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REVIEW ARTICLE

MANAGEMENT OF CARCINOMA BLADDER: A REVIEW LITERATURE

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ABSTRACT: Carcinoma of the bladder is a disease of the elderly. Bladder cancer is three times more common in males than in females and more common in whites than in blacks. Patients with bladder cancer have a 1% to 4% incidence of synchronous or metachronous upper tract urothelial tumors. There are many risk factors for urothelial cancer, classified into (1) Genetic (2) chemical exposure, and (3) chronic irritation. Genetic abnormalities associated with CIS include alterations in the retinoblastoma gene (Rb), p53, and PTEN. Chemical exposure has the most epidemiologic evidence to support it as an inciting agent (Aromatic amines, aniline dyes, and nitrites and nitrates). Chronic irritants include catheters, recurrent urinary track infections, Schistosoma haematobium, and irradiation. There are many studies that suggest high water consumption, vitamin intake, and various diets that are beneficial in preventing bladder cancer. However, none of these have shown any clear benefit with respect to prevention.

KEYWORDS: cancer, chemical, Chronic irritation, genetic material, males, urothelial, cancer.

INTRODUCTION: OVERVIEW: Like all malignancies, carcinoma of the bladder arises from aberration of normal mechanisms governing cell differentiation and proliferation. Essentially a disease of elderly, bladder cancer results from the induction of oncogenes or the negation of tumor suppressor genes resulting in a malignantly transformed cell. Formerly called transitional cell carcinoma, the most common type of bladder cancer is urothelial carcinoma. Exposure of host cells to certain viruses, chemical carcinogens, and chemical/physical stimuli play a dominant role in the carcinogenesis of bladder cancer.

Urothelial cancer has been characteristically defined as a field change disease in which entire urothelium of the renal pelvis to the urethra is susceptible to malignant transformation. These urothelial carcinoma cells can also implant and probably migrate to other sites of the urothelium, thus making it difficult to determine whether a recurrent tumor represents an inadequately treated initial tumor, tumor implantation/migration, or the effects of multifocal carcinogenesis.

EPIDEMIOLOGY: Bladder cancer is three times more common in men than in women.(1) Described as fourth most common cancer in men after prostate, lung and colorectal cancer, and the ninth most common cancer in women.(1) Bladder cancer is a disease of older individuals with greater than 90% of diagnosis in patients more than 55 years of age;although uncommon bladder cancer can occur in young adults and even in children.(2) The incidence of bladder cancer has been gradually increasing by approximately 40% according to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Registry.(3) In united States an over-all risk of developing bladder cancer is approximately 1 in 28.(4,5)

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ETIOLOGY: The etiology of bladder cancer appears to be multifactorial with exogenous environmental factors, as well as endogenous molecular factors playing. The link between bladder cancer and environmental carcinogen has long been observed.[6] Factors related to bladder cancer's development and progression include occupational exposure to chemicals; cigarette smoking; coffee drinking; ingestion of analgesics or artificial sweeteners; bacterial parasitic, fungal and viral infections: harboring of bladder calculi, and receiving genotoxic chemotherapeutic agents.

Molecular instabilities and abnormal metabolic pathways may likewise play a role in BC development and progression. Pathways involved in altered chemical metabolism of exogenous carcinogens have included aberrant cytochrome P450 metabolism(Associated genetic defects), glutathione-s-transferase abnormalities, and N-acetyltransferase genetic and metabolic derangements.[7,8,9,10] Genetic instability may result in abnormal activity of oncogenes resulting in aberrant protein expression, cellular proliferation and resistance to apoptosis.[10,11]

Tumor suppressor genes abnormalities associated with BC include p53, p21, p16 and Rb(retinoblastoma) tumor suppressor genes that may have mutated or inactivated and such defects may thereby predispose to cell dysregulation and tumor cell development and progression.[12-15] Increasing evidence suggests that genetic predisposition has a significant influence on BC incidence especially via its impact on susceptibility to other risk factors.[16,17]

Tobacco smoking is the most important risk factor for BC, amounting for 50% of cases.[16,18] Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons which are renally excreted.

Occupational exposure to aromatic amines, policyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC and such occupational exposure occurs mainly in industrial branches processing paint, dye, metal and petroleum products.[16,19-21] Exposure to arsenic in drinking water increases BC risk.[16,22] It is suggested that cyclophosphamide and pioglitazone are weakly associated with BC risk.[16] Schistosomiasis is a cause of BC particularly SCC.[16]

PATHOLOGY OF CARCINOMA BLADDER: Bladder urothelium is lined by transitional cells that can transform into a variety of malignant tumors. Understanding the pathology of urothelial carcinoma is critical in determining prognosis, as the most important risk factor for progression is tumor grade rather than stage.[23] Up to 80% of urothelial tumors are non–muscle invasive at presentation and can include papillary urothelial neoplasm of low Specific malignant potential (PUNLMP), CIS, and low- and high-grade urothelial cancers. Muscle-invasive bladder cancer is by definition high grade, with the majority spreading via direct extension from surface urothelial carcinoma through the subepithelial connective tissue into the muscularispropria. PUNLMP has minimal cytologicatypia and has very little invasive or metastatic potential but recurrence is seen after resection.[24,25]

CIS is characterized by higher rates of progression and is a flat, high-grade tumor within the superficial epithelium.[23] CIS represents high-grade disease and is associated with genetic alterations that are similar to those found in other high-grade urothelial subtypes. CIS is characterized by a reddish, velvety appearance and can often be mistaken for the edematous changes of radiation cystitis. Despite its unassuming name, CIS can progress to invasive disease and also demonstrate pagetoid spread to the ureters and prostatic urethra in some cases.[26] Genetic abnormalities are different from high-grade lesions and most commonly include deletion of 9q.[27] Higher progression and mortality rates are noted with high-grade disease, believed to be secondary to genetic

abnormalities distinct from low-grade lesions, which confer the ability to invade the underlying stroma. High-grade tumors are composed of fused papillary stalks with undifferentiated cancer in the urothelial layer. Transitional cell carcinoma is the most common subtype and is present in over 90% of tumors.[28]

CLINICAL PRESENTATION, DIAGNOSIS AND EVALUATION: The most common presenting symptom of bladder cancer is painless hematuria which occurs in majority of patients, is continuous or intermittent and gross or microscopic. From microscopic hematuria screening studies, it has been estimated that 1.3% of patients will have underlying diagnosis of BC although it is more likely in patients with gross hematuria.[29,30,31] All patients with hematuria, particularly those without evidence of infection, stone or other causative factors should undergo cystoscopy and upper tract imaging.[32,33] Irritative voiding symptoms including frequency, urgency and dysuria are particularly associated with carcinoma in situ. Indeed the diagnosis of BC is a consideration in patients with irritative voiding symptoms in the absence of infection. (AUA February 12, 2014).

BIMANUAL EXAMINATION: The physical examination of patients with bladder cancer is often unremarkable especially in case of non- muscle invasive disease. A bimanual exam at the time of TURBT may help with clinical staging especially for patients with muscle invasive disease. (AUA February 12, 2114).

URINARY CYTOLOGY: It is important to examine the specimens of urine or bladder- washings for cancer cells as this has high sensitivity in high grade tumors but low sensitivity in low grade tumors. The sensitivity of cytology in CIS ranges from 28 to 100%.[34] The interpretation of cytology is user dependent[35] and evaluation is effected by UTI, low cellular content or calculi; specificity may be even 90% in good hands hands.[36]

URINARY MARKER TESTS: For being a good bladder cancer marker, the test should be technically simple, of low cost, with good reliability, with high specificity and should be able to detect cancer before it escapes curative treatment.[36] There are numerous urinary tests for detection of bladder cancer.[36-42] The recently investigated tests markers include Quanticyt, BLCA-4, Hyaluronic acid, telomerase, Lewis X blood group antigens, microsatellite polymorphism analysis, cyto-keratins and surviving.[43,44] Other tests are BTA stat test, BTA trak test, Nuclear matrix protein (NMP) 22, Immunocyt and UroVysion. Urinary marker tests detect less than half of the low grade tumors that are detected by cystoscopy.[39,42] The quality of follow-up cystoscopy can be impoved by the knowledge of positive test results (microsatellite analysis).[45]

IMAGING: The various imaging techniques are intravenous urography, computed tomography, MRI and ultrasonography. IVP will show filling defects but there is low incidence of significant findings with this method.[46,47,48] Computed tomography is used as an alternative method of investigation in some hospitals instead of intravenous urography.[49] In muscle invasive bladder tumors, Ct urography gives more information than IVU including the status of lymph nodes and adjacent organs.

CYSTOSCOPY AND FLUORESCENT CYSTOSCOPY: The diagnosis of papillary bladder carcinoma depends on cystoscopy examination and histological examination of the tissue. CIS is diagnosed by

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cystoscopy, urine cytology and HPE of multiple biopsies.[50] Flexible instrument with local anesthesia will allow better compliance.[51] If tumor has been visualized previously diagnostic cystoscopy may be omitted.[52] Fluorescent cystoscopy has been investigated to increase the detection of occult papillary lesions and CIS. Intravesical instillation with 5-aminolevulinic acid (5-ALA) is done which enhances the protoporphyrin IX visualization through uptake by cancerous cells. With blue light protoporphyrin IX becomes readily visible with an appropriate filter on the cystoscopy.[53] Improved detection may increase tumor detection rate and facilitate eradication and there by lower recurrence rate.[54,55] 5-ALA enhanced cystoscopy appears to improve sensitivity in detecting NMIBT.[53,56]

TRANSURETHELIAL RESECTION: The diagnosis of bladder carcinoma is made after TUR of the bladder lesion.[57] While tumor is resected at the time of TUR, it provides deep enough resection and biopsy to determine the depth of invasion for adequate staging information.[58]

PROGNOSTIC INDICATORS: The most important prognostic indicator with regard to the disease recurrence and progression has long been the tumor grade.[59, 60,61]A revised consensus classification has been given by members of WHO and international society of urologic pathologists published in 2004.[62] Also other features with prognostic significance as regards to disease recurrence are tumor multiplicity and tumor size.[63,64] T1 tumors histologically portend disease recurrence, response to therapy and progression.[65-69] A number of molecular markers with regard to their ability to predict disease recurrence, response to therapy and progression include Lewis antigen, flow cytometry, tumor suppressor gene p53 and Rb, epidermal growth factor, CD44,matrix metalloproyeinses and urinary plasminogen activator.[44,70,71]

MANAGEMENT OF NON MUSCLE INVASIVE BLADDER TUMORS: Approximately 70% of bladder tumors are non- muscle invasive at presentation out of which 70% present t as stage Ta. Recurrence is common in all patients with non-muscle invasive urothelial cancer but can often be controlled successfully with transurethral surgery, intravesical therapy or a combination.

TURBT: Under regional or general anesthesia is the initial treatment for most of the non-muscle invasive bladder carcinoma. A careful cystoscopy examination of the bladder and urethra should be done before TUR.[72] Small tumors less than 1 cm can be resected en block while larger tumors should be resected in fractions including the exophytic part of the tumor, the underlying bladder wall and the edges of the resection area. This approach will provide good information about vertical and horizontal extent of the tumor and helps to improve the completeness of resection.[73] Complete and correct resection is essential for good prognosis[74] and absence of detrusor muscle in the specimen is associated with higher risk of residual disease and early recurrence.[75] After removal of all visible tumors, adjuvant intravesical immunotherapy or chemotherapy can be used.[76] Compared to mono polar resection, bipolar electro- cautery system may reduce the risk of complications eg., bladder perforation due to obturator nerve stimulation.[77]

OFFICE BASED FULGRATION/ENDOSCOPIC MANAGEMENT: Patients with a history of small, low grade recurrence can be managed in the office setting/OPD using diathermy or laser ablation under intravesical local anaesthesia.[78]

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BLADDER AND PROSTATIC URETHRA BIOPSIES: The risk of prostatic urethra and ducts' involvement is higher if tumor is on trigone or bladder neck in the presence of bladder CIS and multiple tumors.[79,80] So when bladder CIS is suspected, or cytology is positive with no evidence of bladder tumor, or abnormalities of prostatic urethra are visible, prostatic urethral biopsies are recommended.[81]

REPEAT TURBT: Complete tumor resection not always be possible due to excessive tumor volume, anatomic inaccessibility, medical instability requiring premature cessation or risk of perforation. A second TURB should be done after incomplete initial TUR, if there was no muscle in the first specimen, in all T1 tumors and all G3 tumors except primary CIS. If equipment is available, flourescence guided biopsy should be performed instead of random biopsies when bladder CIS or high grade tumor is suspected. Second TURBT can increase the recurrence-free survival.[82,83]

ADJUVANT THERAPY: The high variability in the three month recurrence rate indicates that TUR is incomplete or provokes recurrence in a high %age of patients.[74] Hence it is essential to consider adjuvant therapy in these patients. Early single instillation has been shown to function by the destruction of circulating tumor cells resuloting from TUR and by an chemo resection on residual tumor cells at the resection site and on small overlooked tumors.[84-87] One immediate instillation of chemotherapy after TUR reduces recurrence rate by 11.7% compared to TUR alone.[88] In low risk patients a single immediate instillation reduces risk of recurrence and is considered standard treatment.[88]Also adapting urinary pH, decreasing urinary excretion and buffering the intravesical solution reduces the recurrence rate.[89]

BCG therapy prevents or at least delays the risk of tumor progression.[90,91] Five meta-analysis have confirmed that BCG after TUR is superior to TUR alone or TUR and chemotherapy for prevention of recurrence of non-muscle-invasive tumors.[92,93-96] BCG instillations are given in 6-weekly schedule that was introduced by Morales in 1976.[97] However intravesical BCG therapy is associated with more side effects than with intravesical chemotherapy[98] and BCG should not be administered i) during the first two weeks after TUR, ii)in patient with macroscopic hematuria, iii)after traumatic catheterisation, iv) immune-compromised patients, v) personal history of BCG sepsis and vi) in patients with symptomatic UTI. In non-muscle-invasive tumors, patients may benefit from BCG instillation in cases of recurrence after chemo therapy. Prior intravesical chemotherapy has no impact on effects of BCG therapy.[92]

INTERFERON: Interferons are glycoproteins produced in response to antigenic stimuli. Intra-vesical interferon alfa-2b has been shown to have activity in non-muscle invasive urothelial carcinoma both as monotherapy and most recently in combination with low-dose BCG therapy.[93-97]

INTRAVESICAL CHEMOTHERAPY:

MITOMYCIN C: Mitomycin C is a 334-KD alkylating agent that inhibits DNA synthesis. The drug is usually instilled weekly for 6 to 8 weeks at the dose ranges from 20-60 mg. Methods to enhance the concentration and activity of mitomycin in urine have been described for improved recurrence free survival and prolonged median time to recurrence.[98] Perioperative mitomycin C should not be administered patients with known or suspected bladder perforation following TURBT as a small number of serious complications related to mitomycin C extravasation have been reported.[99,100,101]

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DOXORUBICIN AND ITS DERIVATIVES: Doxorubicin (Adriamycin) is a 580 KD anthracycline antibiotic that act by binding DNA base pairs, inhibiting topoisomerase II, and inhibiting protein synthesis. The principal side effect of intravesical doxorubicin is chemical cystitis, which can occur in up to half of the patients. Valrubicin is a semisynthetic analog of doxorubicin that has been approved by the FDA for treatment of BCG refractory CIS in patients who cannot tolerate cystectomy, with modest efficacy observed in this setting.[102]

THIOTEPA: Thiotepa (triethylenethiophosphoramide) is the only chemotherapeutic agent approved by the FDA specifically for the intravesical treatment of papillary bladder cancer.it is an alkylating agent and is not cell cycle specific. The lower dose appeared to be s effective as higher in a comparative study when the concentrations were same.[103]

GEMCITABINE: Systemic gemcitabine in combination with cisplatin has been shown to result in similar survival rates compared to traditional chemotherapy but with over all better patient tolerability and better safety profile.[104]

PHOTODYNAMIC THERAPY: The photodynamic has antitumor effects due to creation of reactive oxygen species that result from activation of a photo-sensitizing agent. The agent is activated by absorbance of wavelengths of light specific for the spectrum of the agent.[105,106] However there very few reports of the success of photodynamic therapy for bladder carcinoma with long term follow-up.[107,108]

LASER ABLATION THERAPY: Laser is not optimal for treatment of new bladder lesion as tissue samples are requisite to determine depth of invasion and tumor grade. Appropriate patients for this therapy have papillary, low grade tumors and history of low-grade, low-stage tumors.[56]

RADICAL CYSTECTOMY FOR NMIBC: Radical cystectomy can be considered in selected patients with NMIBC. It has been shown in retrospective study that cases with high risk NMIBC who undergo early rather than delayed cystectomy for tumor relapse after initial therapy with TURB and BCG have better survival rate.[109]

FOLLOW-UP OF PATIENTS WITH NMIBC: The potential of disease recurrence and progression even in long term typically requires lifelong follow-up.[76,110,111,112] Patients should be assessed every three months in the first two years followed by every six months for another 2-3 years and then annually.[76,113] In high risk tumors it should be done after 3 months for a period of two years and every 6 months there-after.

MANAGEMENT OF INVASIVE AND METASTATIC BLADDER CANCER: Clinical presentation, diagnosis and evaluation are to be done as already described. Bimanual examination is a sensitive and inexpensive method for obtaining evidence of extra vesical extension of bladder cancer. Restaging TUR not only provide information about residual disease, but in patients for whom bladder sparing strategies are contemplated, the reduction of stage to p0 by second TUR has been associated with favorable long term survival in selected patients.

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RADICAL CYSTECTOMY FOR INVASIVE BLADDER CANCER: Radical cysto-prostatectomy in the male patient which includes complete removal of the bladder and prostate in men and anterior exenteration in the female patient which includes the bladder, uterus and all or part of vagina in women remains the standard surgical approaches to muscle invasive bladder carcinoma.[114]Standard radical cystectomy includes bilateral pelvic lymphadenectomy and, in the male patient, subsequent removal of the prostate and bladder en bloc. In the female patient, anterior exenteration requires removal of the uterus, fallopian tubes, ovaries, bladder, urethra, and a segment of anterior vaginal wall. With radical cystectomy alone, 5 year survival rate with recurrence free survival ranges between 62% to 68%.[115,116] Disease specific and overall survival for patients with high-grade UC are closely linked with pathologic disease stage, with 5 year survival dropping to 26% for men with positive lymph nodes [116]. Studies suggest that surgical techniques including extent of lymph node dissection may influence outcomes after radical cystectomy.[117,118,119]

Recent experiences with laparoscopic and robotic radical cystectomy and lymphadenectomy have similar morbidities and functional outcomes to open approaches.[120]Despite aggressive and often early intervention, many patients with muscle-invasive BC treated by surgery alone still remain at considerable risk for recurrence and death from BC.[115]

RADIATION THERAPY: Results of a clinical trial comparing neo-adjuvant radiotherapy before cystectomy to definitive radiotherapy followed by salvage cystectomy for progressive disease with advanced UC were published by Bloom et al.[121] The 10-year cancer-specific mortality ratio was 1.77 in favor of non-adjuvant radiation followed by surgery over the radiation with delayed salvage cystectomy.[121] A nonrandomized study (Skinner et al) for the efficacy of neo-adjuvant radiation before cystectomy with cystectomy alone showed no effect on time to recurrence or overall survival with 1600 rad of radiation given for 4 days prior to surgery.[122]

CHEMOTHERAPY: Despite excellent control with surgery for localized disease, no of patients recue after radical cystectomy alone especially those with advanced disease at the time of diagnosis. Multiple studies have demonstrated the effects of cytotoxic chemotherapy for UC.[123,124] A no of single-agent therapies have demonstrated some efficacy after radical cystectomy.[125,126] With a lack of clear benefit with single agent therapy, combination chemotherapy has also shown to have a more promising effect on BC.[127] Delay of radical cystectomy has been shown to correlate with decreased survival and may mitigate the advantages of neo-adjuvant therapy.[128] In general, patients are more likely to tolerate the effects of chemotherapy before major surgery and any impairment in renal function after surgery may limit the use of certain effective agents and dosages.[129] A retrospective study has shown that adjuvant chemotherapy is independently associated with improved overall survival especially in highest-risk quintile.[130]

BLADDER SPARING THERAPIES: Herr et al described the results of patients with muscle invasive UC choosing to follow their BT after restaging TUR showed either no residual or only superficial disease.[131] After a follow-up of 10 years 76% patients (75 out of 99) were alive and out of them 57 patients had their bladder intact suggesting that some carefully selected patients with muscle invasive disease could experience long term survival with only local resection.

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METASTATIC AND LOCALLY ADVANCED BLADDER CARCINOMA: Prior to the development of effective chemotherapy median survival with metastatic BC was 3-6 months. Platinum based chemotherapy (Gemcitabine with either cisplatin or carboplatin) may be recommended as initial treatment for patients with advanced invasive urothelial carcinoma.[104] Locally advanced BC (T4b) - each case is to be considered individually and initial treatment with combination chemotherapy followed by reassessment and further local measures.

SURVEILANCE: Bladder cancer is a common, heterogeneous disease associated with high rate of recurrence and that often requires lifelong surveillance.[132-135] Treatment options are limited with initial management involving TURBT followed by adjuvant instillations of chemotherapy or immunotherapy to reduce recurrence and prevent disease progression.[133] Each of the intravesical therapy option has associated toxicities that impair patient compliance.[136-140]

Cystoscopy Surveillance Office –based cystoscopy offers rapid, relatively painless visual access to the urothelium. Papillary tumors are readily identified arising from the smooth bladder surface. CIS is classically described as a velvety red mucosal patch. The absence of recurrence on 3-month surveillance cystoscopy in patients with TaG1 tumor is associated with recurrence rates so low that annual cystoscopy appears safe even at that point beginning 12 months after initial resection.

URINE CYTOLOGY: urine cytology is not a laboratory test – it is the pathologist's interpretation of the morphologic features of shed urothelial cells. Poor cellular cohesion in high grade tumors, especially CIS, enhances the yield of cytology. It is of very high specificity, is the most important featuring of cytology, because a positive reading regardless of cystoscopy or radiographic findings suggests the existence of malignancy in vast majority of patients. Cytology has very high specificity but has low sensitivity for both low grade tumors, including CIS in recently published reports.

CONCLUSION: An old saying a stitch in time saves nine holds true for bladder cancer. In spite of technological advances in imaging, better understanding of the pathology and much wider availability of instrumentation, the number of cases of bladder cancer have increased. This increase can be attributed to greater awareness of the people towards the disease and the presence of better medical facilities available. Early diagnosis of the disease is the most important prerequisite for a complete cure of the disease. Clinical suspicion and early intervention can indeed halt the disease process because bladder cancer is elusive to imaging at an early stage. Medical centers providing specific care for bladder cancer should educate masses regarding the same so that awareness can spread and the disease are nipped in the bud.

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