

## Review of Epidemiologic and Clinicopathologic Features of 403 Hepatocellular Carcinoma (HCC) Patients

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### ABSTRACT

**Objective:** To evaluate the epidemiologic and clinicopathologic features of HCC at NCI, Cairo.

**Methods:** Through the NCI information network, Pathology network and review of log books of Medical Oncology Outpatient Clinics, 681 HCC patients were diagnosed and/or treated at NCI, between 1993 and 1999. Of them 403 records were evaluated retrospectively.

**Results:** The frequency of HCC cases attending NCI steadily increased from 1993 up to 1997 during which relative frequency reached 3.88% of all solid tumours. This was followed by decrease in both number and percentage of HCC in 1998-1999. Median age was 56.0 (18-80) years. Male to female ratio was 2.84:1. Majority of patients (> 97%) came from around the Nile River. Farmers constituted 23.1% of cases. Forty nine percent of patients were smokers and 25.7% were diabetic. Bilharziasis was prevalent in 71.4% and cirrhosis in 86.7% of cases. Twenty-one percent of cases were metastatic at first presentation, mainly intra-abdominal. Tumour burden was greater than or equal 50% of liver size in 67.7% of cases, lesions were multiple in 50.5% and bilateral in 37.4% of HCC patients. Estrogen receptor (ER) status was positive in 14/50 (28%) of HCC patients. Serologic markers of hepatitis C virus (HCV) and/or hepatitis B virus (HBV) were positive in 93.2% of tested patients. Management of HCC was variable and most cases received supportive treatment (49.4%). Overall survival was significantly related to modality of treatment, being best with combined adriamycin with tamoxifen (median 7 months) and lowest (median one month) with non-specific therapy,  $p < 0.001$ .

**Conclusion:** HCC showed an increasing trend in the past few years that could be attributed to more exposure to different risk factors. Active immunization against HCV and HBV early in childhood and population at high risk is important. Strict environmental sanitary measures should be applied. Screening of patients, with chronic HCV and/or HBV with or without cirrhotic liver for earlier detection of small lesions and the choice of more effective line of therapy is recommended.

**Key Words:** Hepatocellular carcinoma (HCC) - Epidemiologic - Clinicopathologic - Survival.

### INTRODUCTION

Hepatocellular carcinoma (HCC) is one of

the most common malignancies in the world and it emerges in cirrhotic liver mostly post hepatitis [3,20]. It is the 6th most common cancer of men and the 11<sup>th</sup> most common cancer of women worldwide [27]. HCC causes an estimated 1250,000 deaths every year worldwide [28]. Although, HCC show geographical differences in frequency with highest incidence in Southern Asia and Subsaharan Africa, yet the behavior in Egypt is similar to the western countries with an overall frequency of 2.3% among other types of cancer [6]. There is an apparent increase in the number of HCC patients attending the various oncology centres in Egypt and all over the world [26]. The annual report of cancer registry of metropolitan Cairo Area (1976 to 1980) had shown rising incidence of primary hepatic malignancies from 1.5 to 2% of total cancers [11]. El-Zayyadi et al. [9] reported 6850 cases of chronic liver disease, the prevalence of HCC among them was 5.4% with a male: female ratio of 4:1. In the same series, 66% of patients were rural and 33% urban, history of bilharziasis was present in 63.2%, HCV-Ab was positive in 73.3%, HbsAg was positive in 16.3% and combined infection of both viruses in 7.2% of patients with only 3.2% of HCC patients negative for both viruses. Because the clinical picture is very variable, the patient may be completely asymptomatic and the tumour is diagnosed incidentally. Alternatively, the presentation may be so florid with uncompensated liver failure [28]. Despite the enrollment of early detection plans, HCC is still diagnosed at an advanced stage when potentially effective treatments such as surgical resection, hepatic transplantation, ethanol injection and transarterial embolization are precluded [25]. Under such circumstances chemotherapy is the most widely applied option. However, the search for other

useful therapeutic approaches is necessary. Prognosis of advanced HCC is grave with a median overall survival of 6 months from onset of symptoms [19]. The aim of this work is to study the epidemiologic and clinicopathologic features of HCC cases at NCI, Cairo between 1993 and 1999.

## PATIENTS AND METHODS

In the period from the beginning of January 1993 to the end of December 1999, 681 cases of hepatocellular carcinoma cases attended NCI, Cairo either for diagnosis and/or treatment. Lists of pathologically proved cases were elaborated through both the Network Information System of the NCI and local network of the pathology department. Because most of HCC patients come at later stage of disease, they are treated with chemotherapy. So, many of the cases were approached through records of the outpatient medical oncology clinics. Twenty patients were not diagnosed through cytologic or pathologic specimens, but only through high serum level of AFP, clinical and radiologic features according to Donato et al. [4]. Lists of patients' names, year of diagnosis and hospital numbers were matched using the computer to avoid duplication of data.

Minimum data set within the patient record were predefined before collection of data to include a record in this retrospective study. It included the following: patient's name, hospital number, year of diagnosis, age, sex, occupation, residence, complaint, symptoms and signs and tool(s) of diagnosis.

Unfortunately, 278 records did not fit this requirement or were not found in the archive. So, a total of 403 records were reviewed for the following:

- 1- Epidemiologic data: age, sex, occupation, residence, time to first presentation, special habits and treatment of other medical diseases.
- 2- Clinical data: symptoms, signs, tool of diagnosis, Child's Pugh classification, liver and kidney functions and line(s) of management.
- 3- Radiologic data: for site of tumour, multiplicity of lesions, tumour burden (through abdominal ultrasonography (US) and/or computerized tomography) and metastasis at first presentation aided by chest X-ray.
- 4- Pathologic data: Bilharziasis, cirrhosis, tumour grade and tumour markers (immunohistochemistry).

- 5- Pattern of markers including alpha fetoprotein and hepatitis markers for hepatitis C and hepatitis B viruses.

Completeness of data was out of question in this retrospective study. So, the total number of valid (unmissed) data will be shown in parenthesis attached to variables with missing data.

- 6- Follow-up data to estimate overall survival.

### Statistical analysis:

Statistical package for social sciences, (SPSS, version 9.0) was used for data management. For comparing median of several groups, Kruskal Wallis ANOVA was used. Chi-square was used for testing proportions independence. Kaplan Meier method was used for estimating survival and Breslow test for comparing curves. *p* value less than 0.05 was considered statistically significant [15].

## RESULTS

**Demographic features** Fig. (1) shows total number of patients per year of diagnosis and the relative frequency to total solid tumours in the same period. Frequency of HCC increased steadily from 1993 (75 cases) to 1997 (172 cases) then started to decrease afterwards. Relative frequency was between 2.54% and 2.96% and it reached a peak in 1997 (3.88%), then decreased in the following years. Age ranged from 18-82 with a median of 56 years. Male to female ratio was 2.8:1. Table (1) shows distribution of cases according to residence, age and sex. About 2/5 (39.2%) of patients were residents of the Metropolitan Cairo Area, 1/3 (29.9%) from Delta and 1/5 (19.9%) from Middle Egypt. Age distribution in the 5 regions specified in table (1), did not differ significantly, the lowest median age was from Delta (53.0 years) and the highest in Upper Egypt (58.0 years), *p* value = 0.43. Male to female ratio varied from 2.2:1 in Middle Egypt to 5:1 in Alexandria, New Valley and Suez canal region with no statistically significant difference. Table (2) shows that farmers constituted 23.1% of patients and housewives 24.9%. Cigarette smoking was a habit in 49.4%. Diabetes mellitus was prevalent in 25.7% (56/218) of patients.

**Clinical presentation and tumour related features** Median time from first complaint till presentation was 3 months (3-730 days). Eighty percent of patients presented with abdominal pain and 26% with abdominal swelling. The rest came with different gastrointestinal and

general manifestations. At presentation, 85.6% had enlarged liver, 27.7% had splenomegaly, 26.3% with ascites, 10.9% with jaundice and 5% with shrunken liver. Diagnosis of HCC was proved histologically in 255/403 (63.3%) of patients while 31.9% were diagnosed through cytology and 5% as having AFP level > 350 ng/ml. According to Child's classification 184/372 (49.5%) were classified as class I, 47.6% class II and 3% class III, table (3). Twenty-one percent of cases were metastatic at first presentation mainly intra-abdominal. Bilharziasis was prevalent in 71.4% and cirrhosis in 86.7% of cases.

Radiologically, lesions were multiple in 50.5% and bilateral in 37.4% of cases. Tumour burden was less than 50% of liver size in 32.3% of cases, table (4). Estrogen receptor status (using monoclonal antibodies) was positive in 14/50 (28%) of HCC patients.

At presentation 103/160 (64.4%) were HCV positive (HCV Ab, ELISA), 17.5% HBV (HbsAg and HBsAb) positive and 11.2% with combined positivity leaving only 6.8% negative

for both markers, table (5). AFP (I.U/L) was > 350 ng/ml in 45.1% of cases (93/206).

#### Modalities of treatment and survival:

Median observation time from starting treatment till death of patients or lost follow up was 2 months in the whole study group. Overall survival was compared according to different modalities of treatment as described in table (6). Median survival time was 1 month with no specific treatment, 4 month with adriamycin, 3 month with tamoxifen, 7 months with combined adriamycin and tamoxifen, 4 months with chemoembolization, 3 months with surgery and 2 months with other treatments. Overall comparison gave a highly statistically significant difference between the groups,  $p < 0.001$ . On pairwise comparisons it was found that: with no specific therapy overall survival is significantly lowered than all modalities used. On the other hand, though combined adriamycin and tamoxifen gave significantly high median survival than other lines, it did not differ significantly from surgery or chemoembolization (Fig. 2).

Table (1): Age and sex distribution among 403 patients with hepatocellular carcinoma classified according to residence.

Province Governorates	Residence		Age		Sex Male : Female ratio
	No.	%	Median	(Range)	
<i>Metropolitan Cairo:</i>	158	39.21	57.0	(18.0-78.0)	2.7:1
Cairo (64)	15.90		56.6		
Giza (59)	14.64		55.7		
Qualiobia (35)	8.68		54.8		
<i>Lower Egypt (Delta):</i>	120	29.78	53.0	(28.0-80.0)	3.4:1
Menofia (32)	7.94		54.0		
Kafr El-sheikh (11)	2.73		56.5		
Behera (8)	1.98		54.0		
Gharbia (19)	4.71		51.5		
Damietta (9)	2.23		55.6		
Dakahlia (16)	2.96		58.5		
Sharkia (25)	6.20		53.4		
<i>Middle Egypt:</i>	80	19.85	56.0	(22.0-78.0)	2.2:1
Beni Suif (25)	6.20		52.6		
Fayoum (32)	7.94		56.2		
Menia (23)	5.71		54.6		
<i>Upper Egypt:</i>	33	8.19	58.0	(32.0-82.0)	3:1
Assuit (6)	1.49		56.2		
Sohag (16)	3.97		57.9		
Kena (6)	1.49		54.5		
Aswan (5)	1.24		54.0		
<i>Others:</i>	12	2.98	56.5	(40.0-72.0)	5:1
Alexandria (1)	0.25				
Suez canal (10)	2.48		54.6		
New Valley (1)	0.25				
Total (403)	100.0		56.0	(18.0-80.0)	2.84:1
<i>p value*</i>			0.43		0.62

\*  $p$  value is significant < 0.05    N.B.: Comparisons done between main provinces not governorates.

Table (2): Occupation, special habits and history of medical diseases in hepatocellular carcinoma patients.

	No.	%
<i>Occupation:</i>		
Farmers	94	23.3
Housewives	100	24.8
Others	209	51.8
<i>Special habits (256):</i>		
Cigarette smoking	127	49.6
Alcohol consumption	10	3.9
Opium, others	1	0.4
<i>Medical diseases (218):</i>		
Diabetes mellitus	56	25.7
Hypertension	19	9.4

Table (3): Characteristics and presentation of HCC patients.

	No.	%
<i>Symptoms:</i>		
Abdominal pain	322	80.0
Abdominal swelling	105	26.0
GIT symptoms	82	20.3
Yellowish colour of skin, mm <sup>o</sup>	26	6.5
General manifestations (weight loss, bony aches, fever, lower limb edema and itching)	67	16.7
<i>Signs:</i>		
Hepatomegaly	335	85.6
Splenomegaly	112	27.7
Abdominal mass	74	18.4
Ascites	106	26.3
Shrunken liver	20	5.0
Jaundice	44	10.9
Lower limb edema	40	9.9
<i>Diagnosis:</i>		
Cytology	128	31.7
Histology	255	63.3
AFP > 350 ng/ml	20	5.0
<i>Child's Pugh's class (372):</i>		
I	184	49.5
II	177	47.5
III	11	3.0
<i>Metastasis at presentation (393):</i>		
Intra-abdominal	87	22.1
Lung	55	14.0
Bone	16	4.1
Lymph nodes	7	1.8
Associated bilharziasis (220)	9	2.3
Associated cirrhosis (285)	157	71.4
	247	86.7

<sup>o</sup>mm: mucus membranes

Table (4): Tumour related features in HCC patients.

Characteristic	No.	%
<i>Site (402):</i>		
Rt. lobe	182	45.0
Lt. lobe	69	17.1
Bilateral	151	45.0
<i>Number of lesions (402):</i>		
Single	200	49.5
Multiple	202	50.5
<i>Tumour burden (402):</i>		
< 50%	130	32.3
≥ 50%	272	67.7
<i>HCC grade (383):</i>		
Grade I	67	17.5
Grade II	232	60.7
Grade III	84	21.8
<i>Estrogen receptors (50):</i>		
Positive	14	28.0
Negative	36	72.0

Table (5): Serologic markers in HCC patients.

	No.	%
<i>Hepatitis markers (160):</i>		
HCV	103	64.4
HBV	28	17.5
HCV & HBV	18	11.2
Negative	11	6.9
<i>AFP (ng/ml) (206):</i>		
≤ 10	42	20.4
> 10-100	50	24.3
> 100-350	21	10.2
> 350	93	45.1

Table (6): Lines of management of HCC at NCI, Cairo in the period from 1993 to 1999.

	N = 403	
	No.	%
Supportive	199	49.4
Adriamycin	27	6.7
Adriamycin+tamoxifen	52	12.9
Tamoxifen	28	6.9
Chemoembolization	26	6.5
Surgery	25	6.2
Others (a)	40	9.9
Unknown	6	1.5

(a) Others, include: 5 flourouracil (5FU), visum, platinol and calcium leucovorine in different combinations or as single agent.

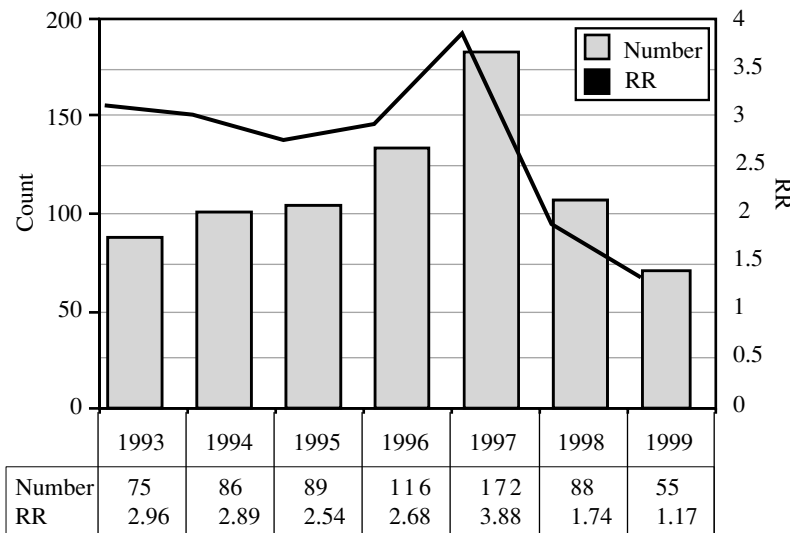


Fig. (1): Total number and relative frequency of 681 HCC cases at NCI, Cairo, from 1993 to 1999. RR= Relative frequency per 100 solid tumours.

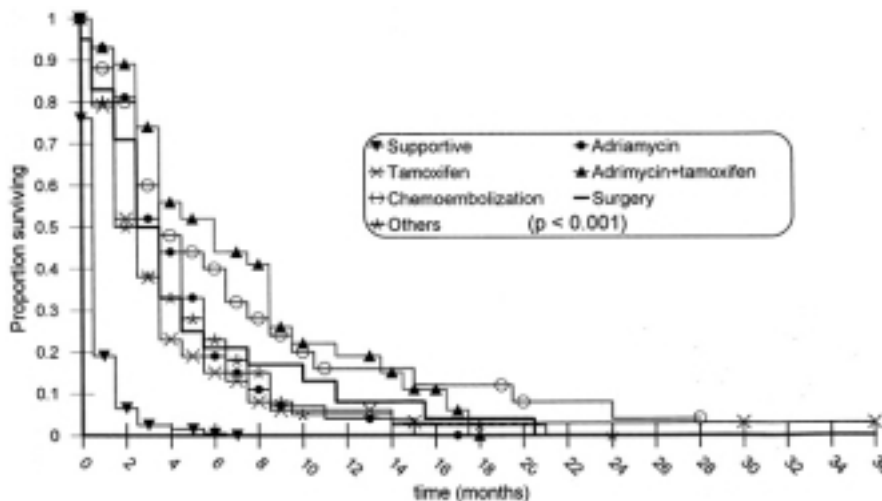


Fig. (2): Overall survival of HCC patients according to modality of treatment. (p < 0.001)

### DISCUSSION

Although results of the present study showed a steady increase in the number of HCC cases attending NCI from 1993 to 1997, yet a drop was seen in both total counts and relative frequency of the tumour in 1998 and 1999. We presume that this is a false decrease and infer that to the fact of establishment of new cancer centres belonging to both Ministry of Health and Universities of Delta, Middle and Upper Egypt. This is supported by our results which revealed that about 60% of patients are residents of the above mentioned areas.

Age incidence of HCC is perhaps related to the age at which exposure to carcinogens occur, as well as the kind and amount in environment [21]. As we are not in a high prevalence area, peak age was 56.0 years which agrees with results of other studies [22,25].

Male to female ratio was 2.84:1. Male predominance may be explained by the higher prevalence of HBsAg carrier state, high susceptibility to environmental carcinogenic factors and greater exposure to them [5].

In the present study, more than 97% of HCC cases came from around the Nile banks. A point which arouses a question; is there an association between the River Nile and high incidence of chronic liver disease (CLD) and hepatocarcinogenesis? An Egyptian study [2] that correlates prevalence of HCV infection in blood donors to residence found that governorates with highest seroprevalence were those around the Nile River. In our series prevalence of hepatitis B virus was 17.5%, hepatitis C virus was 64.4% and combined infection was 11.2%. In the majority of cases, HCC occurs against a background of hepatitis B or C viral infections [16]. High seropositivity regarding hepatitis markers

was proved in this series. HCV markers were positive in 75.6% of cases which support the theory that HCC occurs more frequently in patients with HCV related chronic disease than those with HBV related disease [1]. According to Kew et al. [14], co-infection carries a synergistic role on HCC formation. This result brings us to the importance of follow-up of cirrhotic patients with HCV and/or HBV regularly for earlier detection of HCC.

Any patient, whatever his job is can be affected if exposed to carcinogenic factors with special attention to farmers who are exposed to several risk factors including aflatoxins, insecticides, pesticides and bilharziasis. Hepatitis viruses are also known to be more prevalent in bilharzial patients [8,9,13].

Diabetes mellites is known to be associated with CLD and specially more with HCV infection [10,12]. Twenty six percent of our cases were diabetic.

The commonest physical sign in our patients was hepatomegaly (> 80%). This is in agreement with Shamaa et al. [26]. Other clinical signs were ascites, splenomegaly and edema of lower limbs that are common findings in CLD without HCC, so they are not helpful in early suspicion or diagnosis of HCC.

AFP level was normal in 20.4%, high not diagnostic in 24.3%, and highly suspicious of HCC at a diagnostic level in 55.3% of our patients. This is supported by many studies which showed that serum AFP levels were not diagnostic in about 50% of HCC cases, so could not be used as a single tool for screening [7,17,24].

According to Child's classification 49.5% of our patients were classified as class I, 47.6% class II and 3% class III. Due to the nature of HCC tumour, as one of the most malignant in terms of prognosis [26], 20.8% of our cases were metastatic at first presentation. The advanced nature of HCC made most of our patients not amenable to surgery (done in 6.2% of cases), chemoembolization (done in 6.5%) and 49.6% of them were given nonspecific treatment. Median survival time in untreated patients was one month in this series. Comparing our results with other series [22] showed that median survival time for untreated patients was 8.7 weeks from time of diagnosis. Although, in our study, median survival time was significant-

ly higher in combined adriamycin and tamoxifen treatment, yet it was not different from both surgery and chemoembolization. This might be explained by longer follow-up periods of HCC patients at medical oncology clinic for chemotherapy and lost follow-up of patients undergoing surgery. In a prospective randomized study performed to test the hypothesis that tamoxifen might improve survival of patients with advanced HCC, results showed that median survival was 44 days and 41 days,  $p = 0.7$  in tamoxifen group and placebo group, respectively [18]. Although, in our series, median survival time with tamoxifen treated group was 3 months, yet it was significantly higher than those treated with non specific therapy. Other results [23] suggest that estrogen receptor (ER) positive HCC has less malignant biologic behaviour and better prognosis than ER negative HCC.

*In conclusion:* HCC showed an increasing trend in the past few years that could be attributed to more exposure to different risk factors including environmental pollutants. Our recommendation is: Prevention of both HCV and HBV infection by active immunization early in childhood and population at high risk is important. Raising the standard of environmental antipollutant measures with proper sewage disposal and clean water supply is mandatory. Finally, screening of patients with chronic HCV and/or HBV (with or without cirrhosis) aided by abdominal US and serum AFP levels for earlier detection of small lesions, remains the only realistic approach for improving treatment of HCC patients but its cost-effectiveness is uncertain.

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