guided radiation therapy) significantly contributes to reduction of late toxicity. Rectal bleeding is fairly manageable and the rate of fecal incontinence is low. During radiotherapy planning, maximal effort should be made to keep the doses to rectum and anal canal within tolerance limits.

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