Histopathological comparism between TURT biopsy and cystectomy specimen in Cystectomised patient for invasive bladder tumor

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الخلاصة:

ورم المثانة هو من اكثر الاورام انتشارا .ويتضمن مجال عريض من الانواع النسيجيه المختلفه التي تنشا من بطانة المثانه والحالب .الهدف من الدراسة هو للمقارنة بين نتائج الفحص النسيجي للاورام المستاصلة بالناظور وتلك المستاصله جراحيا.

نستنتج ان العلاج الجراحي يجب ان ياخذ به في المرضى المصابين بورم المثانه المتقدم لان الفحص النسيجي للعينه الماخوذه بالناظور قد يعطي تقييم اقل لسلوك الورم او قد يفشل في تشخيص التغييرات النسيجيه والاختلافات النسيجيه.

ناظور المثانه اساسي لقطع الورم وتجهيز نسيج لغرض المتابعه النسيجيه ولاغراض البحوث.

Abstract

Bladder cancer is one of the most prevalent types of cancer , it comprises a broad spectrum of histological heterogenous tumor types arising predominantly in the epithelium (urothelium)lining of the urinary bladder and the ureters .cystoscopy is essential for resction and provides valuable material for pathological observation and research purposes. The aim of this study is to evaluate the histopathological results of endoscopic biopsy taken by (TURT) from patients with bladder tumor by comparison with the histopathological results of cystectomy specimen .

It is concluded that surgical option in treatment of invasive bladder cancer in surgically fit patients must be solidified because histopathology may under grade the tumor , or it may fail to reveal squamous differentiation and tumor heterogenicity .

Introduction

Bladder cancer is a potentially lethal disease that often demands a radical and aggressive treatment approach.

The decision to proceed to a life-altering major surgical procedure is complicated, unique to each patient.

Several factors impose an inevitable but variable period of delay from presenting symptoms to diagnosis, and subsequently to definitive treatment. These include preoperative medical evaluation, the pursuit of additional therapeutic opinions, limitations of surgical schedules, and patient psychological factors.

One-third of patients with transitional cell carcinoma (TCC) of the urinary bladder will be diagnosed as having muscle-invasive or metastatic tumor. In addition, approximately 30% of patients who are initially diagnosed with a superficial TCC will develop an invasive tumor during follow-up after organ-preserving therapy.(1)

Clinical presentation and Workup

The clinical spectrum of bladder cancer can be divided into three categories that differ in prognosis , management , and therapeutic aims. The first category consists of noninvasive tumors , for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage. The second group encompasses the invasive lesions , and the goal of therapy is to determine if the bladder should be removed or preserved without compromising survival, and to determine if the primary

lesion can be managed independently or if patients are at high risk for distant spread requiring systemic approaches to improve the likelihood of cure ..(2)
The critical concern of therapy for the third group, consisting of metastatic lesions , is how to prolong life . Numerous agents with different mechanisms of action have antitumor effects in this disease .The issue has become how to use these agents to achieve the best outcome .(3)
the most common presenting symptom in patients with bladder cancer is microscopic hematuria , although urinary frequency from irritation or a reduced bladder capacity can also develop. Less commonly , a urinary tract infection is the presenting symptom, or upper tract obstruction or pain may occur for a more advanced lesion. Patients presenting with these symptoms should be evaluated with office cystoscopy to determine if a lesion is present . If one is documented , the patient should be scheduled for a transurethral resection of the bladder tumor to confirm the diagnosis and to determine the extent of disease within the bladder.(4)

Patients and methods

In the peroid from january 2005 and february 2008, 24patients with primary carcinoma of the bladder were enrolled in this prospective study in AL-SADAR TEACHING HOSPITAL .The patients enrolled in the study underwent radical cystectomy for primary carcinoma of the bladder. Bladder cancer was diagnosed by cystoscopic examination and bimanual examination under GA and the diagnosis was confirmed by histopathology of the specimens obtained by transurethral resection of the tumor or transurethral debulking of the tumor.All histological slides obtained from neutral formalin-fixed, and the histological type of tumor, pathological stage and its grade were all assessed by histopathological study by the same laboratory and the same histopathologist. For tumor grading, we used WHO 1973 grading system. According to WHO 1973(14) grading system, carcinoma cases are subdivided into grade 1, 2 and 3.Pathological staging of each case was done according to the 1997 TNM staging system:16 T1 –the tumor invades subepithelial connective tissue; T2 – the tumor invades the muscularis propria; and T3 – the tumor invades perivesical tissue. Preoperative staging work-up involved complete history and physical examination, complete lab work-up, chest radiography, excretory urography, abdominal ultrasound and computerized tomography of the abdomen and pelvis was done for all patients. All patients enrolled in the study were underwent radical cystectomy.The indication for cystectomy was based on cystoscopic and biopsy findings, including tumor invasion of the muscularis propria without evidence of metastasis and recurrent multifocal superficial disease refractory to repeated transurethral resection with or without intravesical chemotherapy .Radical cystoprostatectomy was done for all patients and concomitant urethrectomy was performed in only one patient with tumor proved to be involving the prostatic urethra .All the cystectomy specimens were pathologically examined according to the same protocol used for the examination of the TURT specimens. The tumors were staged according to the TNM system of the American Joint Committee on Cancer (16), and using the same grading system and also by the same laboratory and the same histopathologist.We compare between the histopathological results of that obtained by endoscopy and that which obtained by cystectomy results, regarding the type of malignancy and the grade of malignancy.

Results

Twenty four patients there age range between 24 years - 85 years with mean of 57.5 year. Of those patients 5 were female and 19 were male. Comparative histopathological evaluation of the specimens which were obtained by endoscopy and that obtained by cystectomy has been done.This comparative study show that, the over all results regarding the type of malignancy and the grade of carcinoma were identical in only 10 patients (40%) out of 24 patients which have been enrolled in the study. Those patients show the same results by the type of malignancy and grade of malignancy in which the histopathological type was transitional cell carcinoma in all of those 10 patients and the grade of carcinoma were grade three in 9 patients and grade two in only one patient .On regarding the histopathological type when comparing the histopathological results, it has been found that the overall similarity between the histopathology of endoscopic biopsy and cystectomy specimen, when regarding only the type of malignancy ,were generally found in 18 patients out of the 24 patients (75%) enrolled in this study. 12 patients of those 18 patients, have precisely the same type of tumor by histopathological evaluation of specimen obtained by endoscopy and that specimen obtained by cystectomy.The histopathological type of malignancy in 11 of those patients were transitional cell carcinoma, while it was adinocarcinoma in the last one.While for the other 6 patients of those 18 patients the histopathology show the same type but with more specification by cystectomy specimen,than that of TUR biopsy histopathology, and it was as fallowing. Four patients of them the histopathological study of biopsy were transitional cell carcinoma while that of cystectomy specimen reveal transitional cell carcinoma with foci of squmuos differentiation One patient of them the histopathological study of biopsy was suggestive of rhabdomyosarcoma , while the cystectomy specimen show embryonal rhabdomyosarcoma and the last patient histopathological study of the biopsy show squmous cell carcinoma and the cystectomy specimen histopathology reveal squamuos cell carcinoma with sarcamatoid differentiation.

On regarding only the histopathological type when comparing the histopathological results between the endoscopic biopsy and the cystectomy specimen it has been found that the overall differences in the type of malignancy were found in 6 patients out of the 24 patients enrolled in this study (25%).

In 5 patients out the 24 patients enrolled in this study the bladder biopsy histopathology were transitional cell carcinoma while the histopathological study of cystectomy specimens for the same patients were squamous cell carcinoma and one out of 24 patients enrolled in the study the histopathological study of the endoscopically obtained specimens was transitional cell carcinoma while the histopathology of cystectomy specimen was small cell carcinoma. Further more in 6 patients out of the 21 patients enrolled in this study the histopathological study of the cystectomy specimen give more specification than that by endoscopic biopsy histopathology.

On regading the grade of the tumor, becuase 6 patients out of the 24 patients enrolled in the study were found to have a nother type of malignancy in the histopathology of the cystectomy specimen (other than transitional cell carcinoma) in addition to other three patients in whom the endoscopic histopathological type were nontransitional cell carcinoma(rhabdomyosarcoma in one of them ,squmous cell carcinoma in another, and adinocarcinoma in the last one) so the grade for those patients have to be excluded and only the remainder of the patients with histopathological type of transitional cell carcinoma in both the endoscopic and cystectomy pathology which are 15 patients have

been included in the comparism study of the grade of the carcinoma.
It has been found that 5 patients out of the those 15 patients (33%) have different grade when comparing their grade estimated from histopathology of the endoscopic biopsy and that obtained from cystectomy specimen . Four patients from those 5 were of transitional cell carcinoma of grade 2 by endoscopic histopathology while by cystectomy specimen histopathology they were found to be of grade 3 and one patient was of transitional cell carcinoma grade one by endoscopic histopathology while by cystectomy specimen histopathology was grade three. Of all the 24 patients enrolled in the study only 18 patients (75 %) have the same type of bladder malignancy and 6 patients (25%) have different type of malignancy by cystectomy specimen from that obtained by histopathology of endoscopically obtained sample.
Of the 15 patients with comparable histopathology by endoscopy and cystectomy only 10 of them (75%) have the same grade by cystectomy , and 5 of them (25 %) have up grade by histopathology of cystectomy specimen.On regarding the pathological sage of the tumor our study reveal the following :-In 11 out of the 24 patients (45%) enrolled in this study have the same pathological stage befor and after cystectomy of whome the results were as following7 patiets out of those 11 patients were stage T2 , and three patients were stage T3 , and only one patient was stage T4.
While 13 patients out of the 24 patients (55%) enrolled in this study have understaging of their pathological stage in the pre than post cystectomy pathological study, and their results were as following7 patients out of these 13 patients were have stage T2 in the pre operative assesment of their pathological stage , while found to have stage T3 in cystectomy specimens. 2 patients out of these 13 patients were have stage T3 in the preoperative assesment of their pathological stage while found to have stage T4 in the cystectomy specimens. 2 patients out of these 13 patients were have stage T1 in the preoperative assesment of their pathological stage while found to have stage T3 in the cystectomy specimens. one patient out of these 13 patients was have stage T1 in the preoperative assesment of their pathological stage while found to have stage T4 in the cystectomy specimens.

Discussion

In this study it has been found that, the over all simillarity between the histopathology of endoscopic biopsy and cystectomy specimen, when regarding only the type of malignancy ,were generally found in only 18 patients out of the 24 patients (75%) enrolled in this study,and the overall differences in the type of malignancy were found in 6 patients out of the 24 patients enrolled in this study (25%). In 5 patients out the 24 patients enrolled in this study the bladder biopsy histopathology were transitional cell carcinoma while the histopathological study of cystectomy specimens for the same patients were squamous cell carcinoma and one out of 24 patients enrolled in the study the histopathological study of the endoscopically obtained specimens was transitional cell carcinoma while the histopathology of cystectomy specimen was small cell carcinoma. These results might be explained and attributed to many factors including:-
First:- factors related to the surgical proceduer by which the histopathologicl sample or biopsy has been taken, and this might include the following :-
1- All cystoscopic biopsy available for histopathological analysis in this study, have been taken during transurethral resction of tumor or transurethral debulking of a large vesical tumor, which render them affacted by the necrosis and tissue damage caused by the electrocuaterization and lead to difficulties in thier histopathological analysis.

2-Failure of the TURT biopsy to reach the core of tumor which reflects the real histopathological state.

These factors was supported by the study performed by Witjes JA, Keimeney LA, et al Members of the Dutch South East Cooperative Urological Group, during this study they found that there is a lack of conformity in the actual reporting of the final TUR histology (9), also van der Meijden A, et al found uncertinty in TUR histology and he had list the factors contributing to such difficulties which include poor tissue orientation on prepared slides, and thermal or crush artifacts.,(10) The crucial step in the diagnosis and treatment of any bladder cancer is the initial TUR and there is a study done by the Oesterlinck W. et al Working Group On Urological Oncology of theEuropean Association of Urology (EAU) reported evidence that this TUR is often not performed to adequate standards[2].

This has lead some to suggest a repeat TUR (re-TUR) within one month of the initial TUR aimed at eradicating residual cancers and improving the hitopathological typing, grading, and staging of bladder cancers.18,19,17

Second:-

Factors related to vesical tumor behavoir and its natural history.Bladder cancer is one of the main problems in urology in terms of diagnosis and treatment, due to its high incidence, high recurrence rate, and difficulties in prognosis of its natural history. The natural history of vesical tumor is very difficult to predict and the results which were concluded in this study might be largely attributed to such factors. These factors are due to inheritance characteristic of the vesical tumor. At least three histological phenomenons have been observed to be associated with vesical tumors

1-Heterogeneity:- heterogeneity of the vesical tumor have been well investigated in many studies and it means that the tumor might exhibited heterogenic type of invasion (different type of invasion) and also heterogenic grade of differentiation (different grade) in multiple areas within the same tumor mass or in different areas in multiple location tumor, further more it has been suggested that heterogeneity in type of tumor might also be present.(12,13,14) 3-Histogenesis:-The histogenesis of nonurothelial carcinomas of the urinary bladder is difficult to understand, since the bladder is normally lined exclusively by transitional cell epithelium. The diverse phenotypic variants develop obviously by a metaplastic process as a result of the well-known inherent potential of the urothelium to undergo several pathways of cellular differentiation. There is strong evidence that squamous cell carcinomas arise secondarily from a squamous metaplasia and adenocarcinomas from metaplastic glandular epithelium within pre-existing TCC following complete carcinogenic transformation of the initially bland-looking metaplastic tumor cells. The metaplastic origin of nonurothelial bladder carcinomas is supported by immunohistochemical findings. Metaplastic phenotypic variants of TCC should be recognized as distinct tumor entities with the potential to transform into nonurothelial carcinomas and thus possibly implying a poorer clinical outcome than typical, uniform TCC.(22)

3-Metaplasia:- Metaplasia refers to a change in morphology of one cell type into another type which is considered aberrant (diverdent) for that location. The urothelial carcinoma frequently undergoes either squamous or glandular metaplasia , such metaplasia might be difficult to elecit in TUR biopsy while it is readily available and frequently diagnosed with cystectomy specimens.

In our study study the squmous metaplasia have been found in histopathological analysis of the cystectomy specimens in 4 patients out of 15 patients with cystectomy

specimen transitional cell carcinoma (27%), this finding is simillar to many puplished studies which have estimate the the incidence of squamous differentiation in transitional cell carcinoma (TCC) of the bladder is which ranges from 11% to 60% of the cases (5,6 ,8, 9).

A study done by Alberto A. Antunes et al , Squamous differentiation was observed in cystectomized specimes in 25 (22.1%) of the 113 patients and he found that 16% squamous differentiation were found in patients with superficial high grad carcinoma, 20% and 52% of the patients had T2 and T3 stage respectively.

Alberto A. also found that the presence of squamous differentiation in TCC of the bladder was a poor prognostic factor for disease-specific survival. This finding was associated to a 5.2 times higher risk of dyeing from disease when compared to patients without squamous differentiation.

Another study, is the that done by Frazier HA , Robertson JE , et al ,Department of Surgery, Duke University in which they consider the presence of squamous cell differentiation in the specimen is an indication for adjuvant chemotherapy.ref 20

Failure of cystoscopic biopsy to reveal squamous differntiation as is was indicated in our study and because of relatively high frequency of occurrence even in superficial tumor make the TUR biopsy less sensitive to predict a significant subgroup of patients with high risk.

Because of this low sensitivity of the TUR histopathology to reveal squamous metaplasia many studies investigate the ability of immunohistochemical analysis to enhance the endoscopic biopsy to detect squamous metaplasia as the study done by Antonio Lopez-Beltran, et al, in this study, SqD was assessed by immunohistochemistry using the monoclonal antibody Mac387 in145 urothelial tumours, against keratinized epithelial cell the study show significant number of patients with this differentiation even in superficial bladder carcinoma, and in another immunohistochemical study using Cav-1and Cav-2 with similar results

In our study only 15 patients out of 20 patients (75%) with endoscopic histopathology of transitional cell carcinoma were found to have transitional cell carcinoma at cystectomy specimen

Of those 15 patients, four patients of them have been found to have squamous differentiation at cystectomy specimen.

While 5 patients out of those 20 patients found to have squmous cell carcinoma at cystectomy specimen.

Both group of those patients have histopathological types which are radioresistant and this may explain why some patients with transitional cell carcinoma respond to radiotherapy and other did not .

Martin et al. (8), also analyzed TUR specimens from 100 patients with bladder tumor and reported that while 78% of patients with squamous metaplasia failed to respond to radiotherapy while a 90% response rate was seen among patients without this finding.

It this study it has been found that 5 patients (25%) out of the those 15 patients (which have transitional cell carcinoma in both endoscopic and cystectomy specimes) have different grade when comparing their grade estimated from histopathology of the endoscopic biopsy and that obtained from cystectomy specimen and these results are comparable to the study done by Nadira Mamoon, Muhammad Ashraf Iqbal et al , Department of Histopathology ,Pakistan in which 50% cases the tumors were graded differently at different times by the same pathologist as well , and also comparable to another study done by Bradley C. Leibovich,Liang Cheng et al , they found

undergrading by TUR in 52.3% of patients.
From the results obtained in our study which comparable to the results of several published studies we conclude that one pathologist would recommend conservative treatment while another would advise more aggressive treatment based on their different grading.
These results can be attributed in addition to the heterogeneity of the vesical tumor also can be attributed to the high Interobserver and intraobserver variability of the classification system.
Several groups have examined the variability of hisopathological reporting of bladder neoplasm. Ooms[15] and colleagues examined 67 bladder tumors and found considerably high intraindividual and interindividual inconsistency in grading them according to the WHO Classification. In almost 50% cases the tumors were graded differently at different times by the same pathologist as well.
Tosoni et al[16] found significant interobserver differences in 39% of tumors according to WHO. On the other hand, tumor heterogeneity is an important point, which may affect the outcome of the disease.Urothelial carcinoma of the bladder often contains different histologic types and grades within the same tumor, although the present grading systems does not take this into consideration, and the worst pathological grade is reported. However, according to Cheng12 and Billis et al., 13 grading that takes cancer heterogeneity into consideration allows stratification of patients into different prognostic groups, and seems to be of value in prediction of prognosis.
Urothelial carcinomas of the bladder are often heterogeneous tumors and contain different histologic grades within the same tumor. Cheng et al.12 and Billis et al.13 found different primary and secondary grades in 32% of 52 patients and 28% of 81 patients, respectively. According to these studies, approximately one-third of patients with pTa urothelial carcinoma had cancer containing more than one histologic grade.
They suggested that the grading of urothelial carcinoma that takes cancer heterogeneity into consideration allows precise stratification of patients into different prognostic groups.

Conclusion

It is concluded that surgical option in treatment of invasive bladder tumor in surgically fit patients must be solidified because endoscopic biopsy histopathology may under grade the tumor ,or itmay fail to reveal sequamous differentiation and tumor heterogenecity.

Recommendations

1.Repeat TUR within one month of the initial TUR in an attempt to increase the accuracy of histopathology in typing and grading of the vesical tumors in cases of un certainty in the initial histopathological analysis.
2.The concomitant use of immunohistochemical analysis with the histopathological study to increase the sensitivity of TUR biopsy to reveal such metaplasia.
3.Adopt the new grading system for transitional carcinoma(WHO/ISUP Consensus Classification 1998).

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