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RESEARCH ARTICLE

SCD147: EMMPRIN(EXTRACELLULAR MATRIX METALLOPROTEINASE INDUCER) AS TUMOUR MARKER FOR BLADDER CARCINOMA.

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Abstract

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Introduction:-

Bladder cancer is the second most common cancer of the genitourinary tract. It accounts for 7% of new cancer cases in men and 2% of new cancer cases in women. The incidence is higher in whites than in African Americans, and there is a positive social class gradient for bladder cancer in both sexes. The average age at diagnosis is 65 years, with approximately 75% of bladder cancers are localized to the bladder, 25% have spread to regional lymph nodes or distant sites. *A detailed study of bladder cancer cases registered from 2005 to 2010 in our tertiary care hospital revealed that bladder cancer ranks as the 7th leading cancer and 5.9% of all prevalent cancers in the Kashmiri population(1).*

TNM Staging System:-

The TNM staging system is the most commonly used system. Table 13 (a and b)

Clinical features:-

Hematuria (painless) is the presenting symptom in 85–90% of patients with bladder cancer. It may be gross or microscopic, intermittent rather than constant. In a smaller percentage of patients, it is accompanied by symptoms of vesical irritability: frequency, urgency, and dysuria. Irritative voiding symptoms seem to be more common in patients with diffuse CIS. Symptoms of advanced disease include bone pain from bone metastases or flank pain from retroperitoneal metastases or ureteral obstruction. Patients with large-volume or invasive tumors may be found to have bladder wall thickening or a palpable mass—findings that may be detected on a careful bimanual examination under anesthesia. Hepatomegaly and supraclavicular lymphadenopathy are signs of metastatic disease. Lymphedema from occlusive pelvic lymphadenopathy may be seen occasionally. The most common laboratory abnormality is hematuria. It may be accompanied by pyuria, which on occasion may result from concomitant urinary tract infection. Currently, urine cytology is the standard non-invasive marker. In a recent literature reviews, specificity of cytology ranged from 83% to 99.7% with a mean \pm standard deviation (SD) of 99% and sensitivity ranged from 20% to 53% with a mean \pm SD of 34%(02).

Other tumor markers.

- i. ImmunoCyt/uCyt+ test .
- ii. BTA TRAK Assay .
- iii. BTA Stat Test .

- iv. NMP22 assay .
- v. NMP22 BladderChekTest .
- vi. UroVysion Test .
- vii. sCD147: A new marker sCD147 also known as (EMMPRIN extracellular matrix metalloproteinase inducer), tumor collagenase stimulatory factor (TCSF), Hab 18 G, OX-47, Neurothelin, Basigin(03) is a cell surface protein which is broadly expressed on human peripheral blood cells, endothelial cells, cultured cells of hemopoietic and non hemopoietic origin. Thymocytes strongly express sCD147 (04), significant expression of sCD147 has also been reported in neoplasms of urinary bladder, liver and lung (05).

Various imaging modalities can detect bladder tumors but their presence is confirmed by cystoscopy and biopsy. Superficial (Ta, Tis) bladder cancers are staged with a properly performed TUR. However, higher stage lesions are often understaged, and the addition of imaging by CT and magnetic resonance imaging (MRI) or both have been used to characterize the extent of bladder wall invasion and detect enlarged pelvic lymph nodes, with overall staging accuracy ranging from 40% to 85% for CT and from 50% to 90% for MRI (06,07). The diagnosis and initial staging of bladder cancer is made by cystoscopy and transurethral resection (TUR). Superficial, low-grade tumors usually appear as single or multiple papillary lesions. Higher grade lesions are larger and sessile. CIS may appear as flat areas of erythema and mucosal irregularity. Use of fluorescent cystoscopy with blue light can enhance the ability to detect lesions by as much as 20% (08). Assessment of molecular markers of disease, with immunohistochemical methods, in biopsy specimens, or in cystectomy specimens can yield useful prognostic information.

Treatment [table 14]

CD147 (EMMPRIN):

CD147 is a member of the immunoglobulin family of receptors. Members of this family play a role in intercellular communication involved in many immunorelated functions, differentiation and development. CD147 plays a role in spermatogenesis, lymphocyte activation, expression of monocarboxylate transporters (MCT) and has been identified as a regulatory subunit of the γ -secretase complex in Alzheimer's disease amyloid β -peptide production (09, 10-13). CD147 is involved in the transport of the MCT-1 and MCT-3 to the plasma membrane since reduced accumulation of these transporters has been observed in the retina of *cd147* knockout mice. CD147 has been implicated in many pathological processes, such as rheumatoid arthritis, experimental lung injury, atherosclerosis, chronic liver disease induced by hepatitis C virus, ischemic myocardial injury and heart failure (12). Treatment of transplant patients with a CD147 antibody was effective due to inhibition of T-cell activation (14).

The *emmprin* gene consists of seven exons and six introns spanning 7.5 kb. The 5' upstream sequence of the *emmprin* gene contains no TATA or CAAT box but has a CpG-rich island. A 470-bp fragment upstream of the coding region of *emmprin* has been shown to promote its transcription. A 30-bp element of this sequence (-142 to -112 bp) which contains a binding site for Sp1, was also demonstrated to be important for *emmprin* transcription. CD147, a transmembrane protein of the immunoglobulin (Ig) superfamily and has many designations such as M6, Neurothelin, 5A11, HT7, OX-47, CE9, EMMPRIN, Basigin, and gp42. The transmembrane region harbors a leucine zipper and a charged residue (glutamic acid). The corresponding gene is located on chromosome 19p13.3 and encodes a 29 kDa backbone protein. Three *N* glycosylation sites have been identified and migration on sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) occurs between 39 and 65 kDa depending on the degree of glycosylation. Weak expression has been noted on resting T lymphocytes, whereas expression is increased on activated T lymphocytes and monocytes (15-20).

Expression of CD147 in Cancer:-

High incidence of expression of CD147 in different cancer entities making use of tissue microarrays and monoclonal antibodies (mAb) MEM-M6/1. A lot of 2348 and 608 tissue samples covering 129 distinct tumor types and 76 different normal tissues, respectively, were investigated for their CD147 status with these antibodies. CD147 expression was found in 112 out of 129 tumor entities with the following incidences: squamous cell carcinomas (60-100%), pancreatic (87%), chromophobic kidney (83%), hepatocellular (83%), medullary breast (83%) and glioblastoma multiforme (79%). Homogeneous expression of CD147 was found in tumor types such as squamous cell carcinoma of different types of organs and mesotheliomas. Interestingly, CD147 isoforms differing in presence or absence of Lewis X glycan structures were found on breast cancer cells. A lot of 28 tissue microarrays and 1117 pathological sections of breast tissue samples were analyzed. The incidence of CD147 expression was: cancer of the liver 80% (n=20), lung 62% (n=90), stomach 66% (n=44), colon 58% (n=19), rectum 59% (n=17), breast 64% (n=1055), cancer 80% (n=10), brain 90% (n=52), oesophagus 87% (n=16), ovary 75% (n=40), urinary bladder 85%

(n=41), skin (squamous cell carcinoma) 58% (n=41), larynx 85% (n=63) and kidney 73% (n=33), and 30% of sarcomas such as osteo, chondro- and fibrosarcoma (n=102).

It has been shown that CD147-positive tumor cells and their supernatants induce expression of MMPs such as MMP-1, MMP-2, MMP-3, MMP-9 and MMP-11, in cultured fibroblasts (21,22,23). Therefore, CD147 is also designated as extracellular MMP inducer (EMMPRIN). It was shown that MMP induction can also be mediated by soluble CD147. Soluble CD147 also has been detected in microvesicles (exosomes)(24). CD147 can also be induced in tumor cells by epidermal growth factor receptor (EGFR)-mediated signaling (autocrine mechanism). Controlled degradation of the extracellular matrix is a prerequisite for tumor invasion and metastasis. Transfection of breast cancer cells with *CD147* resulted in increased tumor growth and metastasis after implantation into the mammary gland and correlated with high levels of MMP-2 and MMP-9. The molecular mechanisms of these phenomena have been poorly resolved. Glycosylated CD147 was shown to be a prerequisite for MMP induction at the transcriptional level(25). Induction of MMPs by CD147 was prevented with a monoclonal antibody directed against CD147(25).

Role in MMP dependent and independent Angiogenesis:-

It was found that CD147 expression was significantly upregulated in activated human umbilical venule endothelial cells (HUVEC's). Inhibition of CD147 expression by RNAi led to significantly decreased angiogenesis *in vitro*. CD147 may regulate angiogenesis by several mechanisms including proliferation, survival, MMP secretion and phosphoinositide 3 kinase/protein kinase B (PI3K/Akt) activation. Modulation of remodeling of the extracellular matrix by MMPs and its impact on angiogenesis is a wellknown phenomenon. CD147 is involved in the induction of vascular endothelial growth factor (VEGF). CD147 stimulates VEGF production in tumor and stromal compartments and VEGF induction involves the PI3K/Akt pathway.

Role of CD147 as an Anti apoptotic Protein and Mediator of Chemoresistance:-

In several cancer cell lines, CD147 has been identified as a mediator of anti-apoptotic function and chemoresistance. In HO-8910 ovarian carcinoma cells, *CD147* RNAi reduces tumor cell invasion, tumorigenicity and chemosensitivity to paclitaxel. Up-regulation of CD147 has been observed in several multidrug-resistant cancer cell lines. Independently, involvement of CD147 in resistance of cancer cells to a variety of chemotherapeutic agents was reported. In addition, CD147 was identified as a receptor which promotes androgen-independent growth of tumor cells in hyaluronan-dependent manner. In human oral squamous carcinoma cells (SCC), CD147-directed RNAi reduced X-chromosome linked inhibitor of apoptosis protein (XIAP) expression and increased chemosensitivity to 5 fluorouracil. In breast cancer cell lines, it was shown that CD147 confers resistance to anoikis as demonstrated by activation of caspase 3, increased DNA fragmentation and lower cellular viability. Silencing of CD147 resulted in elevation of Bim protein levels. Treatment of cells with a MAP/ERK kinase (MEK) inhibitor (UO126) or a proteasome inhibitor (epoximycin) also induced Bim-1 accumulation and rendered cells sensitive to anoikis. These results suggest that CD147 protects cancer cells from anoikis and that this effect is mediated at least in part by a MAP kinase-dependent reduction of Bim. It has been shown that expression of CD147 leads to activation of ERK which phosphorylates proapoptotic Bim, resulting in degradation of Bim by the proteasome. Down-regulation of Bim suppresses anoikis and promotes survival of tumor cells detached from matrices as a prerequisite for cancer cell invasion and metastasis. CD147 was shown to stimulate hyaluronan production. Hyaluronan-tumor cell interaction is implicated in multidrug resistance due to activation of the PI3K/Akt pathway. Furthermore, it was demonstrated that CD147 is a mediator of multidrug resistance through hyaluronan-mediated upregulation of ErbB2 signaling and cell survival pathways.

CD147 Association with Cyclophilins (CyPs):-

CyPs are a family of proteins that share peptidyl-prolyl isomerase activity which is involved in their chaperone function. However, there is also evidence that CyPs are involved in intracellular communication. CyPs are located intracellularly as well as extracellularly. A role of CypA in cancer is supported by the finding that CypA and macrophage inhibitory factor (MIF) are the most dominantly expressed proteins in non-small cell lung carcinoma and a novel cyclophilin similar to CypA has been associated with metastasis and shown to be overexpressed in bladder cancer, hepatocellular carcinoma, sarcoma and breast carcinoma.

CD147 as a Target for Treatment of Cancer:-

The molecular interactions of CD147 with associated proteins are poorly defined, interference with small molecules is presently in the focus of drug development. The most obvious mode of intervention is to block CD147 function with mAbs. RNAi-mediated intervention would need more progress regarding the targeted delivery to cancer cells.

A critical issue is the broad expression of CD147, requiring toxicity studies for mAbs in a cross-reactive species. The function of CD147 as a mediator across the blood brain barrier would call for appropriate experiments for a therapeutic mAb. On the other hand, dependence of tumor cells on energy supply by anaerobic glycolysis (Warburg effect) and inhibition of the latter by CD147 mAbs which disrupt interaction with MCT and amino acid transporters makes tumor cells vulnerable to modulation of CD147 function. However, CD147 clearly impacts on invasion, proliferation, angiogenesis, tumor cell metabolism such as glycolysis, and mediates prosurvival signals, multi-drug resistance and PI3K/Akt signaling, which are all hallmarks of oncogenesis.

Studies conducted by Han ZD *et al* in 2010(26) and R. Nawrothin 2010(27) concluded that emmprin can be promising target in the treatment of bladder cancer.

Material and methods:

In this study total of 32 patients were included. These patients were first evaluated for bladder cancer. The first sample was taken pre operatively at the time of admission and these patients were subjected to trans urethral resection of bladder tumor (TURBT). These patients were followed up for 3-5 months and second sample was taken. Same numbers of BHP cases were taken as control group.

Collection of samples:-

Peripheral blood (4ml) was collected from patients by venipuncture, following universal precautions and all aseptic conditions, in sterile serum collection tubes and allowed to clot. The tubes were subjected to centrifugation at 2500rpm for 5 minutes to separate the serum. The clear serum so obtained was aspirated using disposable plastic droppers and poured in 1.5ml microfuge tubes after proper labeling and stored at -20°C till assayed for sCD147 levels.

Test procedure:-

- (I). The standards and controls were prepared as described in the assay protocol and 0.1 ml of each standard and controls were dispensed in the respective wells.
- (II) 0.1ml of patients sample was dispensed in each designated well in the ELISA microplate.
- (III). The ELISA microplate was covered and incubated at 37°C for 90 mins.
- (IV). The contents of the plate were discarded and plate was blotted on to the absorbent paper.
- (V). 0.1ml of biotinylated anti-human Emmpirin antibody working solution was added to each well and plate was incubated at 37°C at 60 mins.
- (VI). The microplate wells were washed three times by wash buffer using an automated washer.
- (VII). The microplate wells were blotted on an absorbent paper and 0.1ml of Avidin-Biotin-Peroxidase-Complex working solution was added to each well and plate was incubated at 37°C for 30 mins.
- (VIII). Washing cycle was repeated five times as described above.
- (IX). 90µl of prepared Tetra Methyl Benzoate substrate solution was added to each well and plate was incubated at 37°C for 25-30 mins in dark.
- (X). The reaction was stopped by adding 0.1ml of stop solution to each well.
- (XII). The absorbance of the respective wells of the was recorded immediately at 450nm using an automated ELISA reader, which recorded the absorbance and calculated the corresponding concentration of sCD147 in the respective wells.

Observation:-

A total number 32 patients were subjected to evaluation for sCD147. The clinocopathological features of this study were:

Based on gender. Table 1

Bladder cancer was more common in males (24/32=75%) as compared to females (8/32=25%)

Based on age. Table 2

Out of 32 cases 20 were >50 yrs of age and 12 were ≤50 yrs of age.

Based on smoking. Table 3

Based on smoking status, out of 32 cases, 18(56.3%) cases were smokers and 14(43.7%) were non smokers respectively.

Presenting symptom. Table 4

On the basis of presenting symptoms 30(93.75%) presented with hematuria, 25(78.1%) presented with pain, 3(9.3%) presented with retention of urine 5(15.6%) had other symptoms respectively.

Histopathological stage. Table 5

Based on histopathological stage out of 32 cases, breakup is as, stage I 4(12.5%) cases, stage II 16(50%) cases, stage III 11(34.4%) cases and stage IV 1(3.12%) cases respectively.

Lymph node involvement. Table 6

Out of 32 cases only 1 case had lymph node involvement.

Metastasis.

Out of 32 cases only 1 had metastasis.

Evaluation of sCD147.

32 patients of bladder tumor showed mean preoperative plasma concentration of 1.0751 and controls had a mean of 1.07343. [Table 7]

Preopvs postop: Table 8

Mean preoperative and post-operative sCD147 levels were compared and showed significant results ($p < 0.001$).

Stage I Preopvs postop. Table 9

Mean stage I preoperative and post-operative sCD147 levels were compared and results were not statistically significant.

Stage II Preopvs postop. Table 10

Mean Stage II preoperative and post-operative sCD147 levels were compared and showed statistically significant results ($p = 0.017$).

Stage III Preopvs postop. Table 11

Mean Stage III preoperative and post-operative sCD147 levels were compared and showed statistically significant results ($p < 0.001$).

Preop intra stage-wise comparison. Table 12

Stage wise comparison of mean sCD147 levels showed statistically significant results between stage I vs stage III and stage II vs stage III ($p < 0.05$).

The suitable statistical tests like Students independent 't' test and paired 't' test have been used to analyse the data. Moreover Analysis of Variance (ANOVA) have been employed to measure the significant difference of the means in the three groups. All the results have been discussed statistically at 5% level of significance i.e, p value < 0.05 considered significant. The variables have been represented with mean \pm SD and appropriate statistical charts.

Discussion:-

Bladder cancer is one of the common cancers worldwide. It was estimated that in 2005, 63,210 new cases of bladder cancer were diagnosed in the United States (Jemal et al, 2005)⁽²⁸⁾. In our study bladder cancer was found more common in males (75%) as compared to females (25%). This is consistent with the study by Jemal et al, 2005⁽²⁸⁾. Bladder cancer was found nearly three times more common in men than in women. Bladder cancer is a multifactorial diseases process. Incidence of disease increases with age and is more common in elderly > 60 yrs of age. We also found that bladder cancer was more common in elderly age group. In our study bladder cancer was more common in smokers (56%) which is inconsistent with the study by Morrison et al, 1984⁽²⁹⁾. Bladder cancer patients present with varied symptoms, commonest being painless hematuria. Painless hematuria was found in (93.75%) patients in our study group. Varkarakis et al, 1974⁽³⁰⁾, found painless hematuria in about 85% of their patients. Histopathological examination of resected tissues showed Transitional cell carcinoma in all patients in our study.

In our study no significant association was found between mean sCD147 levels in bladder cancer patients as compared to the control group. However sCD147 levels were found to be significantly higher in preoperative bladder cancer patients as compared to postoperative bladder cancer patients ($p < 0.001$). In our study, stage II and Stage III bladder cancer patients showed significant high expression of sCD147 as those bladder cancer patients who presented with stage I and stage IV bladder cancer ($P < 0.05$). In our studied group we found sCD147 is over expressed in the serum of bladder cancer patients as has been already observed by various studies which showed its high expression in tumor tissues of bladder cancer patients. A study conducted in 2010 studied the expression and clinical significance of CD147 in genitourinary carcinomas (31). They found that CD147/EMMPRIN was expressed in neoplastic tissues, but not in normal tissues. Positive expression was shown in 41 of 58 (70.69%) of the patients with bladder carcinoma. Positive CD147/EMMPRIN staining was significantly associated with TNM stages and histological subtypes of patients with various urinary carcinomas ($P < 0.05$). They concluded that this may assist in defining the suitability of CD147/EMMPRIN as a therapeutic target and as a method for predicting a poor outcome in patients with various urinary bladder carcinoma. Another study also supports our observation, which studied EMMPRIN (CD147) as a potential therapeutic and prognostic marker in bladder cancer and suggested that

EMMPRIN is a promising biomarker that has the potential for a better prognosis. EMMPRIN is also confirmed as an interesting target for new therapies in bladder cancer(120). A recent study conducted on Chinese patients in 2011 worked on CD147 overexpression is a prognostic factor and a potential therapeutic target in bladder cancer. In this study CD147 expression was detected in 108 bladder cancers CD147 protein expression was associated with poor prognosis ($P < 0.001$), lymph node status ($P < 0.001$), tumor stage ($P = 0.003$), histological grade ($P = 0.011$). Multivariate analysis showed that CD147 over expression was an independent prognostic factor ($P = 0.019$). Their findings suggested that CD147 over expression plays an important role in progression of bladder cancer, and CD147 could be a potential target of bladder cancer therapy. Thus our results provide a new field of study for researchers, where serum sCD147 can be used as one of the prognostic marker for bladder cancer patients.

Tables:-

Table 1:- Based on gender.

Variable	Parameter	Cases N=32, n
Sex	Male	24, (75%)
	Female	08, (25%)

Table 2:- Based on age.

Variable	Parameter	Cases N=32, n
Age in years	>50	20, (62.5%)
	≤50	12, (37.5%)

Table 3:- Based on smoking.

Variable	Parameter	Cases N=32, n
Smoking	Smokers	18, (56.3%)
	Non smokers	14, (43.7%)

Table 4:- Presenting symptom.

Variable	Parameter	Cases N=32, n
Symptom	Hematuria	30, (93.75%)
	Pain	25, (78.1%)
	Retention	03, (9.3%)
	Others	05, (15.6%)

Table 5:- Histopathological stage.

Variable	Parameter	Cases. N=32, n
Stage	Stage I	04, (12.5%)
	Stage II	16, (50%)
	Stage III	11, (34.3%)
	Stage IV	01, (3.12%)

Table 6:- Lymph node involvement.

Variable	Parameter	Cases. N=32
Lymph node	Negative	31
	Positive	1

Table 7:- Evaluation of sCD147. Preopvs controls.

Variable(sCD147)	Group.	Mean Conc. Levels	S.D.	P- value.
	Pre-op	1.0751	0.349	0.984
	Control	1.07343	0.289	

Table 8:- Preopvs postop

sCD147 level	Mean	N	S.D	p-value
Preop	1.0994	29	0.355	<0.001
Postop	0.777734	29	0.262	

Table 9:- Stage I Preopvs postop.

sCD147 level	Mean	N	Std. Deviation	p-value
Stage I preop	0.87035	04	0.091	0.197
Postop	0.777734	29	0.262	

Table 10:- Stage II Preopvs postop.

sCD147 level	Mean	N	Std. Deviation	p-value
Stage II preop	1.003028	16	0.339	0.017
Postop	0.777734	29	0.262	

Table 11:- Stage III Preopvs postop.

sCD147 level	Mean	N	Std. Deviation	p-value
Stage III preop	1.2807	11	0.35116	<0.001
Postop	0.777734	29	0.262	

Table 12 (a and b):- Preop intra stage-wise comparison.

Stage	N	Mean	Std. Deviation	P value
I	4	0.8704	0.09385	
II	16	1.0030	0.33927	0.050
III	11	1.2807	0.35116	
Total	31	1.0844	0.35115	

(I) group	(J) group	Mean Difference (I-J)	Std. Error	Sig. (p value)	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	-.13268	.18256	0.473	-.5066	.2413
	3	-.41038*	.19067	0.040	-.8010	-.0198
2	1	.13268	.18256	0.473	-.2413	.5066
	3	-.27770*	.12791	0.039	-.5397	-.0157
3	1	.41038*	.19067	0.040	.0198	.8010
	2	.27770*	.12791	0.039	.0157	.5397

Table 13 (a and b)

<i>Primary tumor (T)</i>	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades the muscularis
T3	Tumor invades periureteral fat [for renal pelvis only] Tumor invades beyond muscularis into perinephric fat or the renal parenchyma
T4	Tumor invades adjacent organ, or through the kidney into the perinephric fat
<i>Lymph nodes (N)</i>	
NX	Regional lymph nodes cannot be assessed

N0	No regional lymph node metastases
N1	Metastasis to a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node, more than 5 cm in greatest dimension
<i>Distant metastasis (M)</i>	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

The American Joint Committee on Cancer (AJCC) staging system and the TNM system compare as follows:

AJCC	TNM
Stage 0	T0
Stage I	Ta, Tis, T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0
Stage IV	T4 or any T, N+, M+

Table 14:- Cancer Stage wise Initial Treatment Options

Cancer Stage	Initial Treatment
Tis.	Complete TUR followed by intravesical BCG.
Ta (single, low-to-moderate grade, not recurrent).	Complete TUR.
Ta (large, multiple, highgrade, or recurrent).	Complete TUR followed by intravesical chemo or immunotherapy.
T1	Complete TUR followed by intravesical chemo or immunotherapy.
T2-4	i.Radical cystectomy. ii.Neoadjuvant chemotherapy followed by radical cystectomy. iii.Radical cystectomy followed by adjuvant chemotherapy. iv.Neoadjuvant chemotherapy followed by concomitant chemotherapy and irradiation.
Any T, M+,N+	Systemic chemotherapy followed by selective surgery or irradiation

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