

Regional Differences in Histological Features of Bladder Cancer Diagnosed in Post-War Iraq

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Abstract

Objectives Exposure to chemical weapons and depleted uranium (DU) during multiple wars has a tremendous impact on public health in Iraq. This study conducted to evaluate the regional differences in the effects of these weapons on the histological features of bladder cancer (BC), a cancer form highly associated with environmental risk factors.

Patients and Methods

From 172 BC patients enrolled in the study 123 were living in the Kurdistan Region (KR) of Iraq and 49 were living in the Rest of Iraq (RI). Medical history, clinical examinations, biochemical investigation and Transurethral Resection of Bladder Tumour (TURBT) or Radical Cystectomy (RC) were performed. Specimens were collected for histopathological examination. SPSS program (V18) used for statistical analysis.

Results and Discussion The results showed that there are significant differences between the KR and the RI patients in terms of tumour grading and cellular features. Patient samples from the KR patients exhibit high percentage of well differentiated tumours, conversely RI exhibit high percentage of poorly differentiated tumours. Furthermore, histopathological examination showed that majority of tissue samples from KR were transitional cell carcinoma (TCC). The same was true for RI, though previously a higher proportion of tissue samples were squamous cell carcinoma (SCC) in RI.

Conclusion

The tumour grading and histopathology showed more advanced cancers in patients living in RI compared to those living in KR. This is because weapons exposure is correlated with cancer aggressiveness of the tumour. Sex differences were obvious as in Iraq only males were participating in military service.

Keywords: Bladder Cancer, Tumor behaviour, TCC, SCC, TURT, Radical cystectomy, Gulf war, Depleted Uranium, Chemical weapon, Post war area, IDP (Internally Displaced People), Kurdistan Region, Iraq.

Introduction

The worldwide incidence of cancer is increasing and it is a global problem ^[1]. Some cancer increases are due to lifestyle changes and an aging population; others are due to weapons and chemical exposure ^[2-4]. Iraq underwent two major wars during 1991 and

2003, in which different types of weapons were used, including DU. Since 1991 KR being protected independently from the rest of Iraq by the United Nation as a NO Fly Zone; so this region is not exposed to successive wars Iraq faced (Fig. 1).

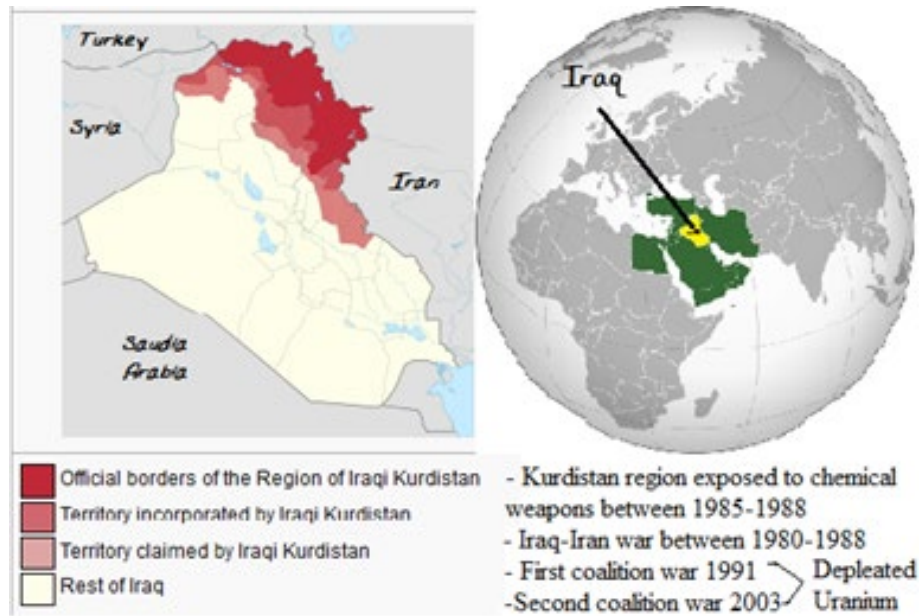


Figure 1: Geo-political background of subdivision of data to KR and RI.

After these wars, the diseases profile has changed in Iraq; new diseases have appeared and incidence of others has increased with marked regional variation. Occurrence of congenital anomalies, different chronic diseases and cancers with aggressive behaviour have emerged in RI but to a lesser extent in KR^[5,6]. Moreover, the number of children diagnosed with cancers and leukaemia has markedly increased and they are more often diagnosed in late stages^[2,3]. In addition, aggressiveness of several cancers in adults in RI has increased dramatically^[7,8].

DU is a highly toxic, radioactive by-product of Uranium enrichment process. It is called "depleted" because the content of the fissionable U-235 isotope is reduced from 0.7% to 0.2% during the enrichment process. The isotope U-238 makes up over 99% of the content of both natural uranium and DU. Contamination by DU can occur via wounding, ingestion or inhalation^[9]. Several in vitro and in vivo studies have shown that DU exposure can induce genomic instability in human cell lines and has demonstrated carcinogenic potential in nude mice^[10,11].

Bladder cancer is strongly associated with environmental risk factors e.g. smoking, toxic agents and radioactive substances^[12].

Till the end of the last century SCC was the predominant histological type of BC in Iraq due to endemic Schistosomiasis but now TCC is the predominant type^[13]. According to the latest WHO data published in April 2011 the age adjusted Death Rate is 7.55 per 100,000 of population ranks Iraq number 3 in the world^[14].

The objectives of this study were to determine the histopathology and presentation of BC in different regions of Iraq post war.

Patients and Methods

Patients were enrolled from the entirety of Iraq and split into two regions for the comparative purposes. The KR includes three Northern provinces in the north of Iraq. The inhabitants are Kurds

(majority), Turkmen, Assyrians, Chaldeans, Arabs and Armenians. The RI consists of the Middle and Southern provinces of Iraq and has a heterogeneous population, with the majority are Arabs. 172 (mean age 56 years) patients recruited with bladder tumours from 2nd January 2010 to 30th December 2012 at the Department of Urology, Rizgary Teaching Hospital, Erbil, Kurdistan Region, Iraq.

Assessment of outcome

Special questionnaire has been designed for this study. It included information about history, clinical examinations, biochemical investigations, TURBT and/or RC performed. Histopathological examination was done to determine the type, stage and grade of the tumour.

Statistical analysis was performed with the statistical package for social sciences (SPSS V18.0) and Microsoft Excel 2010 for configuration of data, tables and figures, comparison between groups done using independent sample t-test. Categorical data were described as frequency and percentage; comparison done by using Chi-square test. P value < 0.05 was regarded as statistically significant.

Ethical Issue

The study has been approved by the Ethics Committee of Erbil Directorate of Health. The research was conducted according to the Helsinki Accords. Both verbal and written consent have been taken from the patients after fully explanation of the study in their native language. The patients have rights to withdraw from the study at any stage.

Results

Among 172 patients aged 34-85 years with mean age of 56years (male 58 years, female 50 years). 142 (83%) were male and 30 (17%) were female (Table 1). The male to female ratio was 4.7:1.

Table 1: Number and percentage of patients gender participating in the study

Gender	No	%
Male	142	82.56
Female	30	17.44
Total	172	100.00

123 (72%) patients were living in KR while 49 patients (28%) reside in RI. 9% of patients in KR aged 70-89 years while 27% of RI patients were in this age group (Table 2).

Table 2: The features of BC were found to be at comparable levels for both patient groups.

Features	KR		RI		P value	
	No	%	No	%		
Patients	123	71.51	49	28.49		
Age Group	30-49	37	30.08	9	18.37	0.647
	50-69	75	60.98	27	55.10	
	70-89	11	8.94	13	26.53	
Stage	Non muscle Invasive	94	76.42	18	36.73	<0.001*
	Muscle Invasive	29	23.58	31	63.27	
Grade	1	42	34.15	6	12.24	<0.001*
	2	56	45.53	21	42.86	
	3	25	20.33	22	44.90	
Histo-pathology	TCC	113	91.87	42	85.71	0.212
	SCC	5	4.07	7	14.29	
	AdenoCa	3	2.44	0	0.00	
Operation	TURBT	114	92.68	24	48.98	<0.001*
	RC	9	7.32	25	51.02	
Weapon Exposure		62	50.41	49	100.00	<0.001*

Among KR patients 76% had non muscle invasive bladder tumours and only 24% had muscle invasive bladder cancer, where as 37% of patients from RI had non muscle invasive BC and 63% had muscle invasive BC (P value <0.001) (Table 2 Fig. 2).

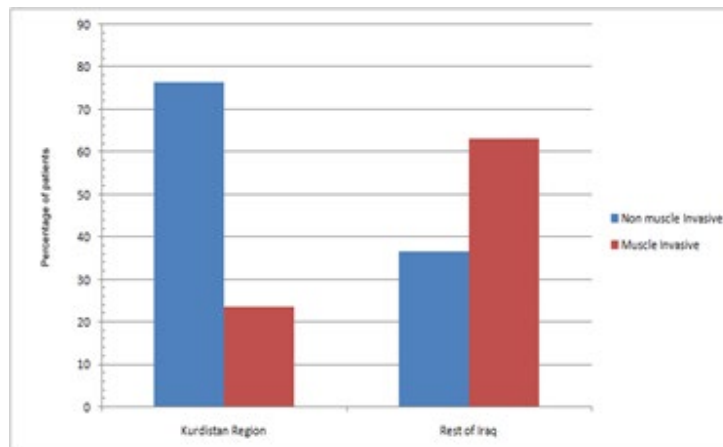


Figure 2: Percentage of degree of muscle invasion of BC in KR and RI.

Comparing tumour grading we found that 34% of KR and 12% of RI patients had well differentiated (G1) tumours while poorly differentiated (G3) was 20% of KR and 45% of RI patients (P value <0.001). Proportion of moderately differentiated (G2) was similar in both groups (Table 2 Fig. 3).

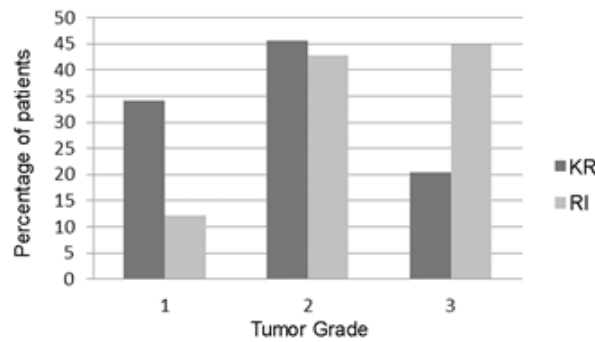


Figure 3: Grades of BC at time of presentation.

Histopathologically 92% of KR patients were TCC while 86% of RI patients exhibited TCC. Squamous cell carcinoma was 4% and 14%, respectively. Few cases of adenocarcinoma were found, all in the KR group (Table 2, Fig. 4).

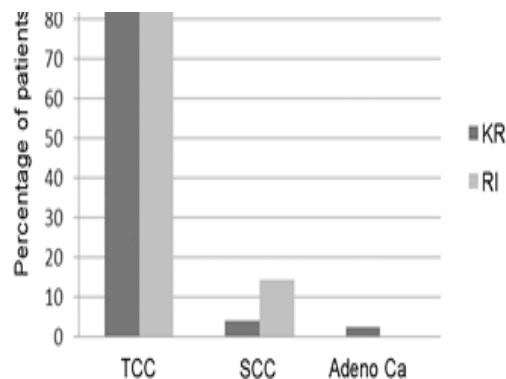


Figure 4: Histological types of BC

Discussion

This study was conducted to highlight the disproportionate occurrence of aggressive BCs in the post-war era Iraq. Different weapons were used during these aforementioned wars, including DU, which has contributed to the development of unusual diseases and cancers^[2,4], congenital anomalies^[5,7], cancers in young people^[11]. Mean age of patients included in this report was 56 years, which is relatively young group when compared with UK mean age; 73 years^[15] or even when compared with neighbouring country like Iran which is 65 years^[16]. Furthermore, male to female ratio was 4.7:1, which is higher when compared to a European population 3.3:1^[17] and Sweden 2.9:1^[18]. This higher ratio could be due to direct exposure of male patients who are the only gender eligible to military services in Iraq. This is besides of their environmental

pollution to which both genders are exposed.

We found that non muscle invasive BCs were 76% and 24% have muscle invasive among KR patients. However, results from Al-Bazzaz. have shown that 67% of BC non muscle invasive tumours^[20]. This discrepancy is might be due to the small sample size of the study. When analyzing RI patients we found a different trend, only 37% of people living in RI have non muscle invasive BC and 63% have muscle invasive BC. This could be due to regional DU exposure^[4]. In terms of tumour grading we found that 34% of KR cases were well differentiated (G1), while in RI the rate was 12%. Poorly differentiated (G3) was 20% and 45% for KR and RI respectively. The results show that there are vast dissimilarities between the two patient cohorts which are due to DU exposure (Table 3).

Table 3. Show the effect of weapon exposure on the grade and stage of the bladder cancer cases regardless of the region of inhabitant.

Bladder Cancer		Weapon exposure				P value
		No		yes		
		No	%	No	%	
Grades	1	23	37.7%	25	22.5%	0.028*
	2	28	45.9%	53	47.8%	
	3	10	16.4%	33	29.7%	
Stages	Ta	2	3.3%	3	2.7%	0.014*
	T1a	12	19.6%	10	9.0%	
	T1b	20	32.8%	23	20.7%	
	T2a	16	26.2%	26	23.5%	
	T2b	7	11.5%	31	27.9%	
	T3a	3	4.9%	9	8.1%	
	T3b	1	1.6%	9	8.1%	

*P value statistically significant.

Histopathological analysis showed 92% TCC and 4% SCC in KR patients. SCC is rare in Northern Iraq as Schistosoma. haematobium is not endemic [19,20] while in RI SCC was predominant till 1990 [13,19] while now TCC is predominant.

All of the patients living in RI had been exposed to DU in 1st Gulf war 1991 and 2nd Gulf war 2003 either directly as in males serving in military system for long periods or indirectly by aircraft bombing on civil areas and using contaminated water and vegetables as in females and retired males. This is also noticed among USA fighters served in Iraq and Afghanistan as they experienced more colon cancer and BC than USA population [15].

We conclude that there is a major difference in both severity and prevalence of BC between KR and RI, which may be due to DU exposure.

The limitations of this study were: the small patient cohort and smoking which may play a role in the development of BC but it is not related to our theme and approximately 80% of both groups were smokers.

We recommend that another study to be conveyed with a large cohort to compare the two regions in terms of both intensity and duration of exposure to DU.

Acknowledgment

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Authors contributions

Dr. Hussein provided patient data, Dr. Jalal is Pathologist who

examined and validated the samples, Dr. Khalid and Ismael performed data analysis and arrangement of figures. Dr. Dizeyi, Dr. Hussein and Dr. Qader, contributed with planning the study, writing and revision of the manuscript.

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