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An investigation of the risk factors associated with late toxicity after whole pelvic irradiation in patients with prostate cancer

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ABSTRACT

Objectives: The research sought to determine the prevalence of patients and cancer-related risk factors associated with late toxicity.

Methods: Fifteen individuals with non-metastatic prostate cancer who had radiation were included in cross-sectional research. The research was conducted at the Baghdad Radiotherapy and Nuclear Medicine Centre in the Baghdad Medical City Complex, Iraq. The study took place from December 2022 to May 2022. The data were acquired retrospectively via a thorough examination of medical records. The study examined the variables of age, residency (address), smoking habits, TNM staging, histopathology, grades, GS, initial PSA concentration, ADT, treatment modality, dose of RT, risk group, and adverse effects including diarrhoea, pain, dysuria, anaemia, retention, haematuria, lymphedema, incontinence, urgency, sexual dysfunction, PTV95%, and OAR constraints doses.

Results: In this study, several adverse effects after RT were recorded. The overall mean PTV of 95% was 93.5 ± 6.57 (median=94%), ranging from 80% to 99.9%. Old age patients were significantly more suffered from diarrhoea (OR=3.33; p=0.046) and dysuria (OR=5.5; p=0.037). Stages of the tumour, either II or III/IV, were a significant risk for pain (OR= 10; p=0.015) and sexual dysfunction (OR=2; p=0.02). High PSA levels significantly enhanced dysuria development (OR=2.5; p=0.05). A high dose of RT was significantly associated with sexual dysfunction (OR=2.8; p=0.04). Extensive PTV95% coverage can affect considerably the risk of diarrhoea (OR=3.6; p=0.033), pain (OR=3.6; p=0.033) and dysuria (OR=4; p=0.023).

Conclusions: As far as we know, this is the first investigation conducted in Iraq to assess the number of patients and the risk variables associated with cancer that contribute to delayed toxicity. Advanced stages, high PSA levels, high GS levels, and the presence of comorbidities characterise prostatic adenocarcinoma in Iraqi individuals. These patients are in the high-risk category because of their old age and smoking habits. Delayed Gastro-Intestinal (GIT) and Genito-Urinary (GUT) toxicities are anticipated to occur only with high doses of Radiation Therapy (RT). Old age, advanced stage, high PSA level, and extensive RT PTV 95% coverage considerably increase the likelihood of developing late toxicities.

Keywords: prostate cancer, toxicity, GIT, risk factors

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INTRODUCTION

Prostate Cancer (PC) is the second most common disease in males, behind lung cancer. It caused 375,304 deaths (3.8% of all cancer-related fatalities), and there were 1,414,259 new cases (7.3% of all new cancer cases) globally in 2020 [1]. By 2040, there is projected to be a 79.7% rise in the incidence of PC [2]. The prevalence of PC in Asia is comparatively lower than in other places, such as North America. The age-standardised incidence rate in Asia is 19.7 per 100,000 people, whereas in the USA, it is 98.27 per 100,000 people [3].

External beam Radiation Therapy (RT) targeting the prostate gland is linked to issues affecting both the Gastro-Intestinal Tract (GIT) and the Genito-Urinary System (GUT) [4–11]. Nevertheless, there is conflicting evidence on whether including PLN irradiation, which involves treating a greater area of normal tissue, leads to increased toxicity [12]. Increased gastrointestinal toxicity has been seen as a result of dose escalation 3D-CRT. Additional escalation of dosage is feasible in both situations. However, it carries the potential for heightened late problems, although it has shown enhanced control of localised tumours in prostate cancer without increasing rates of difficulties in normal tissues. However, although new radiation techniques have improved the ability to manage cancer in a specific area, they have not achieved the same degree of reduced complications as shown in prostate treatment [13].

The organs that are susceptible to chronic pelvic injury include the anus, rectum, prostate, gynaecologic organs, bladder, pelvic bones, and small and large bowel. The most extensively researched long-term consequence is radiation enteropathy, also known as radiation enteritis, which refers to damage to the small intestine [14]. A review of late sequelae of NRG protocols 85-31, 86-10, and 92-02 evaluating almost more than 3000 patients with a median follow-up of 10.3 years for living patients has been reported. All patients received WPRT to approximately 45 Gy and a prostate boost to about 70 Gy plus or minus short-term androgen suppression or long-term androgen suppression. The risk of late GI grade 3 or higher toxicity was 4%, 1%, and 3% for RT alone, short-term ADT and RT, and RT plus long-term ADT, respectively. Late

GU grade 3 or higher toxicity was 9%, 5%, and 6% for RT alone, short-term ADT plus RT, and RT plus long-term ADT, respectively [15]. Grade 5 (lethal) toxicity occurred in 3 of 2906 patients treated for a risk of approximately 0.1%. Data on late toxicity have been reported for the Phase III Canadian intergroup trial (ADT *vs* ADT plus RT), showing minimal additional toxicity via the use of radiation in patients with locally advanced prostate cancer [16, 17]. These data reinforce radiation safety for patients with locally advanced diseases and are consistent with other randomised trials of RT plus ADT [18].

The adverse events related to postoperative radiotherapy result from incidental irradiation of the bladder, rectum, femoral heads, and erectile tissues [19]. Early events occur during or within 90 days of radiotherapy completion, and late events occur or persist after that; the term "chronic" should be avoided because most late events resolve spontaneously or with minor intervention [20].

Late GUT adverse events include vesicourethral anastomotic stricture, urgency, frequency, dysuria, or hematuria. The incidence of late moderate-to-severe (grades 2 to 4) genitourinary adverse events by five years after radiotherapy is approximately 12% but may increase to 20% to 30% by ten years ; the severe (grade 3) adverse event incidence is 2% to 8% [21, 22].

Late GI adverse events may include increased or urgent stools, tenesmus, proctalgia, hematochezia, mucous discharge, and rarely rectal stricture or faecal incontinence. The incidence of late moderate-to-severe (grades 2 to 4) GIT adverse events by five years after radiotherapy is approximately 5% but may rise to 18% by ten years. The severe (grade 3) adverse event incidence is around 1% to 2% [23].

The objective of this research was to assess the incidence of late toxicity in patients and identify the cancer-related risk factors contributing to it.

MATERIAL AND METHOD

The research occurred from December 2022 to May 2022 at the Baghdad Radiotherapy and Nuclear Medicine Centre at the Baghdad Medical City Complex in Baghdad, Iraq. A cross-sectional study of fifteen patients with non-metastatic prostate cancer who had radiation treatment was approved by the College of Medicine/University of Baghdad. In addition to the patient's demographic information, the pathologic characteristics and details of the primary tumour were documented. Using the patient's medical record and/or surgical histopathology reports, we double-checked the data for correctness. To be eligible for inclusion, patients must have a history of prostatic adenocarcinoma, be in one of the risk categories (moderate or high), not have metastasised, and be candidates for Adjuvant Therapy (ADT) or surgery. Metastatic lesions, inability to tolerate high radiation doses, history of pelvic surgery, inflammatory bowel disease, and second primaries (rectum or bladder) are all reasons for exclusion from this study.

Medical records were reviewed to gather data. Age, residence (address), smoking habits, TNM staging, histopathology, grades, GS, initial PSA concentration, ADT, treatment modality, RT dose, risk group, adverse effects (such as diarrhoea, pain, anaemia, retention, hematuria, lymphedema, incontinence, urgency, and sexual dysfunction), PTV95%, and OAR constraints doses were all factors that were examined.

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.
- This study included patients treated with radioactive iodine after full or nearly full thyroidectomy.

The CT pore scanner (Philips® 16 series) is an essential imaging technique in modern medicine, providing a 3-dimensional view of the body for diagnosing illness and treatment planning. The Elekta Synergy system was the first linear accelerator to bring 3D image guidance into the treatment set-up process. Essential imaging tools include 2D, 3D, and 4D volumetric cone-beam imaging for soft tissue visualisation; 2D real-time, fluoroscopic-like imaging for targets that move frequently; and 2D kV imaging for standard and orthogonal planar imaging.

The Elekta Infinity system is a comprehensive treatment system that includes Volumetric Modulated Arc Therapy (VMAT), combining superior dose conformance and treatment speed. Monaco® Elekta HP version 5 is a high-precision radiotherapy treatment planning system that helps clinicians provide the highest standard of care by utilising biological intelligence and standardised class solutions.

The XiO® Elekta system version 5 provides a robust planning system for particle therapy treatments, offering automation tools, advanced dose calculations, easy integration, and a high degree of flexibility. It provides fast contouring, Fusion, Virtual Sim, Planning, and Review Tools in one.

The standard practice for prostate tumour therapy includes the whole prostate and any possible extracapsular extension, with either the base of or the entire seminal vesicles. The risk of involvement of the seminal vesicles is defined using the Roach formulae, and the target volume is chosen accordingly.

The study data were collected and processed using electronic data from the view capture tools (Monaco® Electa HP version 5), and statistical analysis was performed using SPSS v24. Descriptive statistics consist of numbers and percentages, while Odds Ratios (OR) were estimated predictive risk between study variables and GIT and GUT features. A two-sidd p-value of less than 0.05 was considered statistically significant.

RESULTS

Risk findings

The Odds Ratios (OR) between the study factors and the harmful impact of RT are given in Table1. Elderly individuals had a substantially higher incidence of diarrhoea (OR=3.33; p=0.046) and dysuria (OR=5.5; p=0.037). Tumour stages II or III/IV showed a strong correlation with pain (OR=10; p=0.015) and sexual dysfunction (OR=2; p=0.02). A higher PSA level was

shown to substantially increase the development of dysuria, with an odds ratio of 2.5 and a p-value of 0.05. The administration of a high dosage of radiation therapy was shown to have a significant p=0.023). Factors such as patient address, smoking status, comorbidities, GS (Gleason Score), high-risk group classification, and surgery do not affect the development of radiation therapy toxicities.

Tab. 1. Odds ratios between study variables and adverse effect of RT

	RT toxicities						
	Diarrhea	**Pain**	**BPR**	**Dysuria**	**Incontinence**	**Urgency**	**Sexual dysfunction**
	% (OR; p-value)						
Comorbid Yes *vs.* no	26.7 *vs.* 0 (0.714; 0.733)	20 *vs.* 6.7 (0.214; 0.267)	6.7 *vs.* 0 (0.93; 0.93)	20 *vs.* 0 (0.786; 0.8)	6.7 *vs.* 0 (0.93; 0.93)	13.3 *vs.* 0 (0.857; 0.867)	53.3 *vs.* 6.7 (0.571; 0.6)
Stage II *vs.* III/IV	6.7 *vs.* 20 (1.5; 0.64)	13.3 *vs.* 13.3 (10; 0.015)	0 *vs.* 6.7 (1.1; 0.8)	0 *vs.* 20 (1.33; 0.484)	0 *vs.* 6.7 (1.09; 0.8)	0 *vs.* 13.3 (1.2; 0.63)	20 *vs.* 40 (2; 0.02)
GS 6/7 *vs.* 8/9	13.3 *vs.* 13.3 (0.375; 0.4)	20 *vs.* 6.7 (1.7; 0.6)	0 *vs.* 6.7 (1.25; 0.333)	13.3 *vs.* 6.7 (1; 0.74)	6.7 *vs.* 0 (0.9; 0.667)	13.3 *vs.* 0 (0.8; 0.43)	40 *vs.* 20 (1; 0.713)
PSA 0 *vs.* >0	0 *vs.* 20 (1.5; 0.36)	6.7 *vs.* 20 (1.5; 0.63)	0 *vs.* 6.7 (1.1; 0.8)	6.7 *vs.* 13.3 (2.5; 0.05)	0 *vs.* 6.7 (1.09; 0.8)	0 *vs.* 13.3 (1.2; 0.629)	13.3 *vs.* 46.7 (1.43; 0.66)
Risk group High *vs.* intermediate	13.3 *vs.* 13.3 (0.1; 0.154)	20 *vs.* 0 (0.667; 0.36)	6.7 *vs.* 0 (0.92; 0.8)	13.3 *vs.* 6.7 (0.4; 0.516)	0 *vs.* 6.7 (1.5; 0.2)	20 *vs.* 0 (0.833; 0.629)	46.7 *vs.* 13.3 (0.7;0.659)
Surgery Yes *vs.* no	20 *vs.* 6.7 (0.3; 0.476)	26.7 *vs.* 0 (0.7; 0.524)	6.7 *vs.* 0 (0.92; 0.867)	13.3 *vs.* 6.7 (0.18; 0.37)	6.7 *vs.* 0 (0.923; 0.867)	13.3 *vs.* 0 (0.846; 0.743)	60 *vs.* 0 (0.31;0.143)
RT dose (GY/Fx) 66 *vs.* 74	0 *vs.* 26.7 (1.4; 0.733)	0 *vs.* 26.7 (1.4; 0.733)	0 *vs.* 6.7 (1.1; 0.933)	0 *vs.* 20 (1.27; 0.8)	0 *vs.* 6.7 (1.07; 0.933)	0 *vs.* 13.3 (1.16; 0.87)	0 *vs.* 60 (2.8; 0.04)
PTV95% <95% *vs.* >95%	20 *vs.* 6.7 (3.6; 0.033)	20 *vs.* 6.7 (3.6; 0.033)	6.7 *vs.* 0 (0.875; 0.533)	0 *vs.* 20 (1.75; 0.077)	6.7 *vs.* 0 (0.875; 0.533)	6.7 *vs.* 6.7 (0.857; 0.733)	40 *vs.* 20 (4; 0.023)

DISCUSSION

This research is the first investigation conducted in Iraq to assess the long-term side effects after pelvic irradiation in patients with prostate cancer. Additionally, it aims to determine the specific patient and cancer-related variables that contribute to developing these late side effects.

Elderly individuals saw a significant increase in diarrhoea (OR=3.33; p=0.046) and dysuria (OR=5.5; p=0.037). The presence of tumor stages II or III/IV was strongly associated with increased pain (OR=10; p=0.015) and sexual dysfunction (OR=2; p=0.02). The presence of a high PSA level was shown to have a significant impact on the development of dysuria, with an odds ratio of 2.5 and a p-value of 0.05. The administration of a large amount of Radiation Therapy (RT) was shown to have a significant correlation with sexual dysfunction (Odds Ratio=2.8; p-value=0.04). The presence of a large PTV95% coverage has a substantial impact on the development of diarrhoea (OR=3.6; p=0.033), discomfort (OR=3.6; p=0.033), and (OR=4; p=0.023). Factors such as patient address, smoking status, comorbidities, GS (Gleason Score), high-risk group classification, and surgery do not affect the development of radiation therapy toxicities. Parry et al. demonstrated no statistically significant variations in toxicity rates according to age, treatment year, T stage, N stage, or Gleason score (data supplement).

Late GI toxicity was the highest in the WPRT arm of the NHT cohort because the interaction between ADT and radiotherapy did not allow a straightforward assessment of the impact of WPRT on toxicities [24]. Urinary toxicity is known to be associated with higher doses to the bladder, neck and trigone and a history of previous TURP [25, 26]. Late cystitis rates were higher post IMRT in high-risk patients when a larger volume of bladder neck received >75 Gy, and widespread use of TURP in India could account for higher GU toxicity in both arms of the present study [27, 28]. Higher bladder DVH range has been associated with worse urinary obstruction and incontinence [29].

reported that the 3-year cumulative incidence of GI complications was 14% in patients with PPLN-IMRT and 14% in those with PO-IMRT. Men experienced 4.9 GI complications per 100 person-years in the PPLN-IMRT group compared with 5.1 in the PO-IMRT group. The 3-year cumulative incidence of GU toxicity was also comparable with 9% in the PPLNIMRT group and 8% in the PO-IMRT group.

Men experienced 3.2 GU complications per 100 person-years in the PPLN-IMRT group compared with 2.7 in the PO-IMRT group. Also, they adjusted competing risk regression analysis, which showed that the incidence of GI and GU toxicity was similar in both groups (sHR, 1.00, 1.10; p=0.97, 0.50).

RTOG-9413 RCT, which included 1,323 patients and published its results at various time points (2006, 2007, and 2018), showed that PPLN irradiation compared with PO irradiation was associated with an increase in late grade 3 GI toxicity (7% *vs.* 2%), according to the RTOG scale [30–32]. In contrast, the Groupe Etude des Tumeurs Uro Genitales GETUG-01 RCT observed similar findings, in which the observed increase in grade 2 GI toxicity with PPLN-RT was non-significant.

Concluded that WPRT with SIB to the prostate, seminal vesicles or positive pelvic lymph nodes is a feasible and safe technique for patients with intermediate and high-risk localised, locally advanced and node-positive prostate cancer. In addition, the rate of severe late GI and UG toxicities is low and comparable to rates with conventionally fractionated treatments.

CONCLUSION

To conclude, this research is the first investigation in Iraq to assess the long-term side effects of whole pelvic irradiation in prostate cancer patients. Additionally, it aims to determine the specific patient and cancer-related variables that contribute to these late side effects. Furthermore, prostatic adenocarcinoma in Iraqi patients is characterized by advanced age, smoking habits, presence of comorbidities, progression to advanced stages, belonging to high-risk groups, and exhibiting high levels of PSA and GS. Nevertheless, Late Gastro-Intestinal (GIT) and Genito-Urinary (GUT) effects are anticipated only with high doses of Radiation Therapy (RT). Ultimately, the combination of elderly age, advanced stage, high PSA level, and extensive RT PTV 95% coverage is strongly linked to an increased likelihood of experiencing late toxicities.

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