ROLE OF AGE, GENDER, AND TOBACCO IN CAUSING BLADDER CANCER AND PATHOLOGICAL STUDY OF BLADDER CANCER IN KPK

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ABSTRACT

Objective: *To determine assocation of age, gender & tabbaco in causing bladder carcinoma and its causative factors.*

Materials and Methods: *This was a retrospective audit on individuals suffering from bladder carcinoma. All the enrolled individuals in our research study were diagnosed and treated in our set up under strict criteria.*

Results: *Total 156 affected individuals suffering from bladder cancer were diagnosed and treated in our setup. Out of 156 patients, 111 were characterized by isolated painless total hematuria. Bladder carcinoma is associated with age so in 70 patients (age > 60 year) were characterized by high grade cancer with a p = 0.04, while the remaining patients (age <60 years), were characterized by both high and low-grade cancers. The risk of tumor relapse is considerably less in those individuals who take adjuvant BCG therapy or mitomycin C therapy, and the difference between the two groups is statistically significant, with a P < 0.0001.*

Conclusion: *The incidence rate of bladder carcinoma is increasing. Tobacco is one of the most common causative factors for bladder carcinoma in kpk.*

Keywords: *Bacille Calmette-Guerin (BCG) therapy, Bladder cancer, Hematuria, Tobacco, Smoking*

INTRODUCTION

Globally, urinary bladder cancer is the 9th most common cancer. About 90% of all bladder cancers are of the transitional-cell type.[1] It is the 4th and 8th most common cancer in male and female respectively of the western world.[2] According to the Shaukat Khanum Memorial Cancer Hospital and Research Center data registry, bladder cancer is placed at 10th position in the list of malignancies recorded from 1994 to 2004. According to a research study conducted in Pakistan (1998– 2002), bladder carcinoma was ranked 4th.[3] And according to Indian cancer record, BC accounts for an approximately 3.9 percent of all cancer cases.[4] A number of factors such as age, gender and tobacco may cause bladder carcinoma. Its natural history has been correlated with a number of etiological factors and hazards such as viral agents, bacteria and virus associated infections, aniline dyes and tobacco in different form etc are associated with increased risk of bladder carcinoma.[5] Globally, the prevalence of smoking is higher for male (40%) than for female (9%).

Besides these, Smoking has been predominantly an accepted risk factor for the cause of bladder carcinoma and its relapse. Avoiding the tobacco use specially smoking for about fifteen year can minimize the incidence and relapse of bladder carcinoma.[6] It has been stated that gender is also a causative factor of bladder carcinoma. Globally, it affects both gender and its incidence rate is four time more in male than female.[7] Bladder carcinoma is considered as the disease of old age as 90 percent of bladder carcinoma

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affected individuals are mostly above the age of 55 year. Now a days due to technological advancement and health awareness, the Bladder carcinoma affected patients has been diagnosed in early ages.[8]

MATERIALS AND METHODS

A total 156 individuals suffering from bladder carcinoma came to our setup. All the patients were diagnosed and treated here. Their clinical data were mark out from hospital medical record department and studied thoroughly. The available information regarding patients' age, gender, symptoms and mode of presentation, history of tobacco smoking, and use of smokeless tobacco in various forms such as paan masala, tobacco leaves with betel nuts, chewing rolled dried leaves of tobacco were all collected and analyzed. All the patients were passes through the routine hematological, biochemical and radiological examination. After cystoscopy, transurethral resection of bladder tumor (TURBT) was done. Deep muscle biopsy was sent to a pathologist to check the existence of detrusor muscle and record the lack or occurrence of invasiveness of muscle. Those affected individuals that shows the absence or the lack of invasiveness of muscle were subjected for re-resection after 21 days. Otherwise not. Additional treatment like 40 mg of intra vesical Bacille Calmette-Guerin was started to all affected individuals with NMIBC. Those affected individuals who couldn't tolerate Bacille Calmette-Guerin then we administered 40 mg of mitomycin C.

By using the SPSS version 22 software, all the collected data were analyze. The categorical data such as age, gender, smokeless tobacco usage and smoking history were compared using Chi-square test and Fisher's exact test.

RESULTS

Out of 156 affected individuals, one hundred and eleven individuals was characterized by isolated painless total hematuria. Eighteen affected individuals were characterized by Loin pain hematuria syndrome (LPHS), and seventeen affected individuals were characterized by storage or irritative urinary symptoms with hematuria. 10 patients was presented by incidentally detected bladder lesion. The clinical and pathological characteristics of all the affected individuals enrolled in our research study is shown in table 1.

153 affected individuals show symptoms of urothelial carcinoma (Transitional cell carcinoma) and its mutated variants. Spectrum of various histological types of BC observed in our research study are shown in figure 1 and table 2.

Age is an accepted risk factor for the cause of bladder carcinoma. It may developed at any stage of life but mostly it is considered to occur in elder group. Because of the presence of close link between the increasing age and the bladder carcinoma, the incidence of this disease will be increases with the passage of time. In our research study the youngest reported patient was of about the age of 26 year. Who had characterized by a solitary Polypoidal growth and painless total hematuria. And the oldest reported patient was of the age of 84 year. The age distribution of BC in our research study is shown in figure 2.

Age wise pathological distribution of all enrolled individuals with bladder carcinoma in our research study is shown in table 3. Below 60 year of age affected individuals were characterized by both condition i.e low and high grade cancer. And affected individuals of above 60 year of age were characterized by only high-grade cancers. With respects to the stage of the tumor, T1 tumors represents about eighty seven percent of all bladder carcinoma.

The gender affects the cause of bladder carcinoma greatly. Globally, male are affected greatly as compared to female. More than eighty percent of the affected individuals were male. One factor is smoking for such a high ratio of affected male. In our research study a large number of female uses smokeless tobacco while only two female uses smoking. This smokeless tobacco could have been a causative for tumor incidence in female. Transitional cell carcinoma (TCC) of urinary bladder is the 3rd most common cancer in male that is highly linked with smoking. Environmental factor have been considered to play main role to cause urinary carcinoma in both gender. Both gender have been affected at same rate when exposed to chemical such as pesticides and fertilizer. All these, smoking, fertilizer and agriculture pesticides have been considered the causative risk factors for bladder carcinoma. Gender wise distribution of bladder carcinoma is shown in table 4.

We have total number of 156 enrolled affected individuals, and out of this 135 affected individuals were of non-muscular invasive bladder carcinoma

(NMIBC).After initial treatment, 125 affected individual continuous further treatment and 10 patients refuse for further treatment. The chances of relapse is higher in those patients who refuse for further treatment while those patients who keep its treatment continuously goes toward in positive direction. Those patients who uses the Bacillus Calmette Guerin or Mitomycin C therapy for bladder carcinoma treatment have less risk of relapse as shown in table 5. 86 affected individuals were treated by BCG therapy. The difference between the two groups is statistically significant, with a $P < 0.0001$. Table 5 and Figure 3 gives us a detail overview of the treatment given to affected individuals with bladder carcinoma.

DISCUSSION

According to data registered in Delhi Cancer Registry, after cancers of the lung, tongue, larynx, prostate, and esophagus bladder carcinoma occupied the place as a 6th most common cancer globally. Bladder carcinoma is a heterogeneous condition. About seventy percent of affected individual with bladder carcinoma shows superficial tumors that is not a life threatening disorder and by treatment it recover while thirty percent show muscle invasive disease that is life threatening disorder and linked with high risk of death. In India about 5.6 percent men and 1.8 percent female are affected by urothelial cancers.[9] The symptoms of bladder carcinoma is painless hematuria.[10] According to our research study, about eighty three percent affected individuals from total enrolled individuals had the symptom of painless hematuria and about ninety three percent affected individuals had hematuria at some point of time before the diagnosis of the patients.

Transitional cell carcinoma (TCC) is diagnosed in more than fifty thousand patients with bladder carcinoma annually in US. And a number of death occur due to invasive TCC because it show resistant to chemotherapy.[11] Squamoid, sarcomatoid, and glandular differentiation are the different variants associated with TCC are described. Mostly TCCs presents as Non muscle invasive bladder cancer (NMIBC) and its treatment procedure include transurethral resection. Mostly NMIBC patients relapse with the passage of time.[12]

Different environmental factors such as smoking and nonsmoking tobacco play a risky role in the development of bladder carcinoma. Different

Table: 1 Summary of the clinical and pathological characteristics of all affected individuals enrolled in our research study

Characteristics	Number %
Total number of enrolled patients	156
Stage	
T1G1, T1G2	57 (36.6)
T1G3	78 (50)
T2	5 (3.1)
Others**	16 (10.3)
Grade	
Low	57 (36.6)
High	99 (63.4)
Tumor size (cm)	
<3	115 (73.71)
>3	41 (26.28)
Type of growth	
Polypoidal	117 (75)
Sessile	39 (25)
Number of tumors	
Single	121 (77.6)
Multiple	35 (22.4)
Symptoms	
Hematuria alone	111 (71.2)
Irritative symptoms with hematuria	17 (10.9)
Loin pain with hematuria	18 (11.5)
Incidentally detected	10 (6.4)

**Others consist of squamoid, sarcomatoid, undifferentiated, and glandular variants of TCC, TCC: Transitional cell carcinoma.

Table: 2 Spectrum of various histological types of bladder cancers observed in our study

Pathology	Number %
T1G1, T1G2	57 (36.6)
T1G3	78 (50)
T2	5 (3.2)
Sarcomatoid	2 (1.3)
Squamoid	5 (3.2)
Plasmacytoid	1 (0.6)
Undifferentiated	3 (1.9)
Glandular variant	4 (2.6)
Angiomyxoma	1 (0.6)
Total	156 (100)

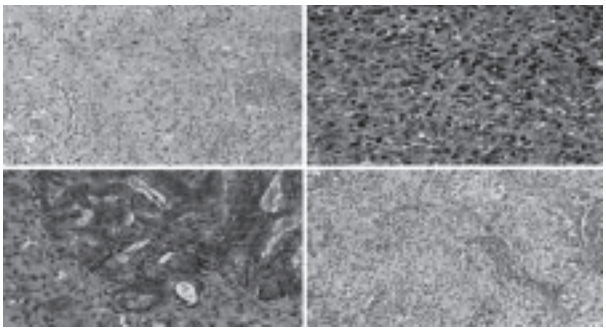

Fig 1: Spectrum of various histological types of TCC bladder. (a) Urothelial carcinoma with squamoid differentiation (H and E ×100), (b) urothelial carcinoma with sarcomatoid differentiation (H and E ×100), (c) urothelial carcinoma with glandular differentiation (H and E ×100), (d) high-grade tumor with dense inflammatory response (H and E ×100)

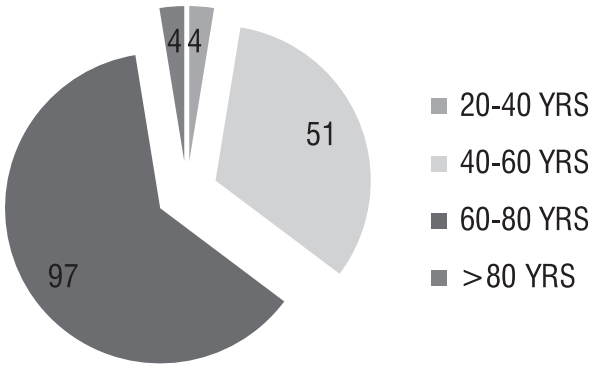

Fig 2: Age distribution of bladder cancer

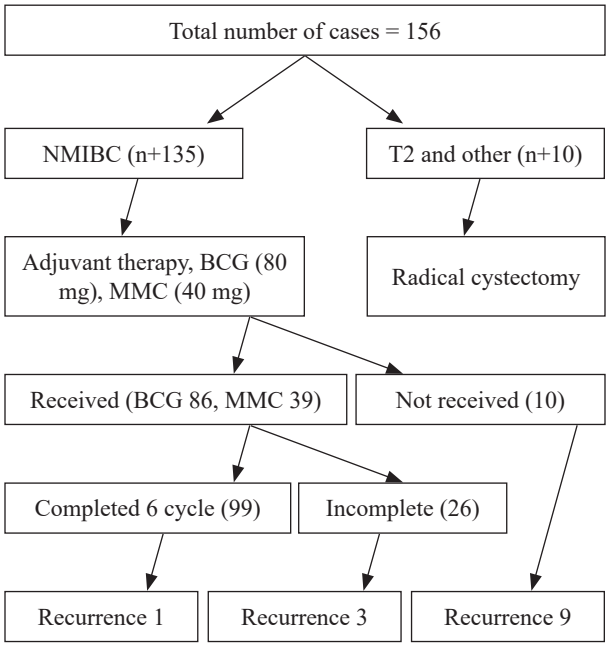

Fig 3: An overview of details of treatment given

Table: 3 Impact of age on tumor grade and stage

Characteristics	< 60	> 60	P value
No of patients	55	101	
Smoker	41	70	0.58
Non smoker	14	31	
Tumor grade (TCC)			
Low (n=57)	26	31	0.039 without yates correction
High (n=99)	29	70	
Tumor stage			
T1 (n=135	46	89	0.08
T2, others (n=21)	3	18	

Table: 4 Impact of gender on tumor grade and stage

Characteristics	Male	Female	P value
No of patients	127	29	
Smokers	109	2	<0.0001
Non smoker	18	27	
Grade			
Low (57)	47	10	0.8346
High (99)	80	19	
Stage			
T1	121	14	0.1411
T2 and others	16	5	
Exposure to risk factors			
Tobacco smokers	109	2	
Non smoker	18	27	
Paan chewer	90	26	
Agriculture pesticides	80	24	

Table: 5 Impact of adequate treatment on final outcome in T1 patients (n=135)

	Adjuvant treatment given 6 cycle	Adjuvant treatment not given/ incomplete [n=36 (26+10)]	P value
Recurrence	1	12	<0.0001
No recurrence	98	21	
Total	99	36	

environmental hazard such as pesticides and other chemical also cause the bladder carcinoma globally.[13] As compared to nonsmoker the chances of bladder carcinoma are 4 time greater in addictive smoker.[14]

In Pakistan the prevalence of male addictive smoker is 36% as compared to women that is 9%.15

In our research work, about seventy one percent were addictive of smokers. Mostly female addictive smoker do not exposed his history of smoking.

Other form of tobacco are also a risk factors to cause bladder carcinoma. As it is stated that the addictive smokeless tobacco incidence is higher in female in rural area of Pakistan. A study conducted in Pakistan on 204 (160 male, 44 female) newly diagnosed as bladder carcinoma patients. The results show that all 44 female patients has a history of addictive smokeless tobacco and this is the main causative factor of bladder carcinoma in these female patients.[16] The Pakistani rural women mostly uses snuff and chewing tobacco as it is described that snuff and chewing tobacco are more carcinogenic. Tobacco specific nitrosamine (TSNA) are the most harmful and risky carcinogen that are present in the snuff and chewing tobacco.

On the basis of relapse and progression, NMIBC has been grouped into three categories such as low risk, intermediate risk and high risk.[17]

A study performed by Shahin on the effect of BCG therapy on bladder carcinoma patients. Its results shows that about thirty percent individuals remain relapse free, other thirty percent individuals relapse after BCG therapy and more thirty percent develop to muscle invasive stage.[18]

The treatment of high grade non-muscle invasive bladder cancer (HGNMIBC) has always remain an interesting and challenging job because of unpredictable nature of the disease.[19] These individuals were advised to check up on routine basis and uses the BCG therapy as a treatment tool.

CONCLUSION

It was concluded through our research study that in kpk Pakistan the incidence rate of bladder carcinoma is increasing. High grade non-muscle invasive bladder cancer is a life threating disease. For individuals suffering from bladder carcinoma, the transurethral resection surgical procedure alone may not be enough, and affected individuals must be advised to go properly for adjuvant therapy and a long- term follow-up. Different causative factors such as age, gender and tobacco have greatly influenced the incidence of bladder carcinoma. The male gender is affected to a great number as compared female gender. And as the age increases the chances of bladder carcinoma became increases. This disease is considered as the old age disease. There should be an awareness campaign about the risk factors that cause bladder carcinoma in kpk Pakistan.

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