

## The Characteristics Women with Cervical Cancer Referred for Radiotherapy and /or Chemotherapy

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### ABSTRACT:

#### BACKGROUND:

Cervical cancer is the most common gynecologic cancer in women in the world, most arise from infection with human papiloma virus. Other host factors also affect the neoplastic progression following initial infection.

#### OBJECTIVE:

To determine characteristics of Iraqi women with carcinoma of the uterine cervix during the last 11 years in Iraq.

#### METHODS:

Retrospective study; done on records in Radiotherapy and Nuclear Medicine Hospital- Baghdad; 488 cases of cervical carcinoma referred for chemotherapy and or radiotherapy , from 1999 to 2009. Clinical and pathological data were reviewed and analyzed.

#### RESULTS:

The data that was obtained from the radiotherapy and nuclear medicine hospital showed that the women with cervical carcinoma constitute only 2.1% of total women with malignancies during 1999-2009. Highest ;were in 2003 and 2004. Largest proportion presented in late stage (62.32%)and only 37.67% with early stage. Squamous cell carcinoma counted 98.38 % and only 1.62% were adenocarcinoma . Median and mean age was 45-50. Median parity between 4 and 6. Majority of patients from Baghdad (43.02%) , Basra (10.93%)and lowest percentage from North; been collectively (10.46%).Only 6.55% had positive family history. (53.72%) with history of smoking; significantly associated with late stage. Most common clinical presentation was vaginal bleeding( 65.81%).The most common stage at time of presentation was stage II (36.51%). Most of referred patients had surgical interventions as total abdominal hysterectomy with bilateral salpingo-oophorectomy(sub optimal surgery) 60.93%.

#### CONCLUSION:

Most patients with carcinoma of cervix in Iraq presented in late stage due to absence of screening program.

**KEY WORDS :** squamous cervical cancer, human papiloma virus, radiotherapy.

### INTRODUCTION:

Worldwide; cervical cancer ranks second among all malignancies for female. Marked differences in the relative frequency of cervical cancer are observed throughout the world because of the differences in the availability of screening programs and risk factors<sup>(1)</sup>. It remains a leading cause of cancer-related death for women in developing countries. Approximately 500,000 new cases are diagnosed each year internationally, 80% of cervical cancers occur in developing countries<sup>(2)</sup>. The life time probability of developing cervical cancer is 1:128. Although

screening programs in US are well established, it is estimated that 30% of cervical cancer cases occur in female who had never have a Pap test<sup>(3)</sup>. The South Asian region harbors one fourth of the burden of cervical cancer<sup>(4)</sup>.

The first preliminary report about incidence of cervical carcinoma in situ in Iraq was reported, in Acta Cytologica; by Professor Kais Kubba<sup>(5)</sup>. Baghdad Cancer Registry for the period 1976-1982 notified that pattern of cancer occurrence resembles that in other Middle-Eastern populations in frequency of respiratory cancer and lymphomas, and apparent deficit of cervix cancer<sup>(6)</sup>.

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Beiki et al compared risk of gynecologic cancer among foreign-born women to the risk among those born in Sweden in a cohort study of 5.3 million women (18,247 had carcinoma of cervix) between 1969 and 2004, They found that risk of Iraqi immigrant women born in Iraq was lowest compared with those born in other countries<sup>(7)</sup>.

**Risk Factors** are:

1. Sexual activity: More than six lifetime sexual partners imposes significant increase<sup>(8)</sup>.

2. Sexually transmitted agents

Human papillomavirus (HPV) ;necessary in development of nearly 70% of cases of cervical cancer<sup>(9)</sup>. It is a heterogeneous group of double-stranded DNA viruses. Seventy seven different genotypes of HPV identified ;6, 11, 16, 18, 26, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 66, and 68 which infect anogenital tissues. Those infect human cervix fall into 2 categories; the low-risk type; HPV 6 and 11 are associated with low-grade squamous intraepithelial lesions (SILs) but never found in invasive cancer. The high-risk type; HPV 16 and 18 are found in 50-80% of SILs and in 90% of invasive cancers. Less common; types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 should also be considered carcinogenic<sup>(10)</sup>.

Human Immunodeficiency Virus (HIV) may put a woman at risk of HPV induced carcinogenesis. Herpes simplex virus 2, may play a causative role<sup>(3)</sup>.

3. Others: Lower Socioeconomic Predictors<sup>(11)</sup>, smoking (both active and passive)<sup>(12)</sup>. Women with seven prior full-term pregnancies have approximately fourfold risk and those with one or two have twofold risk compared with nulliparas<sup>(13)</sup>. In addition; long-term COC use may be cofactor.

In women who are positive for cervical HPV

DNA and use COCs; risks of cervical carcinoma increase by up to fourfold compared with women who are HPV-positive and never users of COCs<sup>(14)</sup>. Controversy on increase risk with lower intake of vitamins A, C, and E. carotenoids and folate<sup>(15,16)</sup>.

### AIM OF THE STUDY :

To explore characteristics of Iraqi women with carcinoma of cervix who were referred to Radiotherapy and Nuclear Medicine Hospital for radiation and or chemotherapy .

### PATIENTS AND METHODS:

A retrospective study done in Radiotherapy and Nuclear Medicine Hospital in Baghdad, Iraq , from April 2009 till April 2010. Approved by Iraqi scientific council of obstetric and gynecology.

We studied (488) incident cases of invasive cervical cancer occurring in Iraq from 1999 to 2009 for which a stage at diagnosis was available. Data from 1999 were used because; this was the most recent year for which all relevant data were available. Hospital records of patients with Ca.cx. from 1999-2009 were revised ,taking into consideration the followings: Age, the marital status, parity, residency, presenting symptoms and signs, histopathological and clinical staging, family history of malignancy, smoking, types of surgical intervention & modality of radio-and/or chemotherapy. Fifty eight cases were excluded from the study ;as fundamental data were missed from patient's records. The term (early stage) was used which refers to stage I to IIA while ( late stage) was beyond stage IIA.

### RESULTS:

Annual malignancy-case referral to Radiotherapy and Nuclear Medicine Hospital from 1999 to 2009 is showed in (Table 1).

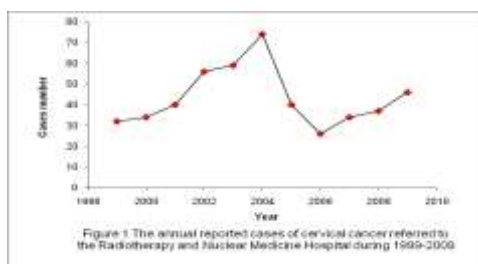
**Table 1: Annual malignancy case referral to Hosp.of Radiotherapy and Nuclear Medicine.**

year	Total patients Male and female	Female patients	Carcinoma of cervix patients (%)
1999	6209	2996	32 (1.068)
2000	7181	3290	34 (1.033)
2001	7559	3501	40 (1.142)
2002	7634	3241	56 (1.727)
2003	5767	2872	59 (2.054)
2004	7064	3524	74(2.099)
2005	6255	3005	40(1.331)
2006	4405	2014	26(1.290)
2007	3739	1978	34(1.718)
2008	5923	2252	37(1.642)
2009	5436	2855	46(1.611)

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Percentage of patients with Carcinoma of cervix, who were referred, did not exceed 2.1% of total women with malignancies during 1999-2009. Highest percents observed in 2003 and

2004. Annual records showed a peak of patients with Carcinoma of cervix referred in 2004 (Figure 1 and Table 2) respectively.



**Table 2: Distribution of cases referred to Radiotherapy and Nuclear Medicine Hospital.**

Year	Missed data Excluded from study	Informed data	Total
1999	0	32	32
2000	4	30	34
2001	4	46	40
2002	5	51	56
2003	12	47	59
2004	17	57	74
2005	0	40	40
2006	3	23	26
2007	1	33	34
2008	0	37	37
2009	12	34	46
Total	58	430	488

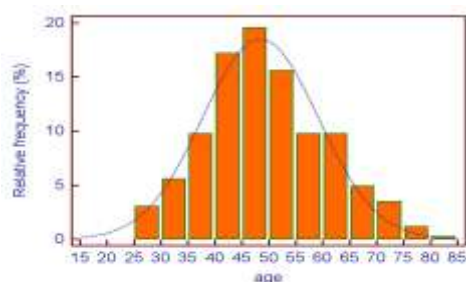
The median and mean age of patients referred for chemo. &/ or radiotherapy were of middle age

group, with higher median age group referred in 2005 and 2006; shown in Table 3, and Figure 2.

**Table 3: Median and mean age of patients referred for chemotherapy and/ or radiotherapy.**

Year	Total	minimum	maximum	median	Mean $\pm$ SD
1999	32	32	70	45	47.875 $\pm$ 9.714
2000	30	33	76	45	48.766 $\pm$ 11.880
2001	46	36	73	48.5	48.130 $\pm$ 11.443
2002	51	27	75	46	48.862 $\pm$ 11.842
2003	47	33	72	47	49.042 $\pm$ 10.206
2004	57	31	76	45	47.816 $\pm$ 11.580
2005	40	34	66	50	49.615 $\pm$ 9.552
2006	23	28	80	52	48.869 $\pm$ 14.666
2007	33	35	47	48	49.166 $\pm$ 9.454
2008	37	36	75	48	47.257 $\pm$ 12.093
2009	34	35	70	46	47.558 $\pm$ 10.554
Total	430	38	80	47	48.447 $\pm$ 11.064

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**Figure 2: Age distribution of Ca.Cx patients attended Radio. and Nuclear Medicine Hospital.**

Median parity ranged between 4 and 6 (Table 4). The highest with para 3 to 4; the peak incidence was 33.92% .

**Table 4: Distribution of carcinoma of cervix according to parity.**

	Total	median	Mean $\pm$ SD
1999	32	5	5.392 $\pm$ 2.671
2000	30	4.5	5.772 $\pm$ 2.893
2001	46	6	6.216 $\pm$ 2.926
2002	51	5	5.941 $\pm$ 3.064
2003	47	4	5.379 $\pm$ 2.583
2004	57	6.5	6.038 $\pm$ 3.180
2005	40	4	5.000 $\pm$ 2.938
2006	23	6	6.000 $\pm$ 2.972
2007	33	6	6.117 $\pm$ 3.018
2008	37	4	5.304 $\pm$ 2.851
2009	34	5	6.035 $\pm$ 2.714
Total	430	5	5.753 $\pm$ 2.863

Distribution of cases in respect to patient's residency and annual referral is as follows ;Majority from Baghdad (43.02%) then Basra (10.93%).The lowest from North of Iraq; collectively account (10.46%).

28 patient out of 430 (6.55%) had positive family history of malignancies, a median age of 46 year, a median parity number of 5 and residency distribution in Baghdad, Basra, Babil, Messan and Najaf.

231 patients out of 430 (53.72%) had history of smoking.

Most common clinical presentation was vaginal bleeding (65.81%, 283 out of 430 cases) ;either postmenopausal , intermenstrual , post coital bleeding or menorrhagia. Vaginal discharge is another presentation of different colour and sometimes it is offensive (Table 5). Pain is less frequently reported which a ccounted 10.69% (46 out of 430 cases).

**Table 5: Clinical presentations of carcinoma of cervix.**

Clinical presentation	No.	Percent
Vaginal bleeding		
Inter-menstrual	99	23.01
Post-menopausal	39	9.069
Post coital	65	15.11
Menorrhagia	80	18.60
Vaginal discharge (offensive, yellow, brown, watery)	70	16.27
Pain		
Abdominal	16	3.720
Pelvic	17	3.953
back	13	3.232
Urine retention	31	7.209

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During 1999-2009, only 1.62 % (7 out of 430) of patients had adenocarcinoma. The remaining were squamous cell carcinoma.

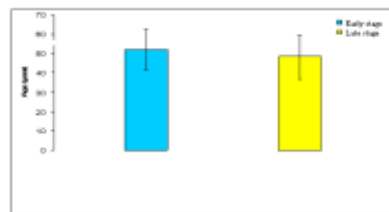
Commonest Staging of cervical carcinoma on presentation was stage II (36.51%); shown in Table 6.

**Table 6: Stages of carcinoma of cervix patients attending the Hospital of Radiotherapy and Nuclear Medicine during 1999-2009.**

Staging	No.	Percent
Stage I	91	21.16
Stage IA	17	3.953
Stage IB	74	17.2
Stage II	157	36.51
Stage IIA	71	16.51
Stage IIB	86	20
Stage III	82	19.06
Stage IIIA	45	10.46
Stage IIIB	37	8.60
Stage IV	71	16.51
Stage IVA	36	8.37
Stage IVB	35	8.13
Vault recurrence	29	6.74

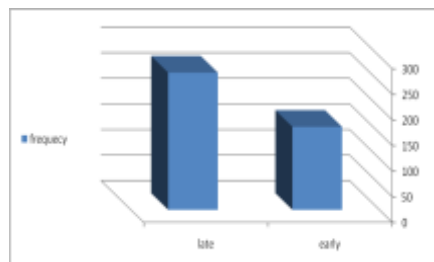
Further analysis revealed that the mean  $\pm$  SD of patient's age presented with early stage was  $51.92 \pm 10.88$  year (95% C.I. 46.75 to 57.09; n=162) that is not significantly higher than those

with late stage which amounted  $48.32 \pm 11.32$  year (95% C.I. 47.15 to 49.49, n=268), as showed in figure 3.



**Figure 3: Difference in age (mean $\pm$ SD) between patients presented with early and late stage carcinoma of cervix.**

Frequency of stage on presentation ; most cases presented in late stage; as shown in Figure 4.



**Figure 4: Frequency of patient presentation of early versus late stage.**

Smoking is significantly associated with carcinoma of cervix presenting with late stage. Odd ratio=4.0675, 95 % CI = 2.6867 to 6.1580, with P value <0.0001.

Table (7) shows mode of treatment performed to

patients. Most were subjected to total abdominal hysterectomy with bilateral salpingo-oophorectomy or just hysterectomy (total or subtotal) accounting for 55.81% (240 out of 430), Wertheim's operation accounts only 2.79%

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(12 out of 430 cases). Inoperable tumor account 41.39% (178/430). Most of cases were managed in hospital by radiotherapy (62.55%) followed by chemotherapy (15.11%) and combined

radiotherapy and chemotherapy (19.3%). P value was  $< 0.0001$  with  $\chi^2 = 58.5$ ; means that patients who received other surgical intervention were significantly higher than inoperable cases or those treated by Wertheim's hysterectomy

**Table 7: Management of referral cases of cervical carcinoma.**

	Radiotherapy	Chemotherapy	Combined Radiotherapy and chemotherapy	Not fit for radio-or-chemotherapy	Total(%)
Inoperable	75	38	57	8	178(41.39)
Wertheim's operation	12	0	0	0	12(2.79)
Other surgical intervention*	182	27	26	5	240(55.81)
Total (%)	269(62.55)	65(15.11)	83(19.3)	13(3.02)	430

\*Total abdominal hysterectomy and bilateral salpingo-oophorectomy, subtotal hysterectomy.

### DISCUSSION :

Annual reported cases of carcinoma of cervix in Iraq, referred for radio-and/or chemotherapy, are relatively low in comparison to other developing countries as in Tunisia, Missaoui et al 2010<sup>(17)</sup>. This study highlighted several points.

#### First;

Hospital records of carcinoma of cervix were so deficient related to socio-demographics, treatment received, staging and histopathology. Patients presented in late stage (62.36%) as compared to only 37.67% with early stage. This finding is similar to the study in Tunisia, Missaoui et al 2010; which showed patients presented in late stage (59%), as compared to only 36% with early stages<sup>(17)</sup>. In developing countries; most cervical cancers are diagnosed in the third or fourth stage<sup>(18)</sup>; emphasizing the need to reinforce early detection of this cancer and its precursor lesions<sup>(19)</sup>.

#### Second:

Annual reports of late stage carcinoma of cervix over 11 years showed a fluctuation related to situation in our country before 2003; due to sanction, and after 2003; due to post-war violence. Statistical analysis of reported cases during 1999-2003 and 2004-2009 revealed no significant differences.

#### Third:

Median age of patients presented with cervical cancer was late forty; in agreement with Munagala et al 2010, while less than the study of Missaoui et al 2010, of a mean age 52.1 years<sup>(16)</sup>. Age factor is not considered a prognostic factor in survival but; survival will be better if early diagnosis and progress in therapy were carried on<sup>(18)</sup>. Regarding parity; our study showed the median parity between 4 and 6, slightly less than that reported by Ikechebelu et al 2010, which

amounted to 6.8<sup>(12)</sup>. There is no doubt that parity plays a role as a risk factor in combination with others such as smoking and oral contraceptive pills<sup>(13)</sup>.

It is expected to find variation in annual records of late stage carcinoma of cervix; the lowest from North, including Erbil, Sulimania, Kirkuk, Dhok and Mosul; collectively account 14.17%; due to presence of radiation and nuclear medicine hospital in Erbil and Mosul.

Odd ratio of the smoking in our study was 4.06%; this confirmed a recent study of Samir et al 2010, who found that smoking exerts unfavorable effects on cervical neoplasia and it can be considered as a true biological cofactor<sup>(20)</sup>.

#### Fourth:

Most common clinical presentation was vaginal bleeding. In our study; intermenstrual bleeding it was (23.01%). Unlike Ikechebelu et al 2010; where the common clinical feature as post-menopausal bleeding (84.0%)<sup>(12)</sup>. Presence of other clinical signs and symptoms may give a clue for progressive, late stage and metastases of carcinoma of cervix<sup>(21)</sup>.

In this study showed that majority of cases were late stage. Reasons for this observation: 1. Poor awareness and utilization of cervical screening test contributed hugely<sup>(21)</sup>. 2. Majority of working health professionals are not adequately equipped with knowledge concerning cervical cancer<sup>(22)</sup>. 3. Vaccination program against human papilloma virus is not available in Iraq. Vaccination is highly effective in preventing high grade precancerous associated with the human papilloma virus; especially in countries where screening program is poor<sup>(22,23)</sup>.

The present results explore that 41.39% cases presented with advanced inoperable cervical cancer, a figure responsible for high morbidity and mortality rate<sup>(24)</sup>. In our study 98.38 % were squamous cell carcinoma & only 1.62% were adenocarcinoma; in agreement with Missaoui et al 2010; were 90.5% SCC and 7.3% of adenocarcinoma<sup>(17)</sup> and Kokawa et al 2010; where squamous cell carcinoma was 80.7% and adenocarcinoma was 19.3 %<sup>(25)</sup>. Our study had several limitations; First; not all patients with cervical cancer were referred to Radiotherapy and Nuclear Medicine Hospital, so not reported. Second; we are not able to assess earlier stages of cervical cancer; as in situ, because they are not reportable to the hospital. Degree of details in administrative data were also limited (e.g. cancer staging system was not as complete as the TNM (tumor nodes metastasis). system, and incomplete list of co morbid conditions in discharge abstract).

### CONCLUSION:

Most patients with carcinoma of cervix in Iraq presented in late stage due to absence of screening program.

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