International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 28-05-2019; Accepted: 30-06-2019
www.medicalsciencejournal.com
Volume 5; Issue 7; July 2019; Page No. 218-222

Study of different types of oncological outcomes in patients with non-urothelial bladder cancer

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Abstract
The urothetial neoplasms are known for their recurrence and morbidity than mortality. All types of neoplasms can be seen in bladder, but more than 95% of bladder tumors are of epithetial in origin and the rest are mesenchymal. Variants like squamous cell carcinoma and adenocarcinoma of urinary bladder carry worst prognosis T whereas prognosis of even high grade urothetical carcinoma stands better survival rate. The challenge is that, early detection and treatment of new or recurrent cases are required to optimize bladder preservation, reduced patient morbidity and increase survival rate. Urinary cytodiagnosis and histopathological study are cost effective and have fairly accurate morphological assessment for early detection of bladder tumors as such patients present with history of painless hematuria. Hence the present study was planned Study of Different types of Oncological Outcomes in Patients with Nonurothelial Bladder Cancer.
The present study was planned in Department of General Surgery, Mata Gujri Memorial Medical College and Lion Seva Kendra Hospital, Kishanganj, Bihar. The study was done from June 2016 to June 2017. The patients diagnose with bladder cancer and referred to our hospital were enrolled in the present study.
Increasing attention in recent years, along with more specific and sensitive markers, has led to heightened recognition of the divergent differentiation often present in urothelial cancer. The most common non-urothelial histologies in bladder cancer are squamous, adenocarcinoma and small cell carcinoma, all of which often present at an advanced stage. Early detection and treatment of new / recurrent cases is required to optimize bladder preservation, reduce patient morbidity and increase quality of life.

Keywords: Oncological outcomes, non-urothelial bladder cancer, carcinoma, etc

Introduction
Bladder cancer is any of several types of cancer arising from the tissues of the urinary bladder. It is a disease in which cells grow abnormally and have the potential to spread to other parts of the body. Symptoms include blood in the urine, pain with urination, and low back pain. Risk factors for bladder cancer include smoking, family history, prior radiation therapy, frequent bladder infections, and exposure to certain chemicals. The most common type is transitional cell carcinoma. Other types include squamous cell carcinoma and adenocarcinoma. Diagnosis is typically by cystoscopy with tissue biopsies. Staging of the cancer is typically determined by transurethral resection and medical imaging such as CT scan and bone scan [1].
Treatment depends on the stage of the cancer. It may include some combination of surgery, radiation therapy, chemotherapy, or immunotherapy. Surgical options may include transurethral resection, partial or complete removal of the bladder, or urinary diversion. The typical five-year survival rates in the United States is 77%, Canada is 75%, and Europe is 68%. Bladder cancer, as of 2017, affected about 1.6 million people globally with 549,000 new cases and 200,000 deaths. Age of onset is most often between 65 and 84 years of age. Males are more often affected than females. In 2017, the highest rate of bladder cancer occurred in Southern and Western Europe followed by North America with rates of 15, 13, and 12 cases per 100,000 people. The highest rates of bladder cancer deaths were seen in Northern Africa and Western Asia followed by Southern Europe [2].
Bladder cancer characteristically causes blood in the urine (hematuria), which may be visible (gross/macroscopic hematuria) or detectable only by microscope (microscopic hematuria). Blood in the urine is the most common symptom in bladder cancer, and is painless. Visible blood in the urine may be of only short duration, and a urine test may be required to confirm non-visible blood. Between 80–90% of people with bladder cancer initially presented with visible blood [3]. Blood in the urine may also be caused by other conditions, such as bladder or ureteric stones, infection, kidney disease, kidney cancers or vascular malformations, though these conditions (except kidney cancers) would typically be painful.
Other possible symptoms include pain during urination (dysuria), frequent urination, or feeling the need to urinate without being able to do so. These signs and symptoms are not specific to bladder cancer, and may also be caused by non-cancerous conditions, including prostate infections, overactive bladder or cystitis. Patients with advanced disease refer pelvic or bony pain, lower-extremity swelling, or flank pain. Rarely, a palpable mass can be detected on physical examination.
Tobacco smoking is the main known contributor to urinary bladder cancer; in most populations, smoking is associated with over half of bladder cancer cases in men and one-third of cases among women, however these proportions have reduced over recent years since there are fewer smokers in Europe and North America. There is an almost linear relationship between smoking duration (in years), pack years and bladder cancer risk. A risk plateau at smoking

about 15 cigarettes a day can be observed (meaning that those who smoke 15 cigarettes a day are approximately at the same risk as those smoking 30 cigarettes a day). Quitting smoking reduces the risk, however former smokers will most likely always be at a higher risk of bladder cancer compared to people who have never smoked. Passive smoking does not appear to be a risk [4].

Thirty percent of bladder tumors probably result from occupational exposure in the workplace to carcinogens such as benzidine. 2-Naphthylamine, which is found in cigarette smoke, has also been shown to increase bladder cancer risk. Occupational or circumstantial exposure to the following substances has also been implicated as a cause of bladder cancer; 4-aminobiphenyl (rubber industry), β-naphtylamine (rubber industry), phenacetin (analgesic), arsenic in drinking water, auramine (dye manufacturing), magenta (dye manufacturing), ortho-toluidine (dye manufacturing), epoxy and polyurethane resin hardening agents (plastics industry), chlornaphazine, coal-tar pitch. Occupations at risk are bus drivers, rubber workers, painters, motor mechanics, leather (including shoe) workers, blacksmiths, machine setters, and mechanics. Hairdressers are thought to be at risk as well because of their frequent exposure to permanent hair dyes [5].

Infection with Schistosoma haematobium (bilharzia or schistosomiasis) has been shown to cause bladder cancer, specially of the squamous cell type. Schistosoma eggs induces a chronic inflammatory state in the bladder wall resulting in tissue fibrosis. Higher levels of N-nitroso compounds (nitrate) has been detected in urine samples of people with schistosomiasis. N-Nitroso compounds have been implicated in the pathogenesis of schistosomiasis related bladder cancer. They are known to cause alkylation DNA damage, specially Guanine to Adenine transition mutations in the H-ras and p53 tumor suppressor gene. Mutations of p53 are detected in 73% of the tumors, BCL-2 mutations accounting for 32% and the combination of the two accounting for 13%. Other causes of squamous cell carcinoma of the bladder include chronic catheterizations in spinal cord injury patients [6].

In addition to these major risk factors there are also numerous other modifiable factors that are less strongly (i.e. 10–20% risk increase) associated with bladder cancer, for example, obesity. Although these could be considered as minor effects, risk reduction in the general population could still be achieved by reducing the prevalence of a number of smaller risk factor together [7].

It has been suggested that mutations at HRAS, PIK3CA, TERT, KRAS2, RB1, TSC1 and FGFR3 may be associated in some cases. Deletions of parts or whole of chromosome 9 is common in bladder cancer. Low grade cancer are known to harbor mutations in RAS pathway (15%) and the fibroblast growth factor receptor 3 (FGFR3) gene (60%), both of which play a role in MAPK pathway. p53 and RB gene mutations are implicated in high-grade muscle invasive tumors. 89% of muscle invasive cancers have shown mutations in chromatin-remodelling and histone modifying genes. Deletion of both copies of the GSTM1 gene has a modest increase in risk of bladder cancer. GSTM1 gene product glutathione S-transferase M1 (GSTM1) participates in the detoxification process of carcinogens such as polycyclic aromatic hydrocarbons found in cigarette smoke. Similarly, mutations in NAT2 (n-acetyltransferase) is associated with increased risk for bladder cancer. N-acetyltransferase helps in detoxification of carcinogens such as aromatic amines (also present in cigarette smoke) [8].

Currently, the best diagnosis of the state of the bladder is by way of cystoscopy, which is a procedure in which a flexible or rigid tube (called a cystoscope) bearing a camera and various instruments is introduced into the bladder through the urethra. The flexible procedure allows for a visual inspection of the bladder, for minor remedial work to be undertaken and for samples of suspicious lesions to be taken for a biopsy. A rigid cystoscope is used under general anesthesia in the operating room and can support remedial work and biopsies as well as more extensive tumor removal. Unlike papillary lesion, which grow into the bladder cavity and are readily visible, carcinoma in situ lesion are flat and obscure. Detection of carcinoma in situ lesions requires multiple biopsies from different areas of interior bladder wall. Photodynamic detection (blue light cystoscopy) can aid in the detection of carcinoma in situ. In photodynamic detection, a dye is instilled into the bladder with the help of a catheter. Cancer cells take up this dye and are visible under blue light, providing visual clues on areas to biopsied and/or resected [9].

Urine cytology can be obtained in voided urine or at the time of the cystoscopy ("bladder washing"). Cytology is not very sensitive for low-grade or grade 1 tumors (a negative result cannot reliably exclude bladder cancer) but has a high specificity (a positive result reliably detects bladder cancer). There are newer non-invasive urine bound markers available as aids in the diagnosis of bladder cancer, including human complement factor H-related protein, high-molecular-weight carcinoembryonic antigen, and nuclear matrix protein 22 (NMP22). NMP22 is also available as a prescription home test. Other non-invasive urine based tests include the CertNDx Bladder Cancer Assay, which combines FGFR3 mutation detection with protein and DNA methylation markers to detect cancers across stage and grade, UroVysion, and Cxbladder.

However, visual detection in any form listed above, is not sufficient for establishing pathological classification, cell type or the stage of the present tumor. A so-called cold cup biopsy during an ordinary cystoscopy (rigid or flexible) will not be sufficient for pathological staging either. Hence, a visual detection needs to be followed by transurethral surgery. The procedure is called transurethral resection of bladder tumor (TURBT). Further, bimanual examination should be carried out before and after the TURBT to assess whether there is a palpable mass or if the tumour is fixed ("tethered") to the pelvic wall. The pathological classification obtained by the TURBT-procedure, is of fundamental importance for making the appropriate choice of ensuing treatment and/or follow-up routines [10].

The urothetial neoplasms are known for their recurrence and morbidity than mortality. All types of neoplasms can be seen in bladder, but more than 95% of bladder tumors are of epithetial in origin and the rest are mesenchymal. Variants like squamous cell carcinoma and adenocarcinoma of urinary bladder carry worst prognosis T whereas prognosis of even high grade urothetical carcinoma stands better survival rate [11]. The challenge is that, early detection and treatment of new or recurrent cases are required to optimize bladder preservation, reduced patient morbidity and increase survival rate. Urinary cytodiagnosis and histopathological study are cost effective and have fairly accurate morphological assessment for early detection of bladder

tumors as such patients present with history of painless hematuria [12]. Hence the present study was planned Study of Different types of Oncological Outcomes in Patients with Nonurothelial Bladder Cancer.

Methodology

The present study was planned in Department of General Surgery, Mata Gujri Memorial Medical College and Lion Seva Kendra Hospital, Kishanganj, Bihar. The study was done from June 2016 to June 2017. The patients diagnose with bladder cancer and referred to our hospital were enrolled in the present study.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria

Data was evaluated for age, gender, clinical symptoms and histopathological characteristics at the time of presentation. A Transurethral resection of the bladder tumor (TURBT) was performed in most of the cases except two cases. Urinary bladder tumor tissue biopsy/ specimen were received by our Histopathology department and subjected to routine histopathology processing. Then tissue sections were studied. The new 2016-based World Health Organization (WHO) and International Society of Urological Pathology (ISUP) classification for Papillary Urothelial neoplasms were used for the pathological grading of the cases studied [13].

Exclusion criteria

Patients with tumors other than urinary bladder neoplasms in the urinary system of both sexes. Patients not willing for management at our cancer centre.

Results & Discussion

Non-urothelial bladder carcinoma accounts for only 5–10% of bladder cancers [14]. It typically presents at a more advanced stage with generally worse overall survival than urothelial carcinoma [15]. Non-urothelial carcinoma originates from both epithelial (squamous cell carcinoma (SCC), adenocarcinoma, and small cell carcinoma) and non-epithelial (sarcoma, spindle cell carcinoma, and signet ring) cell types. In general, the unique biology of non-urothelial bladder carcinoma is less understood [16].

SCC is an epithelial neoplasm defined by characteristic histological features such as squamous pearls, intercellular bridges, and keratohyalin granules [17]. The diagnosis is reserved for tumors without any evidence of urothelial components. HPV has been linked to SCC, but this remains controversial [18]. SCC accounts for 2–5% of all bladder cancers and has two common histological subtypes, bilharzial and non-bilharzial.

Table 1: Demographic details

Variables	No. of Cases	Age (years)	Males	Females	Married
Urothelial cell carcinoma	15	55 - 63	10	5	12
Squamous cell carcinoma	6	48 - 64	4	2	4
Adenocarcinoma	10	53 - 65	7	3	7
Sarcoma	17	51- 60	12	5	16
Small cell	20	52 - 65	14	6	18
Signet ring	12	49 - 56	8	4	11
Spindle cell	10	49 - 63	6	4	8

Table 2: Type of Carcinoma

Variables	Urothelial cell carcinoma	Squamous cell carcinoma	Adenocarcinoma	Sarcoma	Small cell	Signet ring	Spindle cell
High grade	13	4	6	11	13	6	5
T-Stage:							
<T2	7	1	3	4	3	3	2
T2	8	2	12	7	12	4	8
T3	12	7	5	14	18	10	7
T4	3	2	4	10	5	13	3
N-Stage:							
N0	25	10	20	29	27	18	16
N+	3	1	2	4	7	9	2
NX	2	1	2	2	4	3	2

Tumor recurrence or progression could be due to clinical under diagnosis as found by Chenko D8. It could also be due to the synchronous and metachronous multifocality of transional cell carcinoma 9. So the patients are to be followed up by urinary cytology. Mitra *et al* [19] in their study pointed out that it is unlikely for a single market to be sufficient for conclusion to improve the prognosis for patients with bladder tumors, but a combination of multiple markers are required for prognostication. This will be very expensive. Therefore urinary cytodiagnosis and correlation with histopathological study becomes the cheap as well as fairly accurate diagnosis criteria as mentioned by Steiner *et al* and Nabi *et al*. [20]. Lympho vascular invasion (LVI) which is an important determinant of metastasis was seen in 31% high grade and 15% low grade tumors which almost matches with the study of Bolenz *et al*. [21] Incidences of muscular invasion in our study was found in 81% of high grade tumors and 31% in low grade tumors which shows our figures are higher than the study by Karakiewicz *et al*. [22].

Squamous cell carcinoma often presents at an advanced stage, and, until recently, it was unclear whether patients had a worse prognosis on a stage-for-stage basis when compared with patients with urothelial cancer [23]. However,

a recent study of the SEER database by Scosyrev and colleagues has shown that squamous cell carcinoma was more aggressive than urothelial cancer after adjusting for common prognostic factors, such as stage [24].

Primary adenocarcinoma of the bladder is rare in the developed world, accounting for about 1.4% of bladder cancers undergoing radical cystectomy; it is more prevalent in the developing world, accounting for up to 11% [25]. It is the third most common bladder cancer, after urothelial cancer and squamous cell cancer. 1 Primary adenocarcinoma of the bladder can be histologically classified as enteric, adenocarcinoma not otherwise specified, signet ring cell, mucinous, clear cell, hepatoid or mixed. 4 Recent publications have suggested that the extent of signet ring cell expression within the adenocarcinoma may be associated with worsening survival [26]. Furthermore, it also often encompasses urachal cancer, which, while most commonly an adenocarcincoma, can be squamous or urothelial in origin. 4 Results from the SEER database show that urachal cancer makes up about 10% of all adenocarcinomas of the bladder [27].

Small cell carcinoma is slightly unusual with regards to its histological classification in the latest recommendations from the World Health Organization. Any amount of small cell histology, even when present with predominantly urothelial elements, warrants the classification of primary small cell bladder cancer, rather than the classification of urothelial carcinoma with small cell differentiation. 4 This is largely due to the fact that the prognosis of the patient is determined by the small cell histology, even when present in small amounts in a tumour that is primarily urothelial in origin. Non-small cell elements, commonly urothelial or glandular, are often present [28]. Small cell carcinoma is a rare primary tumour of the bladder, accounting for about 1% of cases undergoing cystectomy. 47 The key to management is the realization that small cell carcinoma of the bladder is a systemic disease, and, as such, chemotherapy is crucial to achieving good outcomes [29].

Conclusion

Increasing attention in recent years, along with more specific and sensitive markers, has led to heightened recognition of the divergent differentiation often present in urothelial cancer. The most common non-urothelial histologies in bladder cancer are squamous, adenocarcinoma and small cell carcinoma, all of which often present at an advanced stage. Early detection and treatment of new / recurrent cases is required to optimize bladder preservation, reduce patient morbidity and increase quality of life.

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