

UROLOGY FOR THE PRACTITIONER

SUPERFICIAL BLADDER CANCER

EPIDEMIOLOGY, DIAGNOSIS AND MANAGEMENT

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EPIDEMIOLOGY

Bladder cancer is the second most common urologic malignancy after prostate carcinoma. It is the fifth most common cancer accounting for approximately 2% of all malignant diseases and worldwide it is continuing to rise by 5-10% every 5 years [1]. Transitional cell carcinoma (TCC) is the most common histologic form of bladder cancer accounting for around 90% of bladder cancer whereas squamous cell carcinoma accounts for 7 to 9% and adenocarcinoma for 1 to 2%. Superficial bladder tumors account for approximately 70% to 80% of TCC and of these around 70% are papillary confined to the epithelium (stage Ta), 20% invade the lamina propria (stage T1) and 10% are carcinoma in situ (Tis) [2]. Sixty to 70% of superficial disease recur within 5 years of initial treatment and depending on grade, stage, presence of CIS and length of follow-up anywhere between 10-30% will progress [3]. The remaining 30% of urothelial (transitional cell) carcinomas are muscle invasive at the time of their initial clinical presentation and more than half of them are expected to develop metastatic disease [3].

Bladder cancer has a male-to-female ratio of 3:1 with peak incidence in the sixth to eighth decade. In men it is the fourth most common cancer (6% of new cancer cases) and the seventh most common cause of cancer related deaths. In women it is the ninth most common cancer (2% of new cancer cases) and the tenth to twelfth most common cancer related deaths [3]. This gender bias might be explained at least partially by the relationship between environmental exposure and the development of bladder cancer because more than half of bladder cancer in men can be attributed to cigarette smoking. A variety of other factors including differences in nutritional intake, genetic, hormonal, or anatomic (e.g. relative urinary retention in older men because of prostatic enlargement) predispositions may account for this puzzling trend. It is rare before the age of forty and extremely rare in the first two decades of life. In adolescents and adults younger than age 30, bladder cancer tends to express well differentiated his-

tology and behave in a more indolent fashion. However, the risk for disease progression is the same, grade for grade, in younger patients and in older ones [3].

In Lebanon, bladder cancer ranks one in incidence among malignancies according to a recent broad based study that took into account all the cancer cases registered in Lebanon in years 1993 and 1998 [4]. Studies from Lebanon dating back to the years 1966 and 1985 showed that bladder cancer ranked second after lung cancer in men [5].

RISK FACTORS FOR BLADDER CANCER

Cigarette Smoking • Cigarette smoking increases the risk threefold to sevenfold, depending on the pack-years and smoking habits. Fifty to 80% of all bladder cancers among men are associated with the use of cigarettes. Cigars, pipes, and smokeless tobacco invoke a much smaller risk [6]. Risks associated with cigarette smoking may persist for many years. A decrease in smoking related incidence of bladder cancer to a rate equal to that for the nonsmoking population does not occur until after 12 to 15 years of abstinence [7]. Smoking is the most significant risk factor for late invasive recurrence [8].

Industrial Carcinogens • In 1895, the initial link was made between bladder cancer and exposure to aniline dyes used in the color fabrics [3]. Further connections have been established with the rubber manufacturing and textile printing industries. Exposure to aromatic amines is the most common event, and substances such as 2-naphtylamine, 4-aminobiphenyl, and 4-nitrobiphenyl are believed to be potent carcinogenic elements. The latency period may be several decades [1, 3].

Chemotherapeutic agents • As high as a ninefold relative risk may exist for patients exposed to the immunosuppressive agents cyclophosphamide or ifosfamide. The presence or absence of hemorrhagic cystitis induced by these agents does not correlate with the likelihood of developing carcinoma. The major toxic metabolic agent is acrolein, and most lesions present as muscle-invasive tumors. Administration of Mesna at the time of therapy reduces the urothelial injury by acrolein [3].

Schistosomiasis • *Schistosoma haematobium* is endemic in Egypt and Sudan. 30% of the associated cancers are TCC while 70% are squamous cell carcinomas [6].

Phenacetin • Phenacetin is a major compound of analgesic preparations. Massive cumulative ingestion of this

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compound (5 to 15 kg over a 10-year period), which has a chemical structure similar to that of aniline dyes, is associated with an increased risk for TCC of the renal pelvis and bladder. A long latency period is characteristic [1, 3].

Genetic susceptibility • Aromatic amines from cigarette smoke or occupational exposure are metabolized by N-acetyltransferases (NAT). Polymorphic variations in the genes coding for these enzymes have resulted in varying degrees of acetylation activity (slow versus rapid) that result in varying degrees of detoxification of these substances. The relative risk of developing bladder cancer may be 1.5 to 2.2 times higher in slow versus rapid acetylators [3].

Glutathione S-transferase M1 (GSTM1) is another gene that is known to be polymorphic in humans and is important in the detoxification of chemicals via conjugation to glutathione. Multiple compounds found in cigarette smoke including arylamines, nitrosamines and metabolites of polycyclic aromatic hydrocarbons serve as substrates for GSTM1. Multiple epidemiologic studies have found an association between the GSTM1 null phenotype and an approximately 1.5 times increased risk of developing bladder cancer [1, 3].

Pelvic Irradiation • A 2- to 4-fold increase in bladder cancer incidence has been noted in women treated for cervical malignancy. These tumors are characteristically high grade and locally advanced at the time of diagnosis.

Coffee • Coffee and tea have been implicated in a few studies. The relationship is not strong and is further weakened by the confounding occurrence of associated smoking.

Saccharin • Artificial sweeteners have been shown to result in bladder cancer in experimental animals. No association has been proven in humans.

CLASSIFICATION OF SUPERFICIAL BLADDER CANCER

Bladder TCC is classified into superficial or muscle-invasive depending on whether or not detrusor muscle (muscularis propria) has been invaded by the tumor.

Superficial bladder cancer includes papillary epithelial confined tumors classified as stage Ta (noninvasive carcinoma), flat in situ carcinomas (high grade flat abnormality confined to the bladder mucosa) classified as Tis, and tumors that have invaded the lamina propria classified as stage T1 (superficially invasive carcinomas) [6, 9]. Although not formally characterized in the Union Internationale Contre le Cancer TNM staging of 1997, stage T1 can be further subdivided into stage T1a tumors which extend to but not through the muscularis mucosae and stage T1b tumors which extend through the muscularis mucosae but remain confined to the lamina propria [7].

Until now there is no uniformly accepted grading system of bladder cancer [6]. Most commonly used systems are based on the degree of anaplasia of the tumor cells and group carcinomas into three or four grades corresponding to well differentiated, moderately differentiated, and poorly differentiated tumors. The grading criteria so far have been number of cell layers, cellular and nuclear pleomorphism, nuclear-to-cytoplasmic ratio, base-to-surface cellular maturation, preservation of cell polarity, number of mitotic figures, ploidy, and blood group antigens status. In the 1998 WHO/ISUP (International Society of Urological Pathologists) Consensus Classification, carcinomas were classified as either low grade or high grade. The older Stage Ta grade I carcinoma was further subdivided into papillary neoplasm of low malignant potential (LMP) and low-grade carcinoma [9]. The WHO classification published in 1999 takes more into consideration the clinical evolution and prognosis than that of previous years [10]. It uses the term WHO 1 for low-grade carcinoma and allows for the separation of high-grade carcinoma in WHO 2 and WHO 3 [11]. One study demonstrated that tumors of WHO grades 2 and 3 have different clinical behaviors. Of patients with WHO grade 3 tumors, 45% progressed as compared with 20% of those with grade 2 tumors [10].

Papillomas and low-grade lesions are almost always papillary. Higher grade lesions may be solid or papillary. A strong correlation exists between tumor grade and tumor stage, with most well differentiated and moderately differentiated tumors being superficial and most poorly differentiated tumors being muscle invasive [11]. Stage for stage, however, there is a significant correlation between tumor grade and prognosis. The correlation between tumor stage and prognosis is even stronger.

PRESENTATION

Painless hematuria is the most common presenting symptom of bladder cancer and occurs in about 85 percent of patients. It can be gross or microscopic and the amount of hematuria is not necessarily proportional to the severity of the lesion. The symptom complex of bladder irritability and urinary frequency, dysuria and urgency is the second most common presentation affecting around 20 percent of patients with bladder cancer, particularly those with diffuse carcinoma in situ or invasive bladder cancer. These symptoms however almost always occur with (at least) microscopic hematuria. Other less common presenting signs and symptoms of bladder cancer include flank pain from ureteral obstruction, lower extremity edema and a pelvic mass. Sometimes bladder cancer is discovered incidentally at the time of cystoscopy for totally unrelated reasons such as evaluation for outlet obstruction. Rarely, patients present with symptoms of advanced disease, such as weight loss and abdominal or bone pain.

INVESTIGATIONS

After initial urinalysis, the routine workup consists of imaging of the upper tract and bladder with excretory urography (IVP), ultrasound or CT scan followed by urine cytology and urinary markers and cystoscopy if need be [12-13]. New techniques are being introduced to enhance the sensitivity and specificities of these standard tests.

Excretory Urography • Excretory urography or intravenous pyelogram (IVP) is an excellent modality in the initial investigation of hematuria-bladder cancer to rule out concomitant upper tract involvement or obstruction and to be used as a reference examination for future pyelograms [9]. Unfortunately small bladder tumors and CIS do not show on the bladder film of an IVP.

Ultrasonography • Good imaging modality to assess hydronephrosis, parenchymal renal lesions, small and large bladder tumors with full bladders. It is deficient in evaluating function and details of the pelvicalyceal system and ureter.

Computerized Tomography (CT) • Excellent in identifying masses, details of the urinary system, pelvic and abdominal organs. It is expensive and subjects the patient to higher radiation and rarely needed for superficial bladder tumors.

Conventional Urine Cytology • Urine cytology has been the mainstay of screening and surveillance of TCC. It provides a convenient noninvasive means for observing patients with history of bladder cancer, for evaluating patients with microscopic hematuria or irritative symptoms, and for screening high risk populations such as those exposed to known carcinogens [14]. It is highly specific (81%) for the diagnosis of TCC but is fairly insensitive (40 to 60%). This overall low sensitivity of urine cytology is explained almost exclusively by its unreliable detection of well-differentiated, low-grade lesions because the cells of such tumors so closely resemble normal urothelium and because well-differentiated cancer cells are more cohesive and thus not readily shed into the urine. In contrast, urine cytology has excellent performance statistics in patients with high-grade lesions with a sensitivity of at least 90% and specificity reaching 98 to 100% ; however, it cannot reliably determine whether a lesion is in situ or invasive cytologically because both have similar cytomorphology [14]. Urine cytology has a high positive predictive value such that a positive cytologic diagnosis is highly predictive of TCC, even in the presence of normal cystoscopy because malignant cells may appear in the urine long before any cystoscopically detectable lesion appears [14].

One variable affecting the sensitivity of urine cytology is the type of specimen. Voided urine obtained non-invasively results generally in hypocellular and degener-

ated specimens with significant amounts of skin and vaginal contamination particularly in female patients. Sensitivity is increased by taking 3 separate specimens on 3 separate days or by obtaining catheterized urine and bladder washes which have higher cellularity and less contamination although they require invasive procedure and may introduce instrumentation artifact.

Urethrocystoscopy • Urethrocystoscopy (UCS) is currently the gold standard for the diagnosis of bladder cancer [15]. UCS is performed in an outpatient setting if imaging modalities fail to show the cause of the hematuria. The overall sensitivity of cystoscopy in detecting bladder malignancies is only 70% because although papillary tumors are readily detected, flat urothelial lesions, such as severe dysplasias and CIS, are often hard to distinguish [12]. Therefore, in cases of positive urine cytology and negative cystoscopy random biopsies should be performed. However, if the imaging modalities show a bladder tumor to be the cause of bleeding then cystoscopy will be done as part of the TUR under spinal or general anesthesia.

Flow Cytometry • This technique consists of an automated method of determining bladder cell DNA content. Therefore it can quantitate the aneuploid cell populations and proliferative activity (percent S-phase cells) in a tumor. Arbitrary limits are set to define normality. Aneuploidy is primarily a feature of high-grade TCC and TCC in situ and about 80 to 90 percent of these tumors can be identified by flow cytometry. On the other hand most low-grade bladder cancers are diploid, and therefore assessment of aneuploidy is useless in screening for well-differentiated lesions which often produce false negative results [14]. In addition, inflammatory cells can form a hyperdiploid cell fraction, thus interpretation of standard flow cytometry becomes more difficult. In general, flow cytometry has not been found to be more clinically valuable than conventional cytology.

Urinary Tumor Markers • The clinical applicability of a bladder tumor marker is multifaceted and includes early detection, recurrence monitoring, individualized treatment options, and prognostic capability [11]. New elaborative and rapid assays that may circumvent the low sensitivity and poor reproducibility of urine cytology in particular in low-grade low-stage disease are being studied. Ideally such assays would be fast, cheap, and easy to find, with high sensitivity and specificity and office-based applicability. Currently the most promising urinary tumor markers include bladder tumor antigen (BTA), nuclear matrix proteins, fibrin/fibrinogen degradation products, telomerase, and hyaluronic acid/hyaluronidase [14]. Although these tests offer higher sensitivity than urine cytology, their main limitation is a high false-positive rate when used in patients with history of calculi, lower urinary tract symptoms or cystitis. The view of the current literature is that none of these biolog-

ical markers can completely replace cystoscopy or cytology which remain the gold standards for detection and screening of bladder tumors [11, 15].

H related protein test (BTA stat/TRAK) : A human complement factor H-related protein has been isolated from the urine of patients with bladder cancer but not in the majority of healthy controls. Identifying this factor using monoclonal antibodies in a qualitative (BTA stat) or quantitative (BTA TRAK) assays demonstrates greater sensitivity but lower specificity than urine cytology [14]. In various studies, the overall sensitivity of the BTA stat to detect bladder carcinoma is reported at 57-83%, with specificity in the 57-73% range [20]. The BTA stat test has been approved by the Food and Drug Administration (FDA) for use as an aid in the management of bladder carcinoma patients in conjunction with cystoscopy [11].

TREATMENT

According to the American Urological Association guideline (1999), the standard for all patients with superficial bladder cancer is complete eradication of all visible tumors if surgically feasible and if the patient's medical condition permits [16]. Surgical eradication can be performed by one of several methods, including electrocautery resection, fulguration or laser ablation.

a. Transurethral Resection of Bladder Tumor (TURBT) or Fulguration

Most patients with superficial bladder cancer can be adequately treated with transurethral resection or fulguration of the tumor. TUR will provide diagnosis, stages the disease, assesses the need for additional therapy and cures the problem. Despite a low incidence of complications, TUR for superficial bladder tumors is not morbid-free. In one study by Collado et al., the most common complication was intraoperative and immediate post-operative bleeding, followed by bladder perforation. A higher incidence of complications was correlated with large lesions and multiple tumors but not with tumor stage, grade or location. Some studies showed that perforation is more common in women due to the smaller thickness of the bladder wall [17]. At the time of initial tumor diagnosis, there is little doubt that total transurethral resection of all visible disease is appropriate to achieve optimal histological classification. Few notable exceptions are technically difficult location, very large almost certain to be deeply invasive malignancy and location within a diverticulum.

b. Laser Therapy

A variety of lasers have been employed to treat bladder tumors. For the laser treatment of bladder carcinoma in the fluid-filled bladder, most authors prefer the usage of the neodymium-yttrium-aluminum-garnet (Nd:YAG) laser because of its larger depth of penetration. Laser treatment of superficial bladder cancer has several advantages in comparison with electrocautery. It clearly

results in a decreased rate of local recurrence of superficial bladder cancer most probably because tissue denatured by the thermal energy becomes an infertile field for tumor implantation [12]. Unlike electroresection, laser coagulation is performed in the almost complete absence of bleeding and can even be carried out under anticoagulant therapy [12]. Because laser coagulation causes only little amount of pain, the procedure can be performed under local anesthesia, even in an office setting whereas electrocautery resection is painful and requires general or regional anesthesia. The major drawback of laser therapy is that no tissue is obtained and grading and staging of tumors cannot be performed on coagulated areas, and thus only patients with recurrent low-grade superficial bladder cancer are ideal candidates for laser coagulation. Because many patients with superficial TCC present with the same low-grade papillomas on each resection, it seems justified to laser coagulate this lesion without obtaining a biopsy. Primary bladder malignancies should always be resected to obtain proper material for histopathologic grading and staging of the underlying disease. But after resection the base of the tumor can be laser coagulated to achieve an additional safety zone and for lymphatic sealing.

c. Cystectomy

Total cystectomy is rarely required for patients with superficial bladder cancer except for those with symptomatic, diffuse, unresectable or recurrent T1 tumors.

STAGING

Pathological examination of the resected tumor by TUR (including muscularis propria) along with examination under anesthesia provides the local staging of the disease usually enough to proceed with additional therapy if need be. If the tumor is superficial, more elaborate staging techniques for evaluation of metastasis such as bone scan, computed tomography (CT), and magnetic resonance imaging (MRI) are not usually indicated. Such techniques are reserved for patients with documented muscle-invasive bladder cancer because it is very rare for metastases to be associated with superficial disease.

PROGNOSTIC INDICATORS

Approximately 60% to 70% of superficial lesions recur after therapy and 10 to 30% of these recurrent lesions will progress to a higher grade or stage. Overall 10% to 20% of carcinomas diagnosed initially as superficial will progress to muscle invasive bladder carcinoma [2]. The most clinically useful prognostic parameters for tumor recurrence and subsequent cancer progression in the patient with superficial tumors are tumor grade, stage, lymphatic invasion, tumor size, carcinoma in situ in neighboring or distant urothelial areas, tumor architecture (papillary or solid), multifocality, and time to tumor recurrence. The most important among these are tumor

grade, stage, and presence of carcinoma in situ, T1 sub-stage and time to recurrence [10]. Stage T1 is subdivided as by invasion of the muscularis mucosae [9, 10]. The lamina propria of the bladder contains a thin smooth muscle layer termed muscularis mucosae. Tumors that show invasion above this level are termed pT1a, and those that show invasion to or below the level of the muscularis mucosae are termed pT1b. Most studies report a higher progression rate and a lower 5-year survival rate in stage T1b compared with stage T1a tumors.

Intravesical Therapy

Due to the high rate of tumor recurrence after TURBT (70% within 5 years) and depending on the grade, stage, presence of CIS and length of follow-up, anywhere between 10-40% will progress, adjuvant treatment following the initial TUR became imperative. Since superficial bladder tumor is a field change disease due to an abnormally active urothelium, the concept of treating it by instilling a substance into the bladder to "bathe" the urothelium and prevent tumor recurrence and progression was very appealing. Hence, the concept of intravesical therapy evolved [2, 11]. Identification of patients with superficial bladder tumors who are at risk for tumor recurrence and tumor progression after surgical treatment is very important in the selection of candidates for adjuvant or prophylactic use of intravesical therapy. According to the American Urological Association guideline for the management of non-muscle invasive bladder cancer, intravesical therapy is recommended for treatment of CIS, T1 tumors and high-grade Ta tumors, multiple tumors and rapid recurrence in space and time [16]. Intravesical therapy can be in the form of chemotherapy or immunotherapy.

I. Intravesical Chemotherapy is the instillation of a certain dose of a specific chemotherapeutic agent into the bladder after completing the TUR on a preset schedule. While intravesical chemotherapy delays the time to first recurrence, studies have not been able to show that it has an influence on the time to progression [18]. The most commonly studied agents are the chemotherapeutic agents thiotepa, doxorubicin (Adriamycin), mitomycin C and epirubicin.

Triethylenethiophosphoramide (Thiotepa) : Intravesical chemotherapy began in the 1960s with the introduction of intravesical thiotepa. Before thiotepa, other agents used were silver nitrate, trichloroacetic acid, and podophyllin [3]. Thiotepa is an alkylating agent that acts by cross-linking nucleic acids and proteins regardless of the cell cycle [18]. A frequently recommended regimen includes six to eight weekly treatments followed by monthly treatments for one year. A meta-analysis of nine controlled randomized trials using thiotepa with different schedules as prophylactic treatment after TUR revealed only a slight decrease in tumor recurrence after drug instillation when compared with TUR alone. It is readily absorbed through the urothelium because of its

relatively low molecular weight (198Da) and causes myelosuppression in 15% to 20% of patients. White blood cell and platelets counts should be obtained before each thiotepa treatment [2].

Mitomycin C : Mitomycin (MMC) is a cross-linking agent that, in part, inhibits DNA synthesis. Other less well understood mechanisms contribute to its effectiveness. It is usually instilled weekly for 4 to 8 weeks at dose ranging from 20 to 60 mg. The response rate for CIS (58%) is somewhat higher than for papillary lesions (43%). The significant side effects of MMC are chemical cystitis (40% of patients) that may lead to bladder contraction, mural calcification, and genital skin rashes [3]. Systemic side effects are uncommon (less common than with thiotepa and ethoglucid) due to a low level of transurothelial absorption owing to its high molecular weight MW (334 kDa) [1]. Several trials have shown that mitomycin C is less effective in preventing tumor recurrence than BCG [1, 17]. It is the most expensive agent available [2].

Adriamycin (Doxorubicin) : Adriamycin (580kDa) is an anthracycline antibiotic that acts by binding DNA base pairs, inhibiting topoisomerase II, and inhibiting protein synthesis. The principal side effect is chemical cystitis (up to 50% of patients). It was shown to be less effective than intravesical BCG in the treatment of patients with carcinoma in situ and for prophylaxis against tumor recurrence [3]. Reduced bladder capacity and occasional allergic reactions have been reported. Systemic side effects are rare.

Epirubicin (4'-epidoxorubicin) : This derivative of doxorubicin has similar mechanism of action to doxorubicin with a more favorable toxicity profile [2, 18]. It is initiated 1 to 2 weeks after TUR and administered in a dose range from 50 to 80 mg/ml weekly for a total of 8 weeks and then monthly to complete one year of treatment. A recent study has shown that epirubicin might be more effective than adriamycin in decreasing tumor recurrence after TUR. The most common side effects are mild urinary symptoms [18].

Gemcitabine : The intravesical use of gemcitabine, a chemotherapeutic agent extensively used in the management of advanced and metastatic TCC, has been reported in patients failing traditional intravesical therapy including BCG and continue to have superficial disease and are not candidates for additional aggressive therapy. One to two gms need to be instilled weekly for 4-6 weeks [19].

Recently the practice of a single instillation of chemotherapy immediately following TUR (almost in the recovery room) has gained a wide spread acceptance and application since it has comparable results as the standard regimen as far as recurrence of the disease [20].

II. Immunotherapy

Intravesical Bacille Calmette-Guerin (BCG) Therapy : BCG is an attenuated strain of *Mycobacterium bovis* first used by Morales in 1976 to treat superficial bladder can-

cer [21]. It is currently considered to be the most effective form of intravesical therapy for the prophylaxis and treatment of superficial bladder cancer to prevent recurrences and progression in patients with CIS, T1 tumors and high grade Ta disease [2, 21-22]. In a recently published meta-analysis of 24 trials addressing the issue of the effect of BCG on progression, it was found that BCG reduces the progression by 23% [23]. BCG acts as a non-specific immune stimulant. After intravesical instillation and fibronectin mediated binding and uptake, an early inflammatory response occurs whereby different cytokines including Il-1, Il-2, Il-12, TNF- α and INF- γ are up-regulated [1, 21].

There are currently no clear guidelines for strains, doses and schedules used. The most commonly applied regimen is the weekly instillation of 81 mg dry weight BCG (120 mg wet weight) in 50 ml of saline for six weeks. Many investigators have experimented with smaller doses and different schedules but they have not gained wide spread acceptance. In addition, the issue of repeated courses and/or maintenance have been extensively addressed in the literature [24-25]. Lamm has demonstrated that in the selected patients with CIS, Ta and T1 tumors and following the induction six weeks, three weekly BCG instillations at 3, 6, 12, 18, 24 and 30 months was beneficial [24]. Yet, in a follow-up paper Lamm states that the optimal maintenance schedule remains to be identified [23].

Early administration of BCG after tumor resection is however associated with a higher rate of severe complications. Thus it is prudent to wait at least 2 weeks (and probably 3 to 4 weeks) following tumor resection before starting BCG therapy. The major side effect of BCG is bladder irritability consisting of dysuria, frequency, and urgency in up to 90 percent of patients. Granulomatous prostatitis occurs commonly following BCG therapy. Approximately 2% of patients will develop systemic symptoms (BCGosis) accompanied by fever longer than 48 hours and requiring antituberculosis therapy. About 0.4% of patients can develop frank BCG sepsis [26]. BCG should not be given to immunocompromised patients and should not be given to patients after traumatic catheterization.

Intravesical Interferon : Interferons have antiproliferative, antiangiogenic, and immunostimulatory properties [27]. Among several subtypes, interferon- α 2b has been the most extensively studied [28]. Toxicity is minimal and generally consists of flu-like symptoms in approximately 17% of patients [16]. As a prophylactic agent INF α has been shown to be inferior to BCG [2, 27]. However, several trials have demonstrated the potential superiority of the combination of INF and BCG to BCG alone or the possibility of decreasing the dosage of BCG. Presently the optimal dose or optimal role of interferon in intravesical therapy for superficial disease is incompletely defined.

FOLLOW-UP

There is no evidence-based schedule for patient follow-up. A reasonable approach consists of cystoscopy with cytology every 3 months for a year, followed by an examination every 6 months for a variable period, usually 2 years, after which they are performed once per year [9]. After a long tumor free interval, the frequency of examinations may be reduced [7]. However, some reports mentioned tumor recurrences even after 5 years post TURBT indicating that surveillance probably needs to be continued indefinitely. The newly described tumor markers may play some role in the future in modulating this schedule, perhaps decreasing the cystoscopy interval. Some studies recommend that follow-up may be less intense in patients who present initially with low grade carcinoma (pTaG1) [3, 9]. The development of upper tract tumors in these patients, although classically felt to be low, may be higher than previously suspected (10% to 30% up to 15 years), especially for those patients treated for carcinoma in situ. Therefore regular periodic intravenous urograms might be necessary. There is no established schedule for this monitoring test. Some authors consider routine follow-up urography neither necessary nor cost effective [29].

CONCLUSION

Superficial bladder cancer, defined as cancer that has not invaded the detrusor muscle of the bladder, represents the most common type of bladder cancer (70% to 80% of TCC). It includes papillary epithelial confined tumors (stage Ta), flat in situ carcinomas (Tis) and tumors that have invaded the lamina propria (stage T1). The peculiarity of this disease lies in its high rate of recurrence (60% to 70%) which constitutes a main financial and psychological burden for the patient and his family given the fact that 10% to 30% of these recurrent lesions will progress to a higher grade or stage. Thus treatment of superficial bladder cancer not only aims at eradicating the primary existing disease by resection of the tumor but also at preventing recurrence and progression to muscle-invasive disease by using the different agents of intravesical therapy which are still far from being ideal. Current studies are being conducted to determine tumor markers that can be of use in selecting patients at high risk for recurrence and progression who could benefit from a more aggressive management. Given the fact that in Lebanon bladder cancer ranks among the highest tumors in incidence, more public awareness of the risks of bladder cancer (such as tobacco use) and its most common manifestation (hematuria) must be sought. Possibly, prospective studies may be conducted to determine whether screening high risk populations in Lebanon, such as male smokers, by testing for microscopic hematuria might be a cost-effective way in earlier detection and management of bladder cancer.

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