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Late toxicity after whole pelvic irradiation in prostate cancer patient's irradiation

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ABSTRACT

Objectives: The study aimed to evaluate late toxicity after whole pelvic irradiation in prostate cancer patients.
Methods: A cross-sectional study of 15 non-metastatic prostatic cancer patients treated with radiotherapy were included. The analysis was conducted at Baghdad Radiotherapy and Nuclear Medicine Center, Baghdad Medical City Complex, Baghdad, Iraq, between December 2022 and May 2022. Data were collected retrospectively with the review of medical records. The following variables were studied: age, residency (address), smoking habits, TNM staging, histopathology, grades, GS, initial PSA concentration, ADT, treatment modality, the dose of RT, risk group, adverse effects including diarrhoea, pain, dysuria, anaemia, retention, haematuria, lymphedema, incontinence,urgency and sexual dysfunction, PTV95%, and OAR constraints doses.
Results: The mean age of patients was 68.47 ± 8.15 years, with a median age of 65 and most patients above 60 years. Most of the patients were smokers, 14 (93.3%). Most patients have a history of comorbid condition 14 (93.3%). All prostatic cancer cases in this study were adenocarcinoma. Stage I recorded in 3 (20%) patients, stage III in 6 (40%), and stage IV in 6 (40%). Regarding the Gleason score, the median GS in this study was 7. The mean of PSA was 39.09 ± 38.74 ng/mL (median=23 ng/mL). Yet, no retention, anaemia, hematuria, or lymphedema was recorded. Approximately the percentage of adverse effects was 26.7% diarrhoea, 26.7% pain, 6.7% BPR, 20% dysuria, 6.7% incontinence, 13.4% urgency, and 60% sexual dysfunction. Conclusions: To the best of our knowledge, this is the first study in Iraq to evaluate late toxicity after whole pelvic irradiation in prostate cancer patients.

Keywords: prostate cancer, toxicity, GIT, Prostate Specific Antigen (PSA)

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INTRODUCTION

Prostate Cancer (PC) is the second most prevalent malignancy in men after lung cancer, accounting for 375,304 deaths (3.8% of all cancer-related deaths) and 1,414,259 new cases (7.3% of all new cancer cases) worldwide in 2020 [1]. A 79.7% increase in PC incidence has been predicted by 2040 [2]. The incidence of PC is lower in Asia compared with other regions, like North America. The age-standardised incidence rate in Asia is 19.7 per 100,000, compared with 98.27 per 100,000 in the USA [3]. The diagnosis of PC is conventionally based on an elevated Prostate-Specific Antigen (PSA) level or trans-rectal-ultrasonography needle biopsy of the prostate [4]. The Magnetic Resonance Imaging (MRI) is recommended [5, 6]. There are established risk factors for PC, which include age, ethnicity, and family history. The risk of PC typically increases after the age of 55 years and peaks at age 70 years–74 years [7, 8]. African Americans are about 60% more prone to PC than Caucasians and first-degree relative is affected more [9-12]. Radiation therapy brachytherapy, radical prostatectomy, and Androgen Deprivation Therapy (ADT) are some of the known therapeutic options for patients with Prostate Cancer (PC), which are categorised according to severity and risk [13-22]. Patients at low or intermediate risk are the most common recipients of external-beam radiation therapy; high-risk patients undergoing prostatectomy also often get this treatment as an adjuvant. For high-risk individuals, a combination of ADT and radiation treatment may reduce the likelihood of systemic adverse effects and sexual dysfunction [23].

Chronic pelvic injury may affect several organs, including the anus, rectum, prostate, gynecologic organs, bladder, pelvic bones, small and large intestines, and pelvic bones. The most well-documented long-term complication is radiation enteropathy, sometimes known as -enteritis, which involves damage to the small intestine [24]. The objective of this research was to assess the occurrence of long-term side effects after complete pelvic radiation therapy in patients with prostate cancer.

MATERIALS AND METHODS

The study was conducted at Baghdad Radiotherapy and Nuclear Medicine Center, Baghdad Medical City Complex, Baghdad, Iraq,

between December 2022 and May 2022. After approval from the College of Medicine / University of Baghdad, a cross-sectional study of 15 non-metastatic prostatic cancer patients treated with radiotherapy was included. The patients' demographic information was documented, along with the pathologic characteristics and specifics of the primary tumour. The data was double-checked for every patient using their medical records and surgical histopathology reports, ensuring its correctness. The inclusion criteria are prostatic adenocarcinoma proven, GS ≥6, intermediate and high-risk groups, non-metastatic status, and patients fit ADT and surgery. The exclusion criteria are patients with metastatic lesions, patients unfit for high doses of RT, patients with prior pelvic surgery, patients with inflammatory bowel diseases, and patients with second primaries as bladder and rectum.

Data were collected retrospectively with the review of medical records. The following variables were studied: age, residency (address), smoking habits, TNM staging, histopathology, grades, GS, initial PSA concentration, ADT, treatment modality, dose of RT, risk group, adverse effects including diarrhoea, pain, BPR, dysuria, anaemia, retention, hematuria, lymphedema, incontinence, urgency and sexual dysfunction, PTV95%, and OAR constraints doses.

T-stage, GS and PSA stratify tumours into three prognostic groups of low, intermediate and high risk:

- low risk: T1–T2a and PSA _10 ng/mL and GS 6
- intermediate risk: T2b or PSA 10–20 ng/mL or GS 7
- high risk: T2c–T4 or PSA _20 ng/mL or GS 8–10.

Using measurements of radiation emitted through an item, the CT pore scanner (85 cm) (Philips ® 16 series) can estimate the inside of the object. In contemporary medicine, it is a crucial imaging method. It helps in disease diagnosis and therapy planning by providing a three-dimensional image of the inside of the body—the 2013 Linear Accelerator (InfinityTM and Synergy®) (core beam CT). Regarding treatment setup, the Elekta Synergy system was the first linear accelerator to use 3D picture guiding. Soft tissue visualisation using 2D, 3D, or 4D volumetric cone-beam imaging, frequent target tracking using 2D real-time fluoroscopic-like imaging, and standard and orthogonal planar imaging using 2D kV imaging are necessary. The Elekta Infinity system incorporates VMAT, or Volumetric Modulated Arc Therapy, into its all-encompassing therapeutic approach (VMAT). By adjusting the gantry speed and position, MLC leaves, dosage rate, and collimator angle, doctors using VMAT may "shrink wrap" the radiation around a tumour, thanks to the combination of high dose conformity and rapid treatment times. I am the TPS. Updated version of Monaco® Elekta HP 5. Plan your radiation treatments with pinpoint accuracy. Clinicians can provide the best possible treatment with Monaco's support. Monaco optimises the processes involved in plan generation and treatment delivery by using biological intelligence and standardised class solutions. It helps physicians understand patient biology while offering rapid and efficient planning—the latest XiO® Elekta system version 5. Elekta's XiO provides a powerful system for arranging particle therapy treatments. With XiO, you get all the features you love about Elekta treatment planning—automation tools, sophisticated dosage calculations, simple integration, and flexibility—for precise plans and seamless workflows. You get all the tools you need for planning and workflow, including virtual simulation, rapid contouring, fusion, and review, with XiO.

As a general rule, a CTV is defined as including the whole prostate, any potential extracapsular expansion, and the base or all of the seminal vesicles. The Roach formulas determine the risk of seminal vesicle involvement, and the target volume is set appropriately. Outlining the prostate begins on the mid-glands slice and continues posteriorly along Denovilliers' fascia and the fat plane that separates the prostate from the pelvic floor muscles. Every patient's CTV will include the base of their seminal vesicles. Central seminal vesicles, measuring 1 cm-2 cm, are located proximal to the prostate base, often at the same level as the middle lobe that bulges into the bladder. To account for physiological variations in the prostate's shape, position, and size, the PTV is defined with a 3D margin around the CTV. This margin includes an internal and set-up margin, compensating for uncertainties in the patient's position and set-up during planning and treatment. The rectum, bladder, small bowel, femoral heads, and prostatic plexus nerves situated next to the penile bulb comprise the Osseous and Appendicular Regions (OAR). Approximately 12 centimetres in length, the rectum begins at the inferior level of the ischial tuberosities. It continues at least 1 cm below the PTV to the recto-sigmoid junction above the PTV. Treatment of pelvic nodes must consider the small bowel when determining the target volume.

Statistical analysis was carried out using SPSS v24, and electronic data from the view capture tools (Monaco® Electa HP version 5) was used for data collection and processing (IBM Inc., Chicago, IL, USA). Data presented in a descriptive statistical format may include numerical values and percentages. The derived measures of central tendency, dispersion, minimum, maximum, and standard deviation for classifiable data. To quantify the predictive risk between the study's variables and GUT and GIT characteristics, odds ratios (OR) were used. Statistical significance was defined as a two-sided $p \leq 0.05$.

RESULTS

The results show that the mean age of patients was 68.47 ± 8.15 years, with a median age of 65 years. The majority of patients are above 60 years old (Table 1) (Figure 1).

Tab. 1. Patients' distribution according to age

Age (years)	No. (%)
<60	2 (13.4)
>60	13 (86.6)
Total	15 (100)

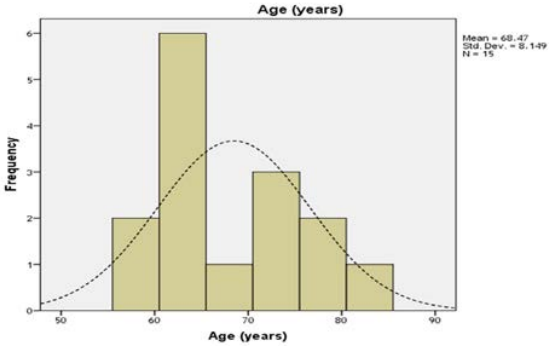

Fig. 1. Patients' distribution according to age

Tab. 2. Patients' distribution according to the address of patients

Address	No. (%)
Baghdad	8 (86.6)
Other	7 (13.4)
Total	15 (100)

Tab. 3. Patients' distribution according to smoking and comorbidity

		No. (%)
Smoking	Smoker	14 (93.3)
	Non	1 (6.7)
Comorbid	Yes	14 (93.3)
	No	1 (6.7)

Tab. 4. Patients' distribution according to cancer stages

Stage	No. (%)
II	3 (20)
III	6 (40)
IV	6 (40)
Total	15 (100)

Tab. 5. Patients' distribution according to GS

GS	No. (%)
6	5 (33.3)
7	5 (33.3)
8	3 (20)
9	2 (13.4)
Total	15 (100)

Tab. 6. Patients' distribution according to PSA (No.=15)

		No. (%)
PSA (ng/mL)	<1	3 (20)
	≥1	12 (80)
Risk group	High	12 (80)
	Intermediate	3 (20)

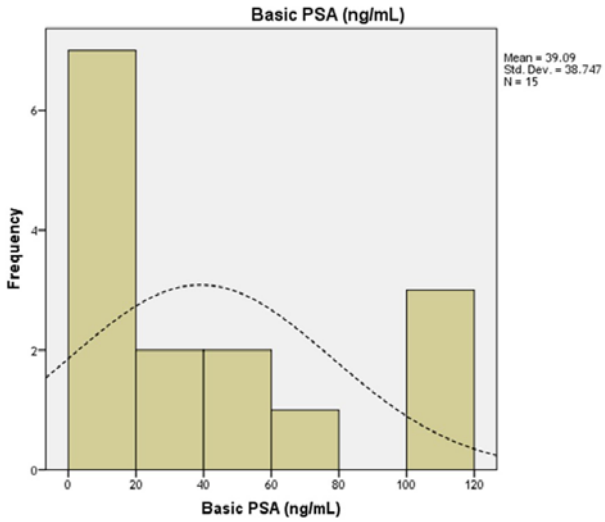

Fig. 2. Patient distribution according to PSA

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Tab. 7. Patients' distribution according to management

Management		No. (%)
Surgery	Yes	12 (80)
	No	3 (20)
RT dose (Gy/F)	70/37	14 (93.3)
	66/33	1 (6.7)

Tab. 8. Adverse effects of RT in this study

Adverse effects	No. (%)
Diarrhea	4 (26.7)
Pain	4 (26.7)
Bleeding per rectum	1 (6.7)
Dysuria	3 (20)
Incontinence	1 (6.7)
Urgency	2 (13.4)
Sexual dysfunction	9 (60)

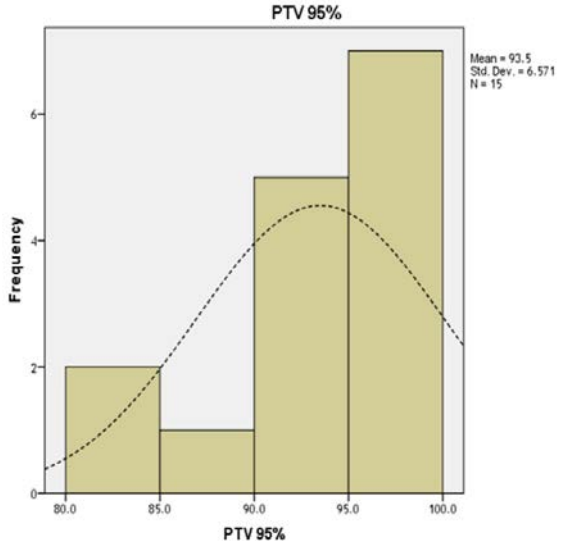

Fig. 3. Patients' distribution according to PTV95%

Tab. 9. The RT doses received by OAR

OAR	Mean ± SD	Median	Min	Max	Tolerance (max)/ mean	
	Dose (GY) / No. (%)					
Rectum	33.55 ± 15.54	35	11	69	≤65; 14 (93.3)	>65; 1 (6.7)
Bowel (intestine)	83.63 ± 69.71	38	0	268	≤250 cm^3; 14 (93.3)	>250 cm^3; 1 (6.7)
Bladder 50GY	55.91 ± 23.98	57	21	96	≤50; 7 (46.7)	>50; 8 (53.3)
Bladder 60GY	37.88 ± 21.43	33	13	91	≤25; 5 (33.3)	>25; 10 (66.7)
Bladder 65GY	30.97 ± 21.56	23	10	89	≤5; 0	>5; 15 (100)
Right femur	17.47 ± 7.75	-	0	53	≤50; 14 (93.3)	>50; 1 (6.7)
Left femur	17.34 ± 7.7	-	0	51	≤50; 14 (93.3)	>50; 1 (6.7)

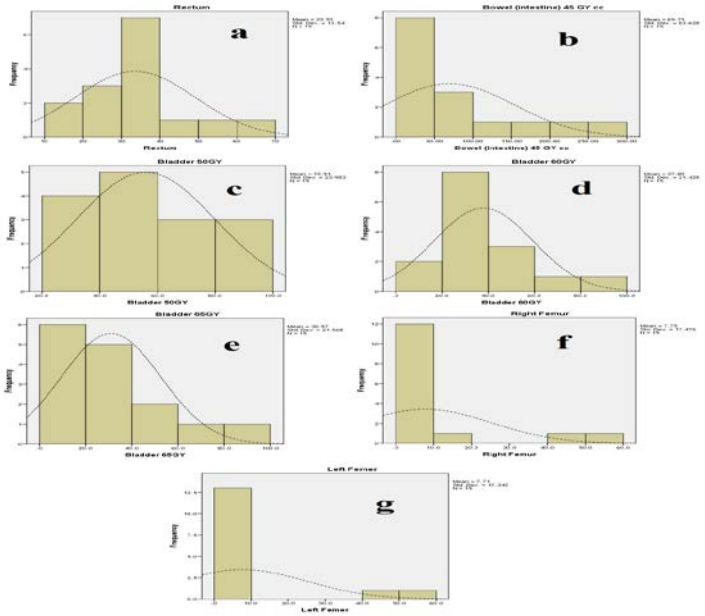

Fig. 4. The RT doses received by OAR

According to the patients' addresses, 13(86.6%) cases were recorded from Baghdad, while the rest were referred to the centre from other Iraqi provinces (Table 2).

Concerning smoking, the majority of patients were smokers 14(93.3%). In addition, most patients have a history of comorbid conditions 14(93.3%) (Table 3).

Prostatic cancer

All prostatic cancer cases in this study were adenocarcinoma in histology. Stage I recorded in 3(20%) patients, stage III in 6(40%), and stage IV in 6(40%) (Table 4).

Regarding the Gleason score, the median GS in this study was 7. The distribution of patients is listed in (Table 5).

Concerning PSA (ng/mL) concentration, 3(20%) cases were recorded with PSA below one at baseline. The rest were found to have high PSA (12, 80%). The mean of PSA was 39.09 ± 38.74 ng/mL (median= 23 ng/mL). Patients were subdivided into high-risk, 12(80%), and intermediate-risk 3(20%) (Table 6) (Figure 2).

According to the management of prostate cancer, all patients received hormonal therapy. Of 15, 12(80%) patients underwent surgical intervention. The standard RT dose used was 74Gy/37F in 14(93.3%) patients, and one case received 66Gy/33F, as shown in (Table 7).

Adverse effects of RT

All adverse effects of RT in patients with prostate cancer are listed in (Table 8). However, no retention, anaemia, haematuria, or lymphedema were recorded.

Radiotherapy

The overall mean PTV of 95% was 93.5±6.57 (median = 94%), ranging from 80% to 99.9% (Figure 3).

The mean, median and maximum with minimum doses, in addition to tolerance doses received by OAR, were listed in Table 9 and (Figure 4 (a-g)). Regarding tolerance, one rectum, one bowel, eight bladders (at 50GY), ten bladders (at 60GY), 15 bladders (at 65Gy), one right femur, and one left femur cases were received a dose above tolerance.

DISCUSSION

To the best of our knowledge, this is the first-time study in Iraq to evaluate late toxicity after whole pelvic irradiation in prostate cancer patients and to estimate the patients and cancer-related risk factors that cause late toxicity.

In this study, the mean age of patients with prostatic adenocarcinoma was 68.47 ± 8.15 years (median = 65 years), with most patients above 60 years. This agrees with Murthy et al. who studied 224 prostatic cancer patients and estimated that the median age was 66 years, whereas disagrees with Parry et al. and Jorgo et al., who found that the median age of two studies was 70 years [25-27]. This could be explained by the long-life expectancy of patients in these studies. According to research conducted in the southern region of Iraq, the condition became more common after age 50. It peaked in the 70-80 age group, with a median age of 71, according to Alhilfi [28]. In the United States, research indicated that around a third were in the 55-64 age bracket, another third was in the 65 years-75 years age bracket, about a quarter of the males diagnosed were 75 years or older, and the median age at diagnosis was 70 years [29].

About smoking, the majority of patients were smokers 14(93.3%). This could be suggested as a risk factor; however, no such relation is mentioned by [25–27]. Otherwise, Alhilfi reported that 66.03% of prostatic cancer were smokers. Smoking is associated with several aggressive tumour features and worse outcomes [28, 30].

In addition, most patients have a history of comorbid conditions 14(93.3%). Alhilfi recorded that 37 patients in his sample had hypertension, while 17 patients had diabetes. It is possible that the high prevalence of hypertension among elderly patients, who are more likely to have other health issues that are associated with prostate cancer, contributed to the numerous prior studies that found a link between hypertension and the development of prostate cancer, as well as a common androgen-mediated mechanism [31]. A lower risk of prostate cancer was found in patients with diabetes mellitus, according to previous research [32]. Parry et al. and Murthy et al. found 72.3% and 78.9% of individuals without diabetes and comorbidities, respectively. The research found that all instances of prostate cancer were classified as adenocarcinoma. Prostate cancer was the primary focus of almost all prior research [25–32].

Tumor stage I recorded in 3(20%) patients, stage III in 6(40%), and stage IV in 6(40%). These dislike findings of Jorgo et al. and Parry et al., reported stage T1-2 in 68%, T3 in 30%, T4 in 2%, N0 in 86% and N1 in 14%. Parry et al. reported stage T1 at 6.85, T2 at 18.75, T3 at 71.7% and 2.8%, N0 at 86.75 and N1 at 13.3%. Regarding the Gleason score, the median GS in this study was 7, in detail, 33.3% with GS 6, 33.3% with GS 7, 20% with GS 8, and 13.4% with GS 9. Disagreement with our, Parry et al. reported 5.1% GS 6, 33.6% GS 7, 25.9% GS 8, 33.8% GS 9 and 1.75 GS 10. Also, a different percentage was reported by Jorgo et al. as GS ≤6 in 20%, GS 7 in 38% and GS ≥ 8 in 42%. Murthy et al. mentioned that 9.8% GS6, 17.4% GS7 (3+4), 23.7% GS7 (4+3), 24.1% GS8, 21.9% GS9 and 3.1% GS10. Research conducted in the United States revealed that 46.3% of men with low-grade Gleason scores (2-6) had the illness, which is concerning since PSA screening has reduced the median age of diagnosis and increased the proportion of men identified with localised disease [33]. According to different research conducted in Turkey in 2014, the GS was six or less in 49.1% of instances, 7 in 27.8%, and > 7 in 20.6%, with six being the most prevalent [34].

Concerning PSA (ng/mL) concentration, 3(20%) cases were recorded with PSA below one at baseline. The rest were found to have high PSA (12, 80%). The mean of PSA was 39.09 ± 38.74 ng/mL (median=23 ng/mL). Patients were subdivided into high risk in 12(80%) and intermediate risk in 3(20%). One of the most significant aspects that suggests the advancement of prostate cancer is an increased PSA level [35, 36]. When PSA levels are more than 100 (ng/ml), all patients are considered to have advanced prostate cancer, according to Korean research. When combined with previous data showing that a larger proportion of patients had high-grade malignancy (poorly differentiated), the 77.35% PSA level >100 ng/ml discovered by Alhilfi increases the likelihood that these patients may have lymph node and distant organ metastasis. This aligns with Jeffrey H. Reese, a urologist at Santa Clara Valley Medical Center (SCVMC) in California, who shared his study's findings at the Annual Meeting of the American Urological Association. Reese confirmed that men initially diagnosed with PSA ≥100 ng/mL had poor survival and significant morbidity. The median first PSA level was 18 ng/mL (range=2-400), with 46% above 20 ng/mL, according to Jorgo et al. Our reported PSA level was lower than that of Murthy et al. who found a median of 32.2 ng/mL. The authors of prospective research that included 162 patients classified them as either high-risk (79%) or intermediate-risk (21%).

According to the management of prostate cancer, all patients received hormonal therapy. Of 15, 12(80%) patients underwent surgical intervention. The standard RT dose was 74Gy/37F in 14(93.3%) patients, and one case received 66Gy/33F. Similarly, Jorgo et al. reported that 90% of patients received hormonal therapy. Murthy et al. reported that 27.6% of patients underwent TURP. All treatment protocols depend on international guidelines such as ESMO, ASCO, ESTRO, and NCCN [37, 38].

In this study, several adverse effects after RT were recorded, yet no retention, anemia, hematuria, or lymphedema was recorded. Approximately the percentage of adverse effects was 26.7% diarrhoea, 26.7% pain, 6.7% BPR, 20% dysuria, 6.7% incontinence, 13.4% urgency, and 60% sexual dysfunction. Jorgo et al. reported late toxicities as GIT and GUT, which six patients (4%) presented grade 3 late GUT toxicity and eight patients (5%) grade 3 late GIT toxicity, and none of the patients experienced acute or late grade 4 side effects.

Fox Chase study participants at high risk for adverse events were given WPRT. While 303 patients were randomised to receive either 70.2 Gy in 2.7 Gy/fraction or 76 Gy in 2 Gy/fraction over 7.5 weeks in this superiority study, the conventional arm was allowed to treat the pelvis up to 56 Gy in 38 fractions and the hypofractionated group up to 50 Gy in 26 fractions. Two percent of patients in each treatment group had GIT grade 3 toxicities. In contrast, three and a half percent and four percent of patients in the other group experienced GUT grade 3 toxicities, respectively [39].

Their 5-year outcomes of substantially hypofractionated radiation treatment with SIB to the prostate were reported by Di Muzio et al. [40]. In a study that included 211 patients, 19.2% had late GU

grade ≥2 toxicity and 5.9% grade ≥3 toxicity, 17% had late GI grade ≥ two toxicity and 6.3% grade ≥3 toxicity, respectively. For a 5-year follow-up, Saracino et al. detailed the outcomes for 110 high-risk men who had WPRT and SIB for the prostate [41]. Three years ago, the incidence of grade ≥ 2 late gastrointestinal toxicity was 2%, and five years ago, it was 5%. Similarly, twelve years ago, the rate of grade ≥ 2 late gastrointestinal toxicity was 5%. Ninety patients at high risk who received significantly hypo fractionated radiation were the subjects of a study by Franzese et al. [42]. At the 25-month mark, 1% had grade 2 GI toxicity and 0% had grade 3, respectively. One percent of patients had late GU grade 3 toxicity, and six percent experienced grade 2 toxicity.

Neither group of patients in the experiment had late-stage IV gastrointestinal or gastrointestinal-related damage; according to Murthy et al., Late gastrointestinal toxicity of grade III was seen in one patient in the WPRT group but not in the PORT group. There was a 6.5% rate of grade II gastrointestinal toxicities in the WPRT group and a 3.8% rate in the PORT group (p=0.39). Neither group differed significantly from the other in terms of cumulative late gastrointestinal toxicity. At the final follow-up, 2.7% of patients in the WPRT group and 0.9% in the PORT group had late-stage gastrointestinal toxicity (grade II) (p = 0.32). Five patients (PORT=2, WPRT=3) had grade III late GU toxicity. A 17.7% vs 7.5%; p=0.03) was the considerably more significant rate of GU toxicity > grade II with WPRT. The grade III toxicity and grade II GU toxicity rates were comparable in the two groups (5.5% vs. 1.9%; p=0.32). However, two individuals in the WPRT arm did have grade III toxicity.

The overall mean PTV of 95% was 93.± 6.57 (median= 94%), ranging from 80% to 99.9%. Regarding tolerance of OAR in this study, one rectum, one bowel, eight bladders (at 50GY), ten bladders (at 60GY), 15 bladders (at 65GY), one right femur, and one left femur cases received dose above tolerance. To determine whether there were any changes in the intended dosage for the bladder and rectum during WPRT or PORT, Murthy et al. used post hoc Dose Volume Histogram (DVH) analysis on a subset of half of the patients in each arm (n =50 each). The WPRT group had a greater bladder volume after 30 Gy-40 Gy (V30, 60 ^ vs. 36%, p <0.001; V40, 41 % vs. 25 %, p <0.001). The volumes of the bladder and rectum exposed to 60-65 Gy were not significantly different between the two groups.

One research asked that all PTVs be treated with 95% of the specified dosage to cover 95% of the target volume (V95% > 95%). The volume of the rectum, bladder, hip joints, and ribs was limited to less than half, twenty percent, 65%, and 10% of the corresponding radioactive elements. Every patient has achieved the dosage constraints for the rectum and hip joints. Because their bladders were generally empty when they planned the CT scan, seven individuals (4.3%) had a V45 greater than 65 percent.

CONCLUSIONS

In conclusion, to the best of our knowledge, this is the first study in Iraq to evaluate late toxicity after whole pelvic irradiation in prostate cancer patients and to estimate the patients and cancer-related risk factors that cause late toxicity. Moreover, old age, smoking, comorbidities, advanced stages, high-risk group, elevated PSA and high GS are features of prostatic adenocarcinoma in Iraqi patients.

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