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IMMUNOHISTOCHEMICAL EXPRESSION OF P53 PROTEIN IN UROTHELIAL CARCINOMA WITH CLINICOPATHOLOGICAL CORRELATION

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ABSTRACT

Background: Urothelial carcinoma (UC), also known as transitional cell carcinoma, is the predominant type of bladder cancer, making up over 90% of cases in the United States. It originates in the urothelial cells lining the urinary tract and contributes significantly to global morbidity and mortality. The current study, highlight that bladder cancer is the seventh most common cancer among Iraqi men, with an incidence rate of 8.5 per 100,000 men. Globally, bladder cancer ranks as the seventh most common cancer in men. **The study aims to** evaluate P53 protein expression in both normal bladder epithelium and transitional cell carcinoma (TCC) of the urinary bladder using immunohistochemical analysis and to correlate P53 expression with various clinicopathological parameters in urothelial carcinoma. **Method:** This cross-sectional study was conducted at Gazi AL-Hariri Hospital and private labs from January to December 2024, with ethical approval from the Scientific Council of Pathology of the Iraqi Board of Medical Specializations. A convenient sampling method was used to enroll 50 patients (40 patients diagnosed with Urothelial Carcinoma and 10 patients diagnosed with cystitis) during 2023, using paraffin-embedded blocks from patient records. The study included patients newly diagnosed with bladder cancer & those with hematuria without bladder mass. With patient known case of bladder carcinoma previously treated as exclusion criteria. Data collected included patient age, sex, histological type, TNM staging (excluding metastasis), tumor grade, muscularis propria invasion, and lympho-vascular invasion. **Results:** The study analyzed patients with predominantly older age (54% aged ≥60 years) and a majority being male (82%). It focused on cystitis (benign lesion) and two types of malignant urothelial carcinomas. Among the findings, 80% had malignant lesions, with papillary type urothelial carcinoma being the most common. The P53 scoring system revealed a significant correlation with histopathological outcomes. High-grade tumors were frequent (77.5%), with most patients in stage T1 (75%). Associations between histopathological findings and factors like lymphovascular invasion and muscularis propria invasion were explored, revealing notable differences between genders and tumor types**.** 50% of P53 scoring system (+3), 18% (+2), and 6% (+1). Patients with negative P53 scores were 26%. Histological type is associated with P53 score (P-value 0.0001). 100% of negative-scoring patients developed cystitis. All patients with solid urothelial carcinoma had P53 score (+3), whereas 60.5% of papillary patients had it. The supplied P-values show that high-grade and T1 stage tumors have higher P53 scores (+2 and +3), however the connections are not statistically significant. **Conclusion:** This study highlights bladder cancer trends, with older males most affected and papillary urothelial carcinoma as the most common type. Solid-type carcinoma is linked to aggressive features like high-grade tumors, lymphovascular invasion, and advanced stages. P53 scoring shows significant utility in distinguishing benign (cystitis) from malignant lesions, with (+3) scores strongly associated with papillary type (60.5%) and solid type (100%) carcinoma. Higher P53 scores (+2, +3) correlate with high-grade and T1 tumors, though statistical significance varies. These findings emphasize the importance of early detection, accurate staging, and tailored treatments for improved outcomes.

KEYWORDS: Urothelial, lymphovascular, muscularis propria.

INTRODUCTION

Urothelial carcinoma (UC), also known as transitional cell carcinoma, is the most common type of bladder cancer, accounting for over 90% of cases in the United States. This malignancy originates in the urothelial cells lining the bladder and can occur anywhere in the urinary tract,

including the renal pelvis, ureter, and urethra. Despite advances in diagnostic and therapeutic strategies, UC remains a significant cause of morbidity and mortality worldwide, necessitating ongoing research to better understand its pathogenesis and improve clinical outcomes.[1,2]

One of the critical factors in the development and progression of urothelial carcinoma is the molecular alterations within the tumor cells. Among the various genetic changes observed, mutations in the tumor suppressor gene TP53, which encodes the P53 protein, are particularly noteworthy. The P53 protein plays a crucial role in maintaining genomic stability by regulating cell cycle arrest, DNA repair, apoptosis, and senescence in response to cellular stress and DNA damage. Therefore, the aberrant expression of P53 due to TP53 mutations can lead to uncontrolled cell proliferation and tumor development.[3,4]

Immunohistochemistry (IHC) has become a widely used technique to assess the expression of P53 protein in tissue specimens. This method allows for the visualization of protein distribution within the tissue context, providing insights into the molecular alterations present in tumors. The immunohistochemical detection of P53 protein has been extensively studied in various cancers, including urothelial carcinoma, and has been associated with different clinicopathological features and patient outcomes.[5,6]

The clinicopathological correlation of P53 expression in urothelial carcinoma is an area of active investigation. Several studies have demonstrated that overexpression of P53 protein, detected by IHC, is associated with high-grade tumors, advanced stages of disease, and poor prognosis.

For instance, a study by Sarkis et al. (2022) found that high P53 expression correlated with muscle-invasive bladder cancer and decreased overall survival, highlighting its potential as a prognostic marker. Another study by Chen et al. (2021) reported that P53 overexpression was significantly associated with lymphovascular invasion and metastasis, further supporting its role in tumor aggressiveness.[7,8]

Moreover, the therapeutic implications of P53 expression in urothelial carcinoma are gaining attention. The status of P53 can influence the response to chemotherapy and radiation therapy, which are standard treatments for advanced UC. For example, patients with wild-type P53 are more likely to respond to DNA-damaging agents, such as cisplatin, due to the intact P53-mediated apoptosis pathway. In contrast, those with mutant p53 may exhibit resistance to such therapies, necessitating alternative treatment strategies. Therefore, assessing P53 expression could aid in tailoring personalized treatment plans for patients with urothelial carcinoma.[9,10]

In addition to its prognostic and therapeutic relevance, the study of P53 expression in urothelial carcinoma also contributes to our understanding of the molecular mechanisms underlying bladder cancer development. The P53 pathway interacts with various other signaling pathways, such as the Rb (retinoblastoma) pathway and the PI3K/AKT/mTOR pathway, which are also frequently altered in UC. Investigating these interactions can uncover potential targets for novel therapeutic interventions and improve our comprehension of bladder cancer biology.[11]

Despite the substantial progress in elucidating the role of P53 in urothelial carcinoma, several challenges remain. One of the primary difficulties is the heterogeneity of P53 mutations, which can lead to variable expression patterns and functional outcomes. Additionally, the standardization of IHC techniques and interpretation criteria is crucial for the consistent assessment of P53 expression across different studies and clinical settings.[12]

The immunohistochemical expression of P53 protein in urothelial carcinoma provides valuable information on the molecular characteristics of the tumor and its clinicopathological correlations.[13] The current study, found that bladder cancer is the seventh most common cancer among Iraqi men, with an incidence rate is 8.5 per 100,000 men. Bladder cancer is the seventh most common cancer in men worldwide.[14]

The aim of study is

1. To evaluate the expression of the P53 protein in both normal bladder epithelium and transitional cell carcinoma (TCC) of the urinary bladder through immunohistochemical analysis.
2. To correlate the expression of P53 in Urothelial Carcinoma with various clinicopathological parameters.

LITERATURE REVIEW

2.1 Normal Histology of Urinary Bladder

The bladder is a hollow viscus with the shape of a four-sided inverted pyramid when empty and of a rounded structure when distended. The layers of the bladder are the mucosa, muscularis propria (MP), and adventitia. The latter is covered by serosa at the dome. The mucosa is consisting of epithelium and lamina propria, which often contains muscularis mucosae (MM). The epithelium of the bladder has been traditionally referred to as transitional, but the preferred term urothelium is more informative and accurate. It is about six to seven cells thick in the contracted bladder, but only two or three cells thick in the distended bladder. The urothelium has three layers: superficial, intermediate, and basal. The superficial layer is made up of a single row of large cells with abundant eosinophilic cytoplasm and referred to as umbrella cells. The umbrella cells may also have large multilobated nuclei and prominent cytoplasmic vacuolization. The intermediate cells have a cuboidal to

low columnar shape, oval nuclei with fine chromatin and frequent nuclear grooves, moderately abundant cytoplasm, and well-defined margins. The basal layer is made up of a row of cuboidal cells that lie on a thin continuous basal lamina. The lamina propria is composed of loose connective tissue containing a rich vascular network, lymph vessels, and a few elastic fibers. The lamina propria divided into an inner and an outer zone. Smooth muscle cells are also present in the lamina propria, usually as isolated bundles, sometimes as a discontinuous thin layer, and rarely as a continuous layer. This layer of smooth muscle is designated as MM. These can be confused with the muscle bundles of the MP when evaluating the depth of invasion of a bladder neoplasm (particularly in a biopsy specimen), a serious problem since tumor staging and treatment are largely based on the presence or absence of MP invasion. Isolated bundles of muscle immediately adjacent to urothelium, with loose haphazard fiber orientation and irregular outlines, favor MM.[15,16]

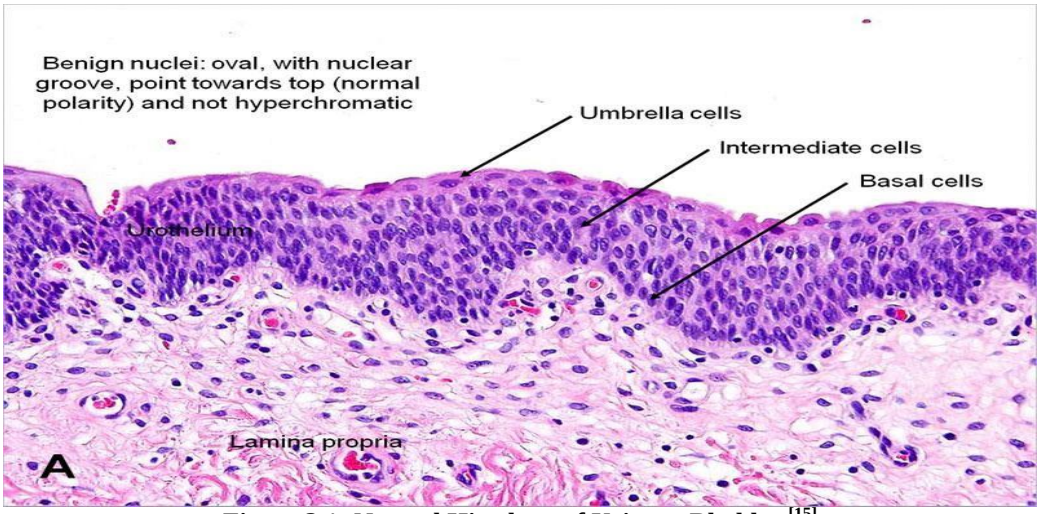


Figure 2.1: Normal Histology of Urinary Bladder.[15]

2.2 Urothelial Carcinoma

2.2.1 Epidemiology

The global incidence of cancer is on the rise, with new cases expected to increase from 14.1 million in 2012 to 20 million by 2025. The proportion of deaths attributed to cancer grew from 14% in 2005 to 16% in 2015. In 2015, cancer accounted for approximately 8.8 million deaths, making it the second leading cause of death worldwide, following cardiovascular disease. Predictions for 2018 anticipated around 18.1 million new cancer cases and 9.6 million cancer-related deaths globally. Additionally, estimates for 2018 suggested that nearly 50% of all new cancer cases and over half of all cancer deaths would occur in Asia.[16]

2.2.2 Risk Factors for Urothelial Carcinoma of the Bladder

Understanding these risk factors is crucial for prevention, early detection, and effective management of the disease.[17, 18]

Non-Modifiable Risk Factors

1. **Genetics**: A family history of bladder cancer significantly increases an individual's risk. Genetic predispositions often involve mutations in tumor suppressor genes or oncogenes that predispose cells to malignant transformations.
2. **Gender**: Men are more frequently diagnosed with bladder cancer compared to women. This disparity is likely due to a combination of genetic susceptibility and lifestyle factors such as higher rates of smoking and occupational exposures in men.
3. **Age**: The risk of developing bladder cancer increases with age. It is rare in individuals under 40, with the incidence rising significantly in those over 55. This correlation is attributed to the accumulation of genetic mutations and prolonged exposure to carcinogens over time.

Modifiable Risk Factors[17-19]

1. **Smoking**: Smoking is the most significant risk factor for bladder cancer, accounting for approximately 50% of cases. Smokers are four times more likely to develop bladder cancer than non-smokers. Tobacco smoke contains carcinogenic substances, such as aromatic amines, which are metabolized and excreted through the bladder, causing damage to the urothelial lining.
2. **Occupational Exposures**: Certain occupations increase the risk of bladder cancer due to exposure to carcinogenic chemicals. Workers in industries such as painting, dyeing, leather, rubber, and textiles are at a higher risk. These industries often involve exposure to chemicals like aromatic amines and polycyclic aromatic hydrocarbons, which are known to be carcinogenic to the bladder.
3. **Chemical Exposures**: Exposure to specific chemicals, such as arsenic in drinking water and chemicals used in the manufacture of dyes, rubber, leather, textiles, and paint products, can increase bladder cancer risk. Benzidine and beta-naphthylamine are notable examples of such

chemicals.

4. **Medical Treatments**: Certain medical treatments, such as the use of cyclophosphamide (a chemotherapy drug) and radiation therapy directed at the pelvic region, can increase the risk of bladder cancer. These treatments can induce DNA damage in the urothelial cells, leading to malignant transformations.
5. **Chronic Infections and Inflammation**: Chronic bladder infections, urinary tract infections, and conditions that cause long-term bladder inflammation, such as schistosomiasis, are associated with an increased risk of bladder cancer. Persistent inflammation can cause cellular changes and mutations that may lead to cancer.
6. **Diet and Hydration**: Diets high in fried meats and fats may contribute to bladder cancer risk, while adequate hydration is thought to have a protective effect. Drinking plenty of fluids dilutes potential carcinogens in the urine and promotes more frequent urination, reducing the contact time between carcinogens and the bladder lining.

2.3 Classification of Bladder Tumors

Bladder tumors are classified based on their histological appearance and biological behavior. The World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) provide a comprehensive classification system that categorizes these tumors into various types. This classification helps in understanding the prognosis, planning treatment, and conducting research.

Urothelial Tumors according to WHO 2022 Classification[20]

1. **Invasive Urothelial Carcinoma**: This type of carcinoma invades the bladder wall's muscle layer and has various subtypes, which include:
   - **Conventional Type Urothelial Carcinoma.**
   - **Urothelial Carcinoma with Squamous Differentiation**: Tumors that show areas of squamous cell carcinoma.
   - **Urothelial Carcinoma with Glandular Differentiation**: Tumors with gland-like structures resembling adenocarcinoma.
   - **Urothelial Carcinoma with Trophoblastic Differentiation**: Tumors showing features similar to trophoblastic cells.
   - **Nested Subtype:** Characterized by nests of urothelial cells that invade the bladder wall.
   - **Tubular & Microcystic Subtype:** Shows small cystic spaces within the tumor.
   - **Micropapillary Subtype**: Characterized by small, delicate papillary structures.
   - **Lymphoepithelioma-like Subtype**: Resembles lymphoepithelioma of the nasopharynx.
   - **Lymphoma-like Subtype**: Appears similar to lymphomas.
   - **Plasmacytoid Subtype**: Resembles plasma cells.
   - **Sarcomatoid Subtype:** Contains both carcinomatous and sarcomatous elements.
   - **Giant Cell Subtype**: Contains large, multinucleated giant cells.
   - **Undifferentiated Subtype**: Lacks distinct histological differentiation.

2. **Non-Invasive Urothelial Neoplasms[21]**
   - **Urothelial Papilloma**: A benign, exophytic growth.
   - **Inverted urothelial Papilloma**: A benign tumor with an inverted growth pattern into the lamina propria.
   - **Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)**: A tumor with a low potential for progression and invasion.
   - **Urothelial Carcinoma in Situ**: A flat, high-grade, non-invasive lesion confined to the epithelium.
   - **Non-Invasive Papillary Urothelial Carcinoma, Low Grade**: A low-grade tumor projecting into the bladder lumen.
   - **Non-Invasive Papillary Urothelial Carcinoma, High Grade**: A high-grade tumor that projects into the bladder lumen but does not invade the bladder wall.

Squamous Neoplasms[22]

1. **Squamous Cell Carcinoma**: This carcinoma is composed entirely of squamous cells and is often linked to chronic irritation or infection.
2. **Verrucous Carcinoma**: A well-differentiated variant of squamous cell carcinoma with a warty appearance.
3. **Squamous Cell Papilloma**: A benign squamous cell growth.

Glandular Neoplasms[23]

Adenocarcinoma**: Includes several subtypes such as:**

- **Enteric Type**: Resembles colorectal adenocarcinoma.
- **Mucinous Type**: Produces significant amounts of mucin.
- **Signet-Ring Cell Type**: Contains cells with a signet-ring appearance due to mucin vacuoles.
- **Clear Cell Type**: Resembles clear cell carcinoma seen in other organs.

2. **Villous Adenoma**: A benign glandular tumor with a villous architecture.

Neuroendocrine Tumors[24]

1. **Small Cell Carcinoma**: An aggressive tumor similar to small cell carcinoma of the lung.
2. **Large cell neuroendocrine carcinoma.**
3. **Carcinoid**: A well-differentiated neuroendocrine tumor.
4. **Paraganglioma**: A neuroendocrine tumor arising from paraganglia.

Melanocytic Tumors[25]

1. **Malignant Melanoma**: Rare, but when present, these tumors contain melanocytes.
2. **Nevus**: A benign melanocytic lesion.

Mesenchymal Tumors[26]

1. **Rhabdomyosarcoma**: A malignant tumor derived from skeletal muscle.
2. **Leiomyosarcoma**: A malignant tumor originating from smooth muscle.
3. **Angiosarcoma**: A malignant tumor derived from blood vessels.
4. **Osteosarcoma**: A rare malignant tumor that produces osteoid or bone.
5. **Malignant Fibrous Histiocytoma**: A pleomorphic sarcoma.
6. **Leiomyoma**: A benign smooth muscle tumor.
7. **Hemangioma**: A benign tumor of blood vessels.

Hematopoietic and Lymphoid Tumors[27]

1. **Lymphoma**: A malignant tumor derived from lymphoid tissue.
2. **Plasmacytoma**: A tumor of plasma cells.

Miscellaneous Tumors[27]

1. **Carcinoma of Skene, Cowper, and Littre Glands**: Tumors arising from these periurethral glands.
2. **Metastatic Tumors and Tumors Extending from Other Organs**: Tumors that spread to the bladder from other primary sites.

2.4 Molecular Genetic Features of Urothelial Carcinoma

Urothelial carcinoma (UC) is a common malignancy with distinct molecular genetic features. These features are crucial for understanding the disease's pathogenesis, prognosis, and therapeutic response. UC can be broadly classified into two categories based on molecular genetics: low-grade non-muscle-invasive bladder cancer (NMIBC) and high-grade muscle-invasive bladder cancer (MIBC). Low-grade NMIBC is often associated with activating mutations in the FGFR3, HRAS, and PI3K/AKT pathway genes. These mutations lead to enhanced cellular proliferation and survival, contributing to the tumor's growth while maintaining a relatively non-aggressive behavior.[28]

In contrast, high-grade MIBC exhibits a more complex genetic landscape. Key alterations in these cancers include mutations in tumor suppressor genes such as TP53 and RB1, as well as disruptions in chromatin remodeling genes like ARID1A, KDM6A, and EP300. TP53 mutations, occurring in approximately 50% of MIBC cases, result in the loss of cell cycle regulation and genomic stability, driving tumor progression. Similarly, RB1 mutations lead to dysregulated cell cycle control, further promoting invasive and aggressive tumor behavior. Moreover, MIBC often demonstrates significant genomic instability, characterized by a high mutation burden and frequent chromosomal alterations. Common chromosomal aberrations include amplifications of E2F3, CCND1, and ERBB2, and deletions of CDKN2A. These genetic changes collectively contribute to the aggressive phenotype of MIBC.[29]

The understanding of UC at the molecular level has led to the identification of distinct molecular subtypes within MIBC, each with unique genetic and epigenetic profiles. For instance, luminal and basal subtypes have been identified, with luminal tumors typically exhibiting FGFR3 mutations and higher expression of uroplakin and GATA3, whereas basal tumors are often characterized by squamous differentiation and higher expression of cytokeratins 5/6 and CD44. Advancements in molecular genetics have also paved the way for targeted therapies. FGFR inhibitors, immune checkpoint inhibitors, and therapies targeting specific mutations or pathways offer promising avenues for personalized treatment, aiming to improve outcomes for patients with UC. Understanding these molecular genetic features is essential for developing more effective diagnostic, prognostic, and therapeutic strategies in urothelial carcinoma.[30]

2.5 Diagnosis

The diagnosis of Urothelial Carcinoma (UC), involves a multi-faceted approach integrating clinical, radiological, and pathological evaluations to ensure accurate detection and characterization of the disease.

Clinical Evaluation: Initial diagnosis often starts with patient-reported symptoms such as hematuria (blood in urine), dysuria (painful urination), and increased urinary frequency. A thorough medical history and physical examination are essential to rule out other potential causes of these symptoms.[31]

Urine Tests: Non-invasive urine tests play a significant role in the initial evaluation. Urinalysis can detect microscopic hematuria, while urine cytology can identify malignant cells shed into the urine. However, the sensitivity of urine cytology is higher for high- grade tumors than for low-grade ones.[32]

Imaging Studies: Imaging techniques are crucial for evaluating the extent of the disease. Ultrasonography is often used as a first-line imaging tool, but more definitive imaging includes computed tomography (CT) urography and magnetic resonance imaging (MRI). These modalities provide detailed information on tumor location, size, and potential spread to surrounding tissues or organs.[33]

Cystoscopy: Cystoscopy is a pivotal diagnostic procedure involving the insertion of a cystoscope through the urethra to visually inspect the bladder. It allows direct visualization of bladder lesions and facilitates biopsy or transurethral resection of bladder tumors (TURBT). TURBT is both diagnostic and therapeutic, allowing histopathological examination of the resected tissue.[34]

Histopathological Examination: The definitive diagnosis of UC relies on histopathological analysis of tissue obtained through biopsy or TURBT. Pathologists assess the tissue for the presence of malignant urothelial

cells, grading the tumor based on cellular differentiation, and staging it according to the depth of invasion into the bladder wall.[35]

Molecular Diagnostics: Emerging molecular diagnostic tools are increasingly being integrated into routine practice. Fluorescence in situ hybridization (FISH) can detect chromosomal abnormalities specific to UC, while molecular markers such as FGFR3 mutations can provide additional diagnostic and prognostic information.[36,37]

The staging of Urothelial Carcinoma (UC) is a crucial process in determining the extent of disease, guiding treatment decisions, and predicting prognosis. The most widely used system for staging UC, particularly bladder cancer, is the TNM classification developed by the American Joint Committee on Cancer (AJCC). This system assesses the tumor based on three primary components: Tumor (T), Nodes (N), and Metastasis (M).[38]

2.6 Staging and Grading of Urothelial Carcinoma

2.6.1 Staging of Urothelial carcinoma

Table 2.1: TNM Classification of Urothelial Carcinoma, 8th Edition.[38]

Primary tumor (pT)
pTX: cannot be assessed
pT0: no evidence of primary tumor
pTa: noninvasive papillary carcinoma
pTis: carcinoma in situ
pT1: invades lamina propria
pT2a: invades inner half of muscularis propria
pT2b: invades outer half of muscularis propria
pT3a: microscopically invades perivesical tissue
pT3b: macroscopically invades perivesical tissue
pT4a: directly invades prostatic stroma, seminal vesicles, uterus or vagina
pT4b: directly invades pelvic wall or abdominal wall
Regional Lymph node
pNX: cannot be assessed
pN0: no regional lymph node metastasis
pN1: metastasis in one true pelvic lymph node
pN2: metastasis in greater than one true pelvic lymph node
pN3: metastasis in common iliac lymph node
Distant Metastasis (M):
pM1a: metastasis in nonregional lymph node (ex: caval / aortic, inguinal)
pM1b: metastasis in other distant site

Note: Regional lymph nodes are the true pelvic lymph nodes, which include the following (Perivesical, Hypogastric / deep obturator / fossa of Marcille / internal iliac, Obturator, External iliac, Presacral / sacral / lateral sacral / sacral promontory).

Based on the TNM classification in table 2.1, the stages of UC are grouped to reflect the progression and severity of the disease.

Table 2.2: AJCC Prognostic Stage groups.[38]

Stage group 0a:	**Ta**	**N0**	**M0**
Stage group 0is:	**Tis**	**N0**	**M0**
Stage group I:	**T1**	**N0**	**M0**
Stage group II:	**T2a - 2b**	**N0**	**M0**
Stage group IIIA:	**T3a - 4a**	**N0**	**M0**
	T1 - 4a	**N1**	**M0**
Stage group IIIB:	**T1 - 4a**	**N2 - 3**	**M0**
Stage group IVA:	**T4b**	**any N**	**M0**
	any T	**any N**	**M1a**
Stage group IVB:	**any T**	**any N**	**M1b**

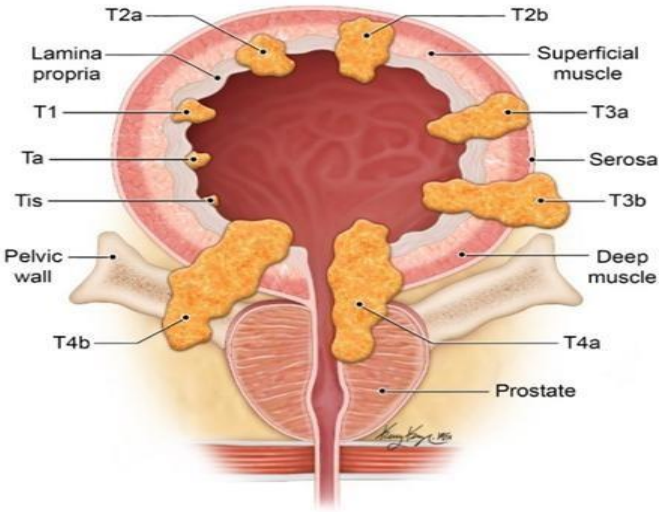


Figure 2.2: Staging of Urothelial carcinoma.[38]

Importance of Staging

Accurate staging is essential for the following reasons:

1. **Treatment Planning**: It helps clinicians choose the most appropriate treatment modality, which may include surgery, chemotherapy, radiation, immunotherapy, or a combination of these.
2. **Prognosis**: It provides important prognostic information, helping to predict the likely course and outcome of the disease.
3. **Research and Clinical Trials**: Staging allows for standardized classification, which is crucial for enrolling patients in clinical trials and comparing outcomes across studies.

- In summary, the staging of Urothelial Carcinoma using the TNM system is a detailed process that involves assessing the primary tumor, regional lymph nodes, and distant metastasis to determine the extent of the disease and guide clinical management.[39]

2.6.2 Grading of Urothelial Carcinoma.[40]

- Grading of (papillary) urothelial neoplasms is depend on the level of orderedness of the urothelial lining at intermediate power and nuclear atypia.
- Orderedness represents a continuum, varying from very well ordered to disordered with increasing nuclear atypia
- We have two grading systems (WHO 1973 and 2004 / 2016) cannot be translated directly into each other due to overlapping grades, as shown in figure 3.
- In urothelial carcinomas with grade heterogeneity, the highest grade is reported.

Table 2.3: Grading of papillary urothelial neoplasm, according to WHO 2004/2016 classification.[41]

Papillary urothelial neoplasms				
		Papillary urothelial neoplasm of low malignant potential (PUNLMP)	**Low grade**	**High grade**
Architecture	**Papillae**	Delicate Rarely fused	Delicate Occasionally fused	Delicate Fused and branching
	Organization	Normal polarity Cohesive cells	Minimal crowding and loss of polarity Cohesive cells	Crowding Overlapping cells Loss of polarity Often discohesive cells
Nuclei	**Size and nuclear/cytoplasmic ratio**	Mildly increased	Increased	
	Nuclear size variability	No	Some	Marked
	Shape	Elongated Uniform	Elongated—oval— round Slight variability	Pleomorphic
	Chromatin	Fine	Fine with some variability	Frequently coarse with marked variability
	Nucleoli	Absent to inconspicuous	Usually inconspicuous	Prominent Single to multiple
	Mitoses	Rare Basal if present	Infrequent Mostly basal if present	Frequent At any level
Invasion		Non-invasive	Rarely invasive	Invasive

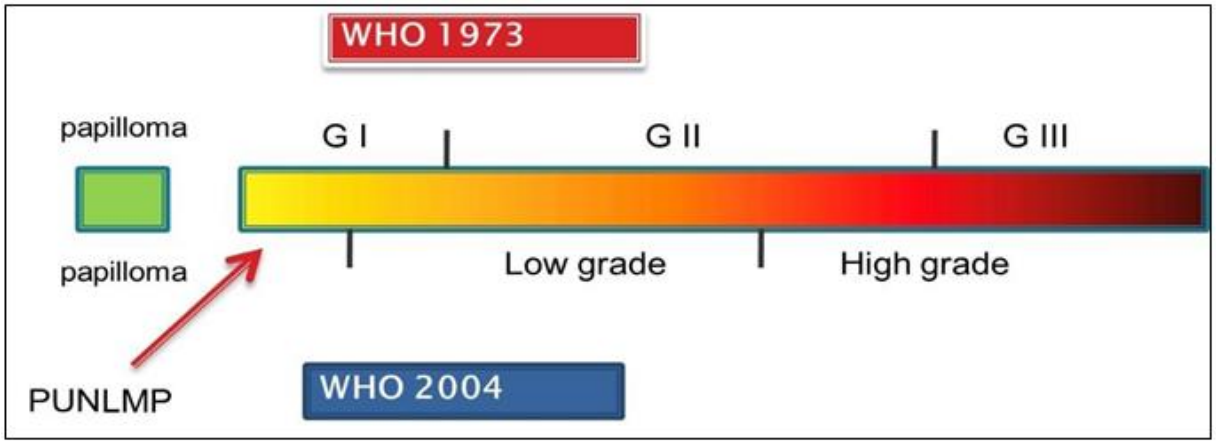
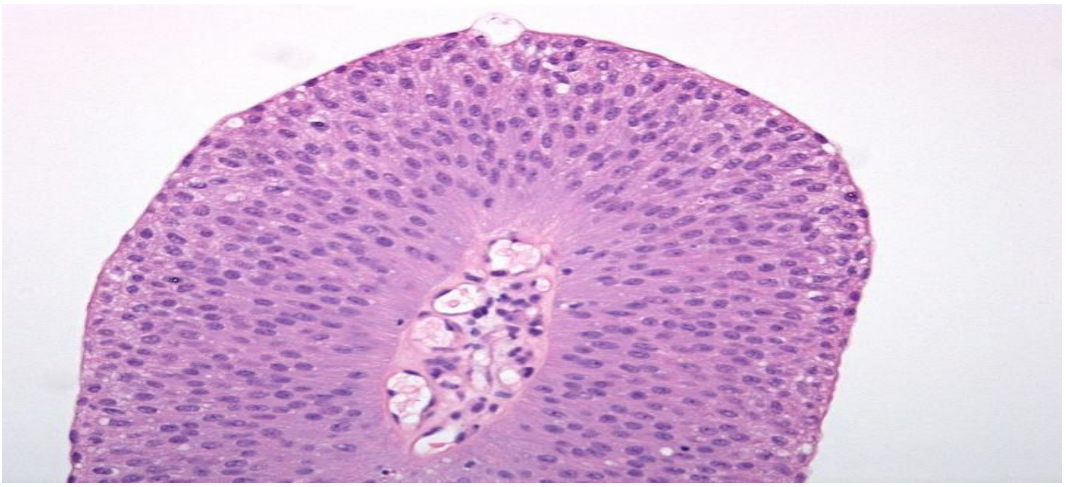
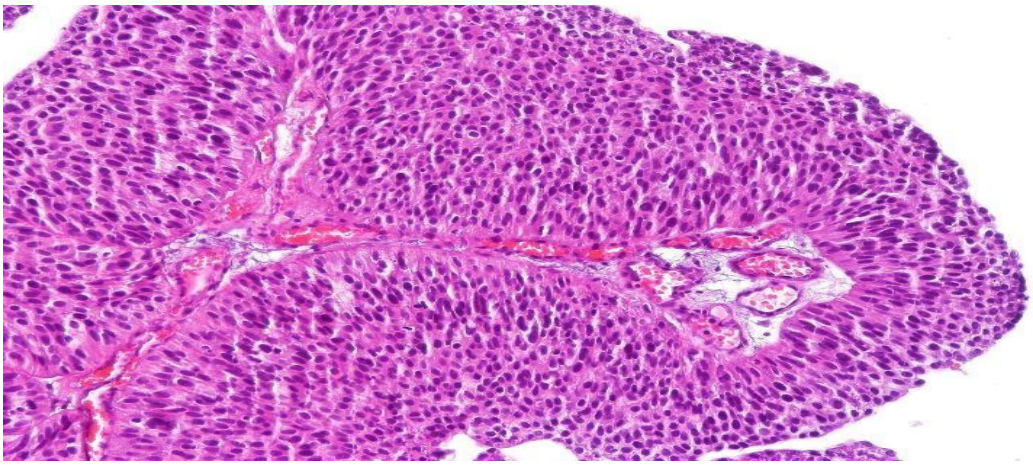


Figure 2.3: Comparison of the WHO 1973 grading system and WHO 2004 classification of urothelial neoplasms. The color gradient of the bar indicates increased disorderedness and nuclear atypia.[40]



(A)



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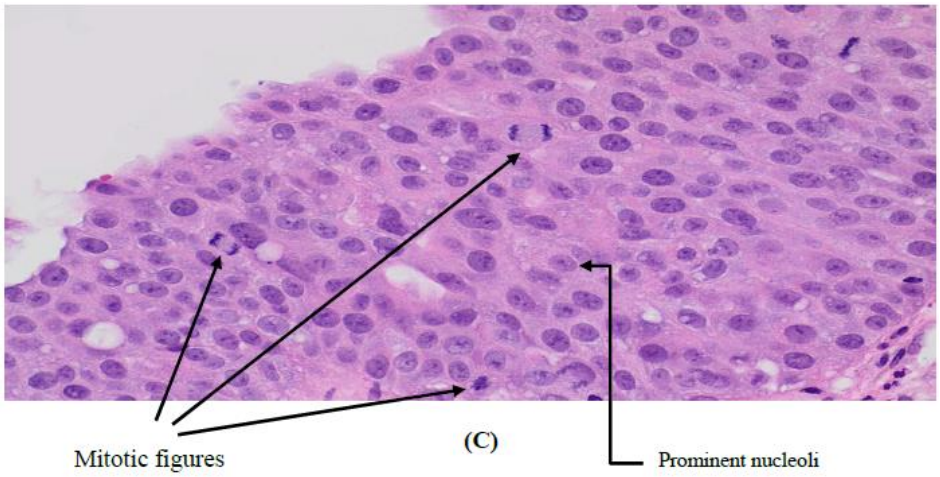

Figure 2.4: photomicrographs showing (A) PUNLMP showed Slim papillae without atypia, no thickening of the urothelium, low power view. (B) low grade papillary urothelial carcinoma showed Papillae have increased layers, atypia is rare, polarity conserved, intermediate magnification. (C) high grade papillary urothelial carcinoma showed pleomorphism, multiple mitoses, euchromatin and relatively prominent nucleoli, and uneven distribution of nuclei, high power view.[42]

2.7 Prognosis

The prognosis of Urothelial Carcinoma (UC), depends on several factors, including the stage at diagnosis, tumor grade, molecular characteristics, patient health, and response to treatment. Here's an overview of the key elements influencing the prognosis of UC.[43-45]

1. Tumor Stage

- **Early-Stage Disease (Ta, Tis, T1)**: Patients with non-muscle invasive bladder cancer (NMIBC) generally have a favorable prognosis. The 5-year survival rate for these patients can exceed 90% when managed with appropriate local therapies such as transurethral resection of bladder tumor (TURBT) and intravesical therapies.
- **Muscle-Invasive Disease (T2, T3, T4)**: Muscle-invasive bladder cancer (MIBC) has a less favorable prognosis. The 5-year survival rate drops significantly, with stage II around 63%, stage III around 46%, and stage IV around 15% due to the higher likelihood of metastasis and more aggressive tumor behavior.

2. Tumor Grade

- **Low-Grade Tumors**: These are less likely to invade and spread, and they generally have a better prognosis.
- **High-Grade Tumors**: These are more aggressive, with a higher risk of invasion, recurrence, and metastasis, leading to a poorer prognosis.

3. Molecular Characteristics

- Specific genetic mutations and molecular markers can influence prognosis. For example, tumors with FGFR3 mutations tend to have a better prognosis, while alterations in TP53 and RB1 are associated with more aggressive disease and poorer outcomes.

4. Treatment Response

- **Surgical Treatment**: The success of surgical interventions, such as cystectomy, significantly affects outcomes. Complete removal of the tumor and clear surgical margins improve survival rates.
- **Chemotherapy and Radiation**: The effectiveness of neoadjuvant (pre-surgical) or adjuvant (post-surgical) chemotherapy and radiation therapy also plays a crucial role. Patients responding well to these treatments tend to have better outcomes.
- **Immunotherapy**: Recent advancements in immunotherapy, such as checkpoint inhibitors, have shown promise in improving survival for advanced and metastatic UC.

5. Patient Factors

- **Age and General Health**: Younger patients and those in good overall health tend to have better outcomes due to a higher tolerance for aggressive treatments.
- **Comorbidities**: The presence of other health conditions can complicate treatment and negatively impact prognosis.

2.8 The TP53 gene

TP53 gene, often referred to as the "guardian of the genome," plays a crucial role in maintaining cellular integrity and preventing cancer development. Located on chromosome **17p13.1**, the TP53 gene encodes the P53 protein, a tumor suppressor that regulates the cell cycle, promotes DNA repair, induces apoptosis, and prevents genomic instability.[46]

2.8.1 Structure and Function of P53 protein

1. P53 Protein Structure[47]

- **Transactivation Domain**: This domain, located at the N-terminus, is responsible for activating the transcription of target genes.

- **DNA-Binding Domain**: The central part of P53 binds to specific DNA sequences, enabling the regulation of gene expression.
- **Tetramerization Domain**: This C-terminal domain allows P53 to form a tetramer, which is necessary for its functional activity.
- **Regulatory Domain**: The extreme C-terminus, involved in the regulation of P53's activity and stability.

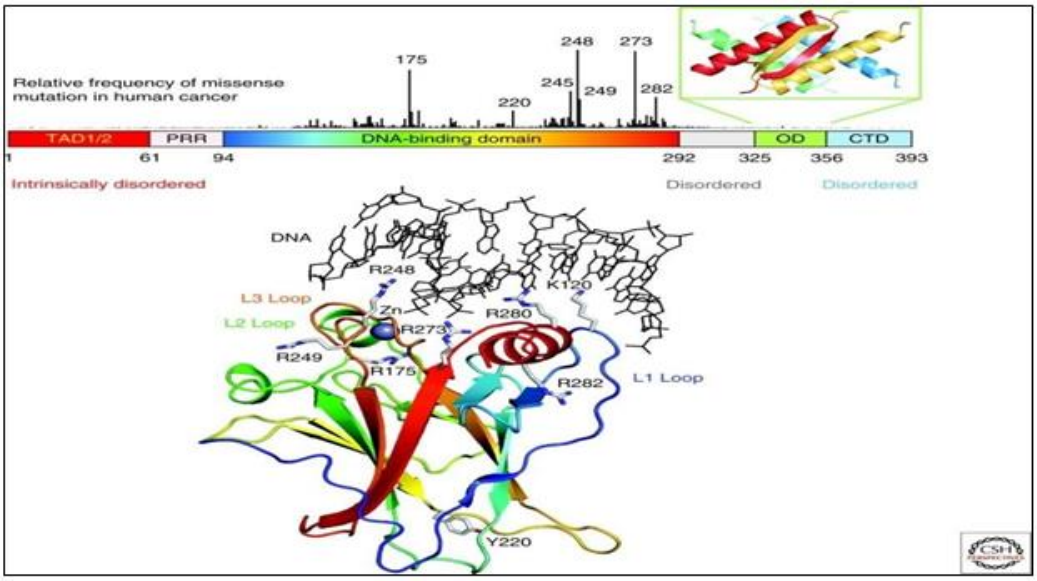

Figure 2.5: Structure of P53 protein.[47]

2. P53 Protein Functions[48]

- **Cell Cycle Regulation**: P53 plays a pivotal role in controlling the cell cycle. In response to DNA damage, P53 induces the expression of P21, a cyclin-dependent kinase inhibitor that halts the cell cycle at the G1/S checkpoint, allowing for DNA repair.
- **DNA Repair**: P53 upregulates genes involved in DNA repair mechanisms, such as GADD45, which participates in nucleotide excision repair.
- **Apoptosis**: If DNA damage is irreparable, P53 can initiate programmed cell death (apoptosis) by activating pro-apoptotic genes like BAX, PUMA, and NOXA.
- **Senescence**: P53 can induce cellular senescence, a state of permanent cell cycle arrest, to prevent the proliferation of damaged cells.
- **Genomic Stability**: By regulating these processes, P53 helps maintain genomic stability and prevents the accumulation of mutations that could lead to cancer.

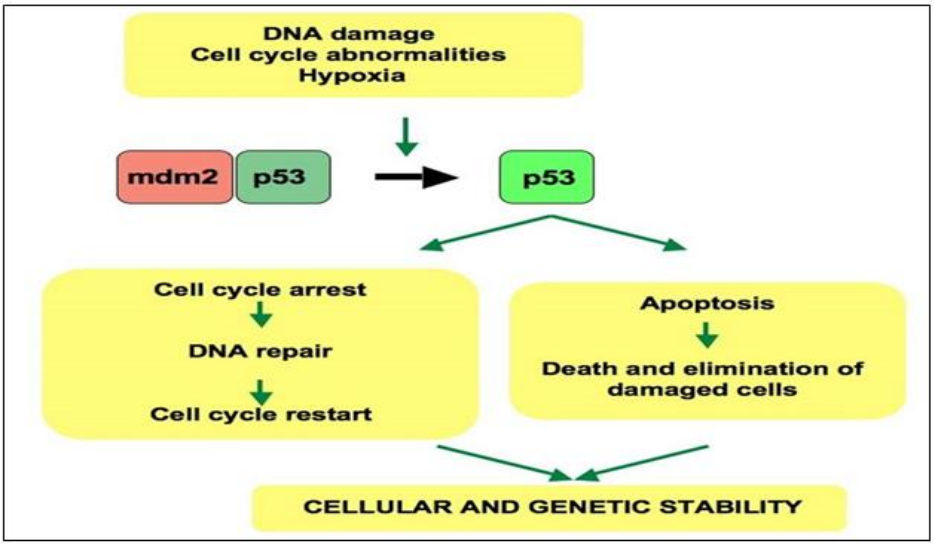

Figure 2.6: P53 pathway in a normal cell, P53 is inactivated by its negative regulator, mdm2. Upon DNA damage

or other stresses, various pathways will lead to the dissociation of the P53 and MDM2 complex. Once activated, P53 will induce a cell cycle arrest to allow either repair and survival of the cell or apoptosis to discard the damaged cell.[48]

2.8.2 TP53 Mutations and Cancer[49]

Mutations in the TP53 gene are among the most common alterations in human cancers, occurring in approximately 50% of all malignancies. These mutations can be inherited (as in Li-Fraumeni syndrome) or acquired. TP53 mutations are often associated with more aggressive tumor behavior, resistance to therapy, and poorer prognosis.

Types of TP53 Mutations

- **Missense Mutations**: These are the most common and result in the production of a dysfunctional P53 protein that cannot bind DNA or regulate target genes effectively.
- **Nonsense Mutations**: These lead to a truncated, non-functional P53 protein.
- **Frameshift Mutations**: Insertions or deletions that alter the reading frame, resulting in a non-functional protein.
- **Loss of Heterozygosity (LOH)**: This occurs when the second, normal copy of the TP53 gene is lost in cells already carrying one mutant allele, leading to complete loss of P53 function.

P53 Expression Patterns in Carcinomas . Normal vs. Mutant P53 Expression

- **Normal P53:** In healthy cells, p53 is typically expressed at low levels and remains inactive under normal conditions. It is quickly degraded via the ubiquitin- proteasome pathway, primarily mediated by MDM2, an E3 ubiquitin ligase that targets p53 for degradation.
- **Mutant P53:** In carcinoma cells, mutations in the TP53 gene often lead to the production of a stable, dysfunctional P53 protein. These mutations typically result in missense mutations, where a single amino acid change can lead to a protein that not only loses its tumor-suppressive functions but can also gain oncogenic properties. Mutant P53 proteins are often more stable than their wild-type counterparts and accumulate to high levels in cancer cells.

2.9 P53 Regulation

The regulation of the P53 protein is a complex process involving various mechanisms that ensure its proper function as a tumor suppressor. This regulation is critical because P53 must be tightly controlled to prevent unnecessary cell cycle arrest or apoptosis in normal cells, while allowing a rapid response to cellular stress or DNA damage. Here are the key aspects of P53 regulation

2.9.1 Post-Translational Modifications[50]

1. Phosphorylation

- Phosphorylation of P53 occurs mainly at the N-terminus in response to DNA damage. This modification stabilizes P53 by preventing its interaction with MDM2, a negative regulator.
- Key kinases involved include ATM, ATR, and DNA-PK, which phosphorylate P53 on serine and threonine residues, enhancing its stability and transcriptional activity.

2. Acetylation

- Acetylation of P53 at the C-terminus by acetyltransferases such as p300/CBP and PCAF enhances its DNA-binding ability and transcriptional activity.
- This modification is crucial for P53's role in apoptosis and cell cycle arrest.

3. Ubiquitination

- MDM2, an E3 ubiquitin ligase, ubiquitinates P53, targeting it for proteasomal degradation. This is a key mechanism for maintaining low P53 levels under normal conditions.
- In response to stress, ubiquitination is inhibited, leading to P53 stabilization and activation.

4. Methylation

- Methylation of P53 can have varying effects depending on the site and context. For example, SET7/9-mediated methylation enhances P53 stability, while methylation by SET8 suppresses P53 activity.
- These modifications influence P53's ability to regulate target genes involved in cell cycle arrest and apoptosis.

2.9.2 Interaction with Regulatory Proteins[51]

1. MDM2 and MDMX

- MDM2 binds to P53, inhibiting its transcriptional activity and promoting its degradation. MDMX (also known as MDM4) similarly inhibits P53 but does not promote degradation.
- The P53-MDM2 interaction is regulated through a negative feedback loop, where P53 induces the expression of MDM2, which in turn controls P53 levels.

2. ARF (Alternate Reading Frame)

- The ARF tumor suppressor protein inhibits MDM2, preventing P53 degradation and promoting its activation in response to oncogenic signals.
- ARF thus acts as a critical regulator of P53 stability, especially in the presence of oncogenic stress.

3. ASPP Family Proteins (Apoptosis stimulating P53 protein)

- ASPP1 and ASPP2 enhance the apoptotic function of P53 by promoting its interaction with pro-apoptotic target genes.

- iASPP inhibits P53-mediated apoptosis, highlighting the complex regulatory network involving P53 and ASPP proteins.

2.9.3 Cellular Localization[52]

- **Nuclear Import and Export**
  - P53 localization is regulated by nuclear import and export signals. Under stress conditions, P53 accumulates in the nucleus to activate target genes.
  - In normal conditions, P53 is continuously shuttled between the nucleus and cytoplasm, with cytoplasmic P53 being less active.

2.9.4 Regulation by Non-Coding RNAs[53]

- **MicroRNAs (miRNAs)**
  - Several miRNAs, such as miR-125b and miR-504, negatively regulate P53 by directly targeting its mRNA, reducing P53 protein levels.
  - Conversely, some miRNAs can stabilize P53 by targeting negative regulators like MDM2.

2.9.5 Feedback Loops[54]

- **Positive Feedback Loops**
  - P53 activates the expression of genes like P21, which stabilizes P53 by inhibiting CDK activity and promoting cell cycle arrest.

- **Negative Feedback Loops**
  - P53 induces MDM2, which in turn downregulates P53, creating a tightly regulated feedback mechanism to prevent excessive P53 activity.

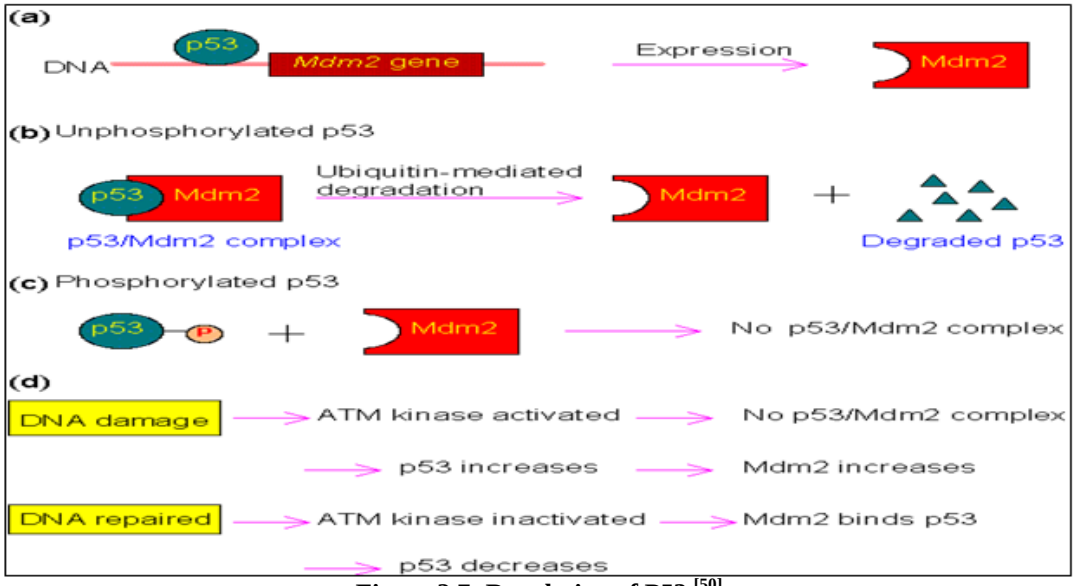

Figure 2.7: Regulation of P53.[50]

2.10 Role of P53

- The TP53 gene, encoding the P53 protein. Its role in disease is profound due to its involvement in cell cycle regulation, DNA repair, apoptosis, and genomic stability. Mutations and dysregulation of P53 are linked to a wide range of diseases, primarily various cancers, but also some non-cancerous conditions.[55]
- The TP53 gene and its product, the P53 protein, are central to the cellular defense against cancer. Understanding the mechanisms of P53 function and the consequences of its inactivation has profound implications for cancer diagnosis, prognosis, and treatment. Ongoing research into TP53-targeted therapies holds promise for improving outcomes in patients with P53-deficient cancers.

- **Role of P53 in Non-Cancerous Diseases[56, 57]**

1. **Neurodegenerative Diseases**

- **Alzheimer's Disease:** Abnormal P53 function has been implicated in the pathogenesis of Alzheimer's disease. Increased oxidative stress and DNA damage in neuronal cells can lead to P53 activation, contributing to neuronal cell death and the progression of neurodegenerative disorders.

2. **Cardiovascular Diseases**

- **Atherosclerosis:** P53 is involved in the cellular response to oxidative stress and inflammation, both of which play key roles in the development of atherosclerosis.

Dysfunctional P53 can lead to increased apoptosis of vascular cells, contributing to plaque formation and instability.

3. **Ischemic Injury**

- **Stroke and Myocardial Infarction:** In response to ischemic injury, P53 can be activated, leading to cell death and tissue damage. Modulating P53 activity in such conditions might provide therapeutic benefits by reducing cell death and improving recovery.

4. Aging

- **Cellular Senescence and Aging:** P53-induced cellular senescence is a double- edged sword. While it prevents cancer by stopping the proliferation of damaged cells, it also contributes to aging by promoting the accumulation of senescent cells, which can impair tissue function and regeneration.

2.11 Detection and Analysis[58]

1. Immunohistochemistry (IHC)

- **Technique:** IHC is a common method used to detect P53 expression in tissue samples. Antibodies specific to P53 are used to stain the protein, which can then be visualized under a microscope.
- **Interpretation:** High levels of P53 staining often indicate the presence of mutant P53, as these proteins are more stable and accumulate in the cell. Conversely, weak or absent staining might suggest wild-type P53, which is typically present at low levels in non-cancerous cells.

2. Genetic Sequencing

- **Technique:** Sequencing the TP53 gene can identify specific mutations present in the carcinoma cells. This can provide detailed information on the type and location of mutations within the gene.
- **Applications:** Genetic sequencing is valuable for confirming the presence of TP53 mutations and understanding their potential impact on p53 function.

2.12 Implications of P53 Expression in Carcinomas[59]

1. Prognostic Marker

- **Mutant P53:** High levels of mutant p53 expression are generally associated with a worse prognosis. These mutations often correlate with more aggressive tumor behavior, higher rates of metastasis, and resistance to conventional therapies.
- **Wild-type P53:** The presence of functional, wild-type P53 is typically associated with a better prognosis, as these tumors retain the ability to undergo P53-mediated cell cycle arrest and apoptosis in response to DNA damage.

2. Therapeutic Target

- **In Cancer Therapies**

- **Restoration Therapies:** Efforts are being made to develop drugs that can restore the normal function of mutant P53 or mimic its activity. Compounds like APR-246 (Eprenetapopt) aim to refold mutant P53 into a functional conformation.
- **MDM2 Inhibitors:** For tumors with wild-type P53, strategies to inhibit MDM2 can stabilize and activate P53. Nutlin-3 and RG7112 are examples of MDM2 inhibitors under investigation.
- **Gene Therapy:** Approaches to deliver functional TP53 gene to cancer cells using viral vectors are being explored to restore P53's tumor suppressor functions.

- **Non-Cancer Therapies**

- **Neuroprotective Strategies:** Modulating P53 activity to prevent excessive neuronal cell death could be beneficial in treating neurodegenerative diseases.
- **Cardioprotection:** Inhibiting P53-mediated apoptosis in cardiomyocytes might help in reducing damage during ischemic events like myocardial infarction.

3. Resistance Mechanisms

- **Chemotherapy and Radiotherapy:** P53 status can influence the response to chemotherapy and radiotherapy. Tumors with functional P53 are more likely to undergo apoptosis in response to these treatments, while those with mutant P53 may exhibit resistance.
- **Targeted Therapies:** Understanding P53 expression and mutation status can guide the use of targeted therapies, potentially improving treatment efficacy.

2.13 Expression in Specific Carcinomas[60]

1. Breast Cancer

- **Prevalence:** TP53 mutations occur in about 20-30% of breast cancers, with higher rates in triple-negative and HER2-positive subtypes.
- **Prognostic Value:** High p53 expression in breast cancer is often associated with poorer outcomes and more aggressive disease.

2. Colorectal Cancer

- **Prevalence:** Approximately 50% of colorectal cancers harbor TP53 mutations.
- **Therapeutic Implications:** The presence of TP53 mutations can influence the choice of chemotherapy regimens and the development of resistance.

3. Lung Cancer

- **Prevalence:** TP53 mutations are found in about 50-70% of non-small cell lung carcinomas (NSCLC) and a higher percentage in small cell lung carcinomas (SCLC).
- **Clinical Impact:** p53 status can affect the response to targeted therapies and immunotherapy.

2.14 Urothelial Carcinoma Treatment

Based on the tumor's stage and grade. The main treatment approaches include.

1. **Transurethral Resection of the Bladder Tumor (TURBT):** For non-muscle- invasive bladder cancer (NMIBC), TURBT is the first-line treatment.
2. **Intravesical Therapy:** After TURBT, medications are delivered directly into the bladder to reduce recurrence and progression. Bacillus Calmette-Guérin (BCG) and chemotherapy agents like mitomycin C are commonly used.
3. **Radical Cystectomy:** For muscle-invasive bladder cancer (MIBC) or high-risk NMIBC unresponsive to BCG.
4. **Systemic Chemotherapy:** Used for advanced or

metastatic disease, either before or after surgery to shrink tumors or address micro metastases.

5. **Immunotherapy:** Immune checkpoint inhibitors (e.g., atezolizumab, pembrolizumab) are options for metastatic or BCG-unresponsive bladder cancer.
6. **Targeted Therapy:** FGFR inhibitors (e.g., erdafitinib) are used in specific cases with genetic alterations.[61]

Role of BCG in Urothelial Carcinoma

BCG is a cornerstone treatment for high-risk NMIBC. Its role includes.

- **Immune Activation:** BCG triggers an immune response in the bladder wall, enhancing the body's ability to attack residual cancer cells.
- **Reduction of Recurrence:** It significantly lowers the recurrence rate of NMIBC after TURBT.
- **Prevention of Progression:** BCG reduces the likelihood of progression from NMIBC to MIBC.
- **Indications:** It is particularly effective for carcinoma in situ (CIS), high-grade Ta, and T1 tumors.
- Patients receiving BCG therapy require regular monitoring due to potential side effects, such as bladder irritation or, rarely, systemic BCG infection.[62]

PATIENTS AND METHOD

3.1 Study design and setting

A cross-sectional study was conducted in the Gazi AL-Hariri Hospital for specialized surgeries in medical city and private labs. during the period from the first of January 2024 to December 2024.

3.2 Ethical approval

The study has been proposed and subsequently, approval has been obtained from the Scientific Council of Pathology of the Iraqi Board of Medical Specializations. All information was kept anonymous, and the collected data were used for scientific purposes only.

3.3 Study subject

3.3.1 Sampling method

A convenient sampling method was adopted to enroll fifty (50) patients (forty of them were diagnosed with Urothelial Carcinoma and the other ten diagnosed with cystitis during 2023). The paraffin-embedded blocks of those patients were retrieved from the patient's records.

3.3.2 Inclusion criteria

1. Patients newly diagnosed with bladder cancer
2. Patients with hematuria without bladder mass

3.3.3 Exclusion criteria: Patient known case of bladder carcinoma previously treated.

3.4. Data collection

The data was collected from the patient's records using a checklist that was adopted by the researcher after a review of similar articles and then revised by the supervisor The data included the age of the patients, sex, TNM staging, tumor grade, muscularis propria invasion, lymphovascular invasion and histopathological diagnosis.

3.5 Immunohistochemistry staining for P53

3.5.1 Procedure

Interpretation of immunohistochemistry staining begins with tissue sectioning, where the sample is cut by microtome into 4 µm thick sections. The sections are then placed on water at 45°C to ensure proper stretching. After that, the tissue sections are carefully picked up on positively charged slides to enhance adhesion. The slides are subjected to fixation by placing them in a hot oven at 65°C for 30 minutes, which ensures that the tissue remains attached to the slide and is ready for subsequent processing.

Dewaxing (deparaffinization) follows, where the slides are treated with xylene in three consecutive steps, each lasting 5 minutes, to remove any remaining paraffin. Re-hydration of the tissue is achieved by passing the slides through a graded series of alcohol (100%, 90%, 80%, and 70%), followed by rinsing in tap water, with each step lasting 5 minutes. This step restores the tissue to a hydrophilic state necessary for the antigen retrieval process.

The next critical step is epitope antigen retrieval, which involves immersing the slides in Tris-EDTA solution (pH 9) and placing them in a water bath at 99°C for 30 minutes. The solution is then allowed to cool for 15 minutes at room temperature to optimize antigen exposure without causing tissue damage. After antigen retrieval, the slides are transferred to a wash buffer solution (phosphate buffer saline, PBS 1, pH 7.4) to rinse away residual reagents.

To localize the area of interest, the sections are marked around the perimeter using a hydrophobic Pap-pen. This confines the antibody reagents to the tissue section, enhancing staining specificity. To block any endogenous peroxidase activity that could interfere with the staining process, a 3% peroxidase block is applied for 10 minutes. After blocking, the slides are rinsed with wash buffer for 10 minutes to remove any excess blocking reagent.

The primary antibody against P53 is then applied for 30 minutes, allowing sufficient time for antigen-antibody binding. Following this, the slides are washed again with buffer for 10 minutes. A mouse linker is added for 30 minutes to facilitate the detection of the primary antibody. Another wash with buffer for 10 minutes ensures that unbound reagents are removed. Subsequently, the secondary antibody, labeled with horseradish peroxidase (HRP) and specific for the mouse antibody, is applied for 30 minutes. This step introduces the enzyme that will catalyze the colorimetric reaction in the presence of a chromogen.

The slides are again washed with buffer for 10 minutes before adding the DAB chromogen. The DAB solution is prepared by mixing 1 mL of substrate buffer with one drop of DAB chromogen. The slides are rinsed with wash buffer for 10 minutes, followed by counterstaining with hematoxylin for 1 minute. A quick rinse under running tap water for 1 minute helps to remove excess hematoxylin.

The slides are then dehydrated by passing through a series of alcohol concentrations (70%, 80%, 90%, and 100%) for 1 minute each, ensuring that the tissue is free from water, which could interfere with long-term preservation. The final step in slide preparation involves covering the section with a mounting medium (DPX) and applying a coverslip, which seals the tissue and protects the staining for microscopic analysis.

Throughout the procedure, a colorectal adenocarcinoma sample serves as a positive control to confirm the accuracy of the staining process, ensuring that all reagents and steps are functioning correctly. Technical negative control was done by omitting the primary antibody. After completing the staining protocol, the samples are examined under a light microscope to evaluate the presence and intensity of the target antigen, providing insight into the biological and pathological characteristics of the tissue.

3.5.2 Interpretation of immunohistochemistry staining[63]

- The percentage of P53-positive tumor nuclei in major cancer foci was used to develop a P53 immunohistochemical scoring system.
- The proportion of P53-immunoreactive tumor cells was graded on a scale from 0 to +3 in P53-positive regions.
- Nuclear P53 expression in ≥10% of tumor cells was considered an aberrant overexpression.

- **The P53 scoring system classified expression as follows**
  - Less than 10% as "-ve".
  - 10%-30% as "+1".
  - 31%-50% as "+2".
  - Greater than 51% as "+3".

- Over 1,000 tumor cells were counted across multiple high-power fields to assess the percentage of P53 expression.
- The slides were reviewed multiple times to ensure accuracy and to exclude any errors.

3.6 Statistical analysis

Statistical analysis done by statically package for social science(SPSS), version 22, frequency and percentage used for categorical data, mean, median and SD for continuous data. Chi-square used for assessed association between categorical variables. P-value less or equal to 0.05 is consider significant.

RESULTS

- Age Groups:
  - Often older patients, with 54% aged ≥60 years.
  - 26% are aged 50-59 years.
  - 12% are aged 40-49 years.
  - Only 8% are aged 20-29 years.
- Gender:
  - Predominantly male patients constitute 82% of the total.
  - Female patients make up 18%.

Overall, the study population is often older adults, with a significant majority being male. As in table 4.1.

Table 4.1: distribution of patients according to study variables. (N=50).

variables		frequency	percentage
Age groups (years)	**20-29**	4	8.0
	40-49	6	12.0
	50-59	13	26.0
	≥60	27	54.0
Gender	**Female**	9	18.0
	male	41	82.0
Total		50	100

As shown in Fig. 4.1; twenty percent of patients with cystitis (benign lesion) while 80% of them with malignant lesion: 76% of them with Papillary type Urothelial Carcinoma and 4% of them with solid type Urothelial Carcinoma. As shown in Fig. 4.2; 50% of P53 scoring system (+3), 18% of P53 scoring system (+2) while 6% of P53 scoring system (+1). Negative P53 scoring system represented 26% of patients.

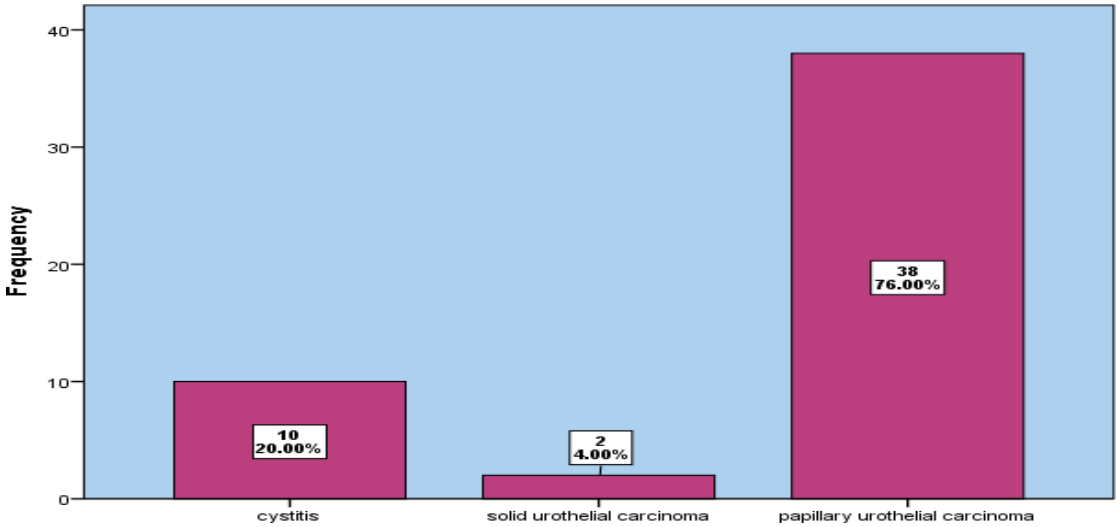

Fig 4.1: Distribution of patients according to histopathology.

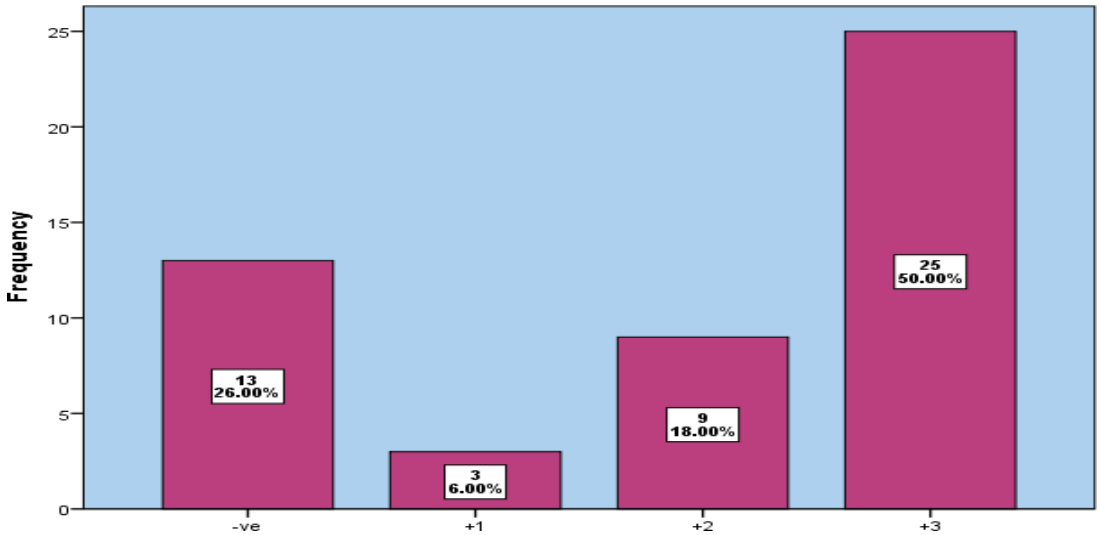

Fig 4.2: Distribution of patients according to P53 scoring system.

Table 4.2: examines the association between histopathological findings and sociodemographic variables in the study population. Key observations include:

- **Age Groups:** Among patients aged 20-29 years, 30% had cystitis, and 2.6% had Papillary type. In the 40-49 age group, 10% had cystitis, and 13.2% had Papillary type. For those aged 50-59 years, 30% had cystitis, and 26.3% had Papillary type. Among patients aged 60 years and above, 30% had cystitis, 100% had solid type, and 57.9% had Papillary type, with no significant association (P-value 0.1).
- **Gender:** A significant difference is noted between genders (P-value 0.001). Among females, 60% had cystitis and 7.9% had Papillary type. No females had solid type. Among males, 40% had cystitis, 100% had solid type, and 92.1% had Papillary type.
- **P53 scoring system:** There is a significant association with the P53 scoring system (P-value 0.0001) with histological type. All patients with negative scoring (100%) had cystitis. Papillary type urothelial carcinoma type found significantly in 60.5% of patients with P53 scoring (+3), while all patients with solid type urothelial carcinoma type had P53 scoring (+3).

Table 4.2: association between histopathology and sociodemographic. (N=50).

Variables		Histological Type			P-value
		Cystitis	solid type Urothelial Carcinoma	Papillary type Urothelial Carcinoma	
Age groups (years)	20-29	3	0	1	0.1
		30.0%	0.0%	2.6%	
	40-49	1	0	5	
		10.0%	0.0%	13.2%	
	50-59	3	0	10	
		30.0%	0.0%	26.3%	
	≥60	3	2	22	
		30.0%	100.0%	57.9%	
Gender	Females	6	0	3	0.001
		60.0%	0.0%	7.9%	
	Males	4	2	35	
		40.0%	100.0%	92.1%	
P53 scoring system	Negative	10	0	3	0.0001
		100.0%	0.0%	7.9%	
	+1	0	0	3	
		0.0%	0.0%	7.9%	
	+2	0	0	9	
		0.0%	0.0%	23.7%	
	+3	0	2	23	
		0.0%	100.0%	60.5%	

Table 4.3: details the distribution of patients according to various study variables in malignant histology. Key findings include:

- **Lymph vascular Invasion (LVI):** 85% of the patients did not have lymphovascular invasion, while 15% had LVI.
- **Muscularis Propria Invasion (MPI):** 75% of the patients did not have muscularis propria invasion, whereas 25% did.
- **Grade:** A majority of the patients (77.5%) had high-grade tumors, and 22.5% had low-grade tumors.
- **Stages:** Most patients were in stage T1 (75%), followed by stage T2 (25%).

Table 4.3: distribution of patients according to study variables in malignant histology. (N=40)

variables		frequency	percentage
LVI	NO	34	85.0
	YES	6	15.0
MPI	NO	30	75.0
	YES	10	25.0
Grade	HIGH	31	77.5
	LOW	9	22.5
Stages	T1	30	75.0
	T2	10	25.0
Total		40	100

Table 4.4: presents the association between histopathological findings and variables such as grade, lymphovascular invasion (LVI), muscularis propria invasion (MPI), and stages in patients with malignant histology. Key findings include:

- **Grade:** All patients with solid type had high-grade tumors (100%), while 76.3% of those with Papillary type had high-grade tumors. Low-grade tumors were only observed in patients with Papillary type (23.7%) with no significant association (P-value 1.000).
- **Lymphovascular Invasion (LVI):** LVI was present in 10.5% of patients with Papillary type and 100% of those with solid type, showing a significant association (P-value 0.019).
- **Muscularis Propria Invasion (MPI):** MPI was found in 21.1% of patients with Papillary type and 100% of those with solid type with significant association (P-value 0.04).
- **Stages:** Among patients with Papillary type, 78.9% were in stage T1, 21.1% in stage T2. All patients with solid type were in stage T2 (100%) with significant association (P-value 0.04).

Table 4.4: association between histopathology and (Grade, LVI, MPI, stages) in malignant histology, (N=40).

Variables		Diagnosis P-value		
		Solid type	Papillary type	
Grade	High	2	29	1.000
		100.0%	76.3%	
	Low	0	9	
		0.0%	23.7%	
LVI	No	0	34	**0.019**
		0.0%	89.5%	
	Yes	2	4	
		100.0%	10.5%	
MPI	No	0	30	**0.04**
		0.0%	78.9%	
	Yes	2	8	
		100.0%	21.1%	
stages	T1	0	30	**0.04**
		0.0%	78.9%	
	T2	2	8	
		100.0%	21.1%	
Total		2	38	
		100%	100%	

Table 4.5: examines the association between the P53 scoring system and both tumor grade and stage in malignant histology (N=40).

1. **Grade (High vs. Low)**
   - High-grade tumors show higher P53 scores (+2 and +3), with 88.9% and 72.0% of cases respectively.
   - Low-grade tumors have lower P53 scores, with 28.0% at +3 and 11.1% at +2.
   - The **P-value (0.5)** suggests no statistically significant association between P53 scoring and tumor grade.
2. **Stage (T1, T2):**
   - T1 stage tumors are more likely to have higher P53 scores (+2 and +3), with 88.9% and 72.0 % of cases respectively.
   - T2 stages show lower P53 scores, with T2 having 28.0% at +3 and having only 11.1% at +2.
   - The **P-value (0.7)** indicates no statistically significant association between P53 scoring and tumor stage.

Table 4.5: Association between P53 scoring system and (Grade, stages) in malignant histology, (N=40).

		SCORING				P-value
		-ve	+1	+2	+3	
Grade	HIGH	2 66.7%	3 100.0%	8 88.9%	18 72.0%	0.5
	LOW	1 33.3%	0 0.0%	1 11.1%	7 28.0%	
		SCORING				P-value
		-ve	+1	+2	+3	
Stage	T1	2 66.7%	2 66.7%	8 88.9%	18 72.0%	0.7
	T2	1 33.3%	1 33.3%	1 11.1%	7 28.0%	
Total		3 100.0%	3 100.0%	9 100.0%	25 100.0%	

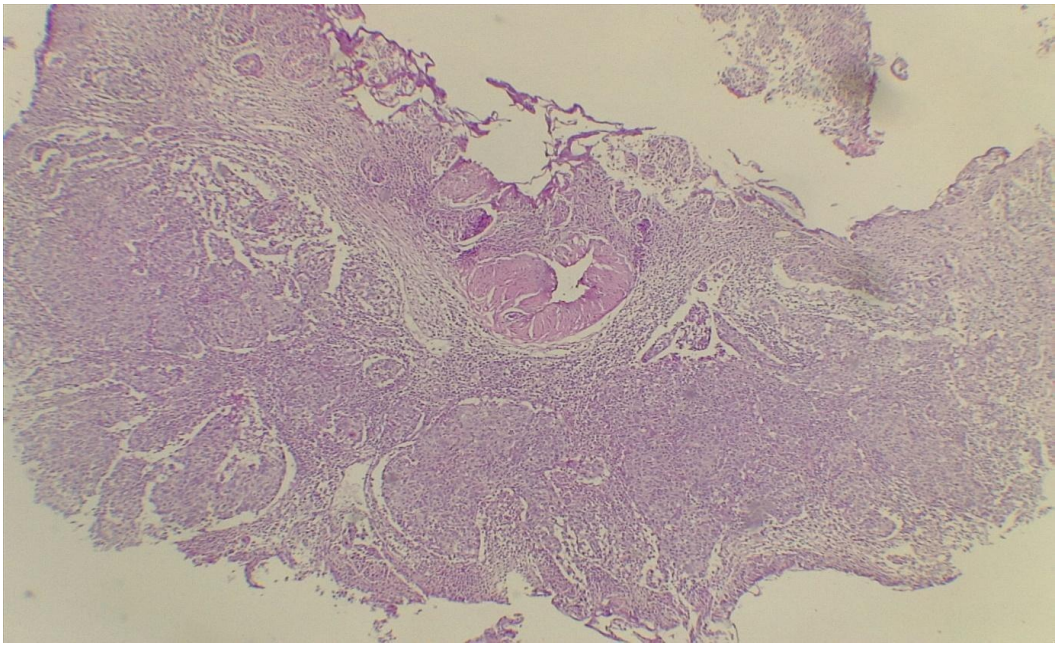

Fig 4.3: Photomicrograph showing, invasive high grade solid type urothelial carcinoma, H&E, 4x.

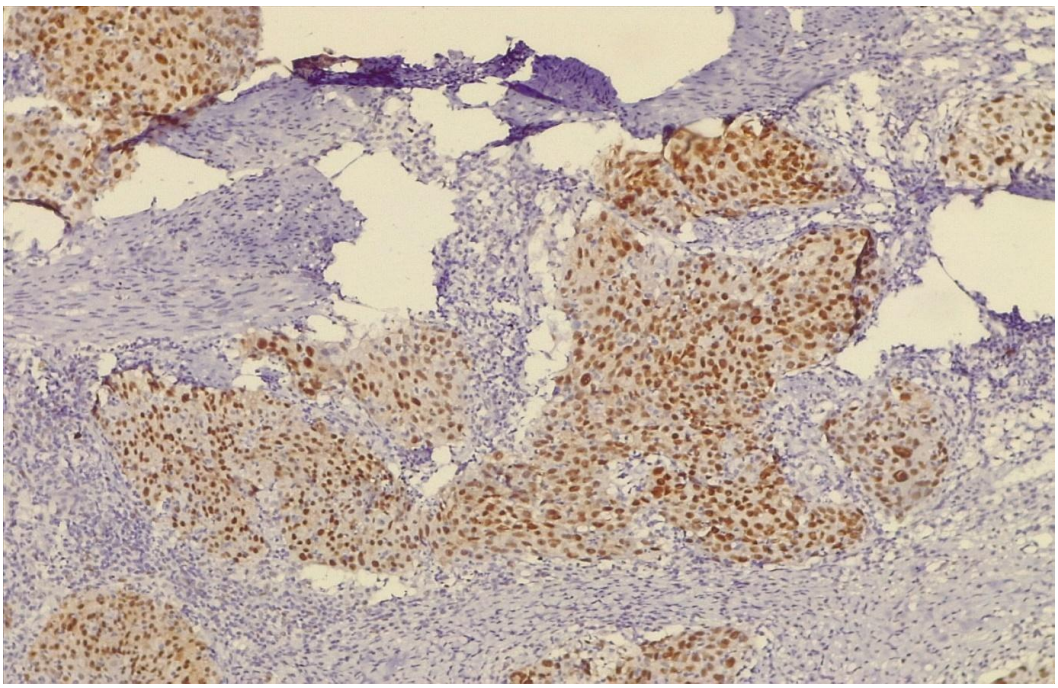

Fig 4.4: Photomicrograph showing invasive high grade solid type urothelial carcinoma with positive IHC with P53, score (+3), 10x.

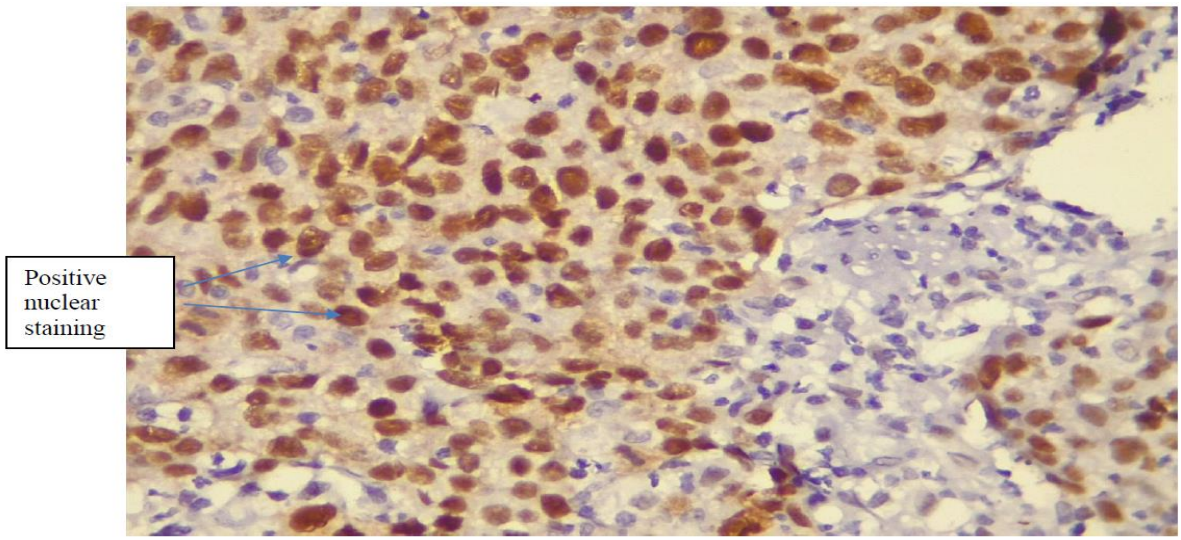

Fig 4.5: Photomicrograph showing invasive high grade solid type urothelial carcinoma with positive IHC with P53, score (+3), 40x.

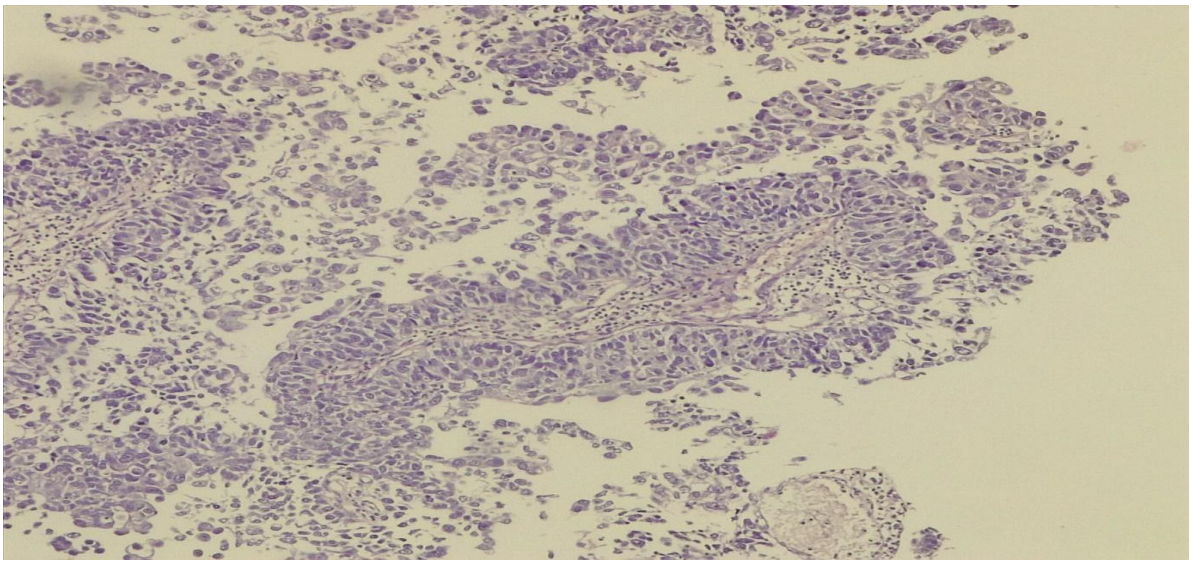

Fig 4.6: Photomicrograph showing invasive high grade papillary type urothelial carcinoma, H&E, 10x.

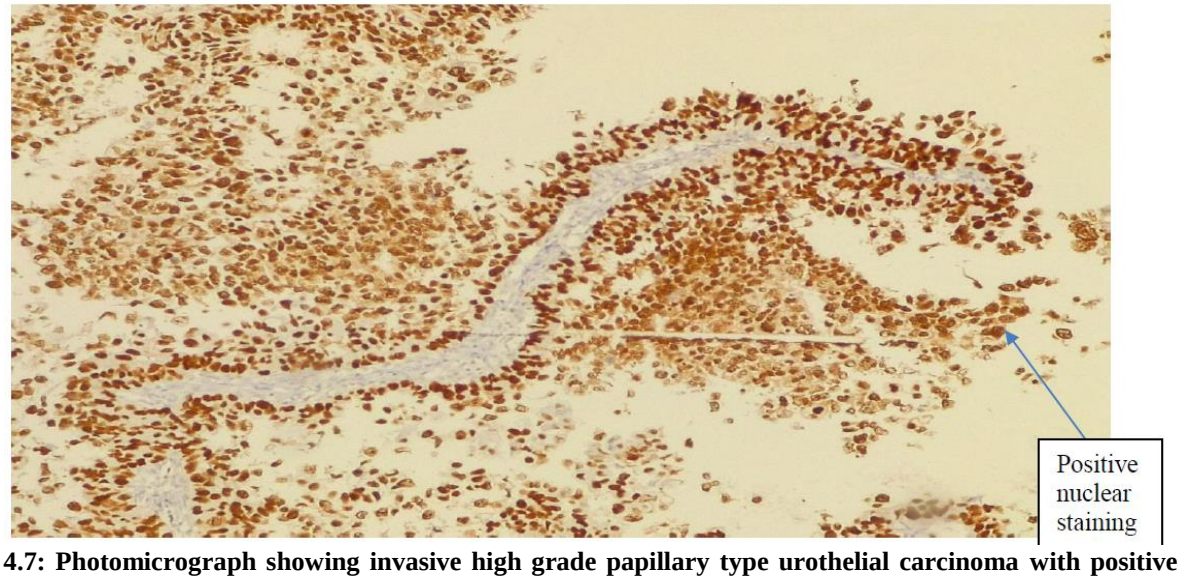

Fig 4.7: Photomicrograph showing invasive high grade papillary type urothelial carcinoma with positive IHC with P53 score (+3), 10x.

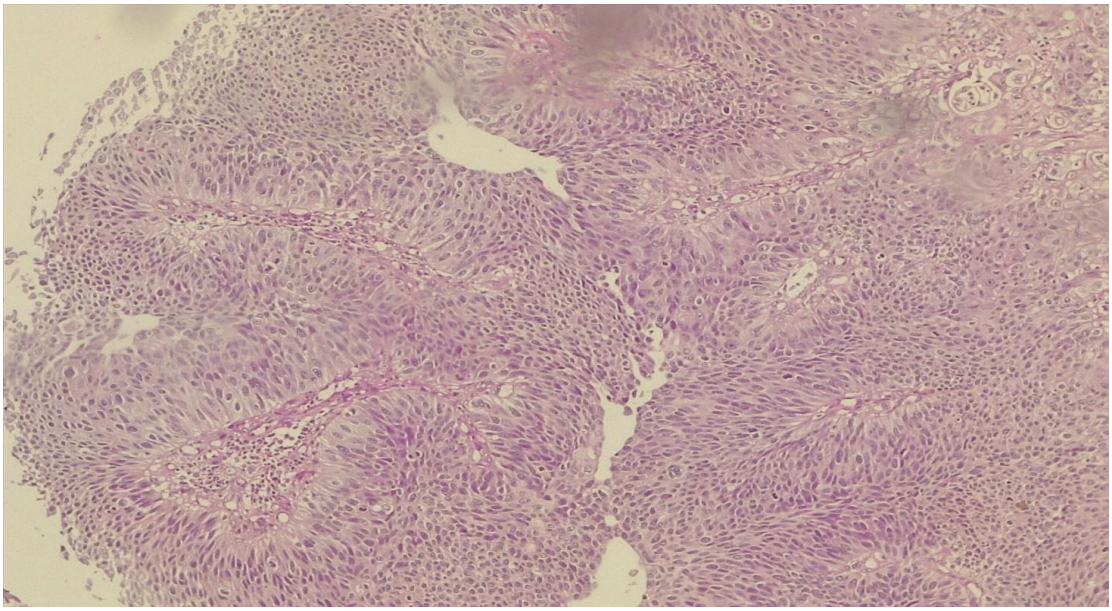

Fig 4.8: Photomicrograph showing invasive high grade papillary type urothelial carcinoma, H&E, 10x.

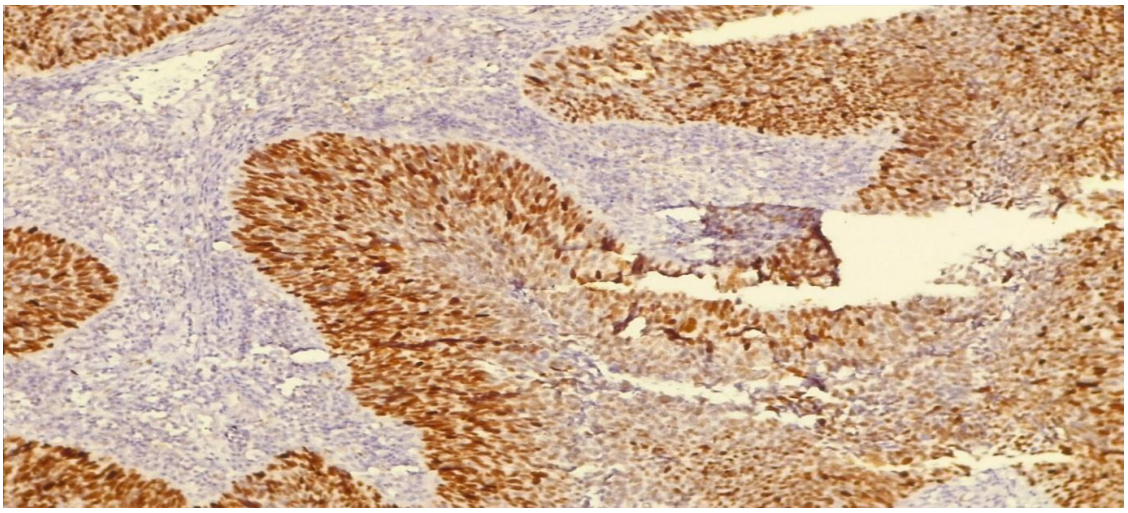

Fig 4.9: Photomicrograph showing invasive high grade papillary type urothelial carcinoma, with positive IHC with P53 score (+3), 10x.

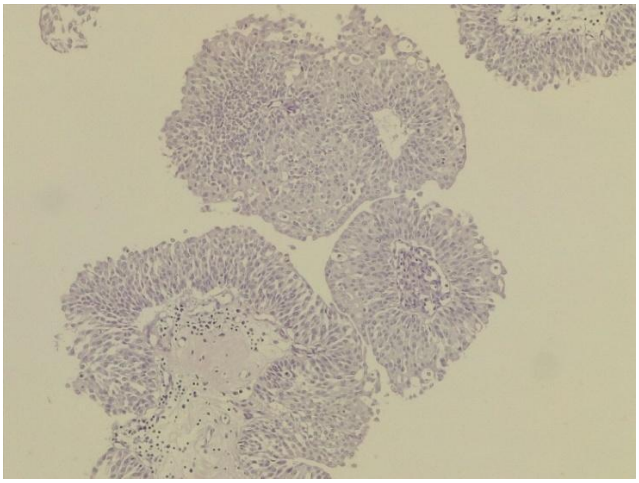

Fig 4.10: Photomicrograph showing low grade papillary type urothelial carcinoma, H&E, 4x.

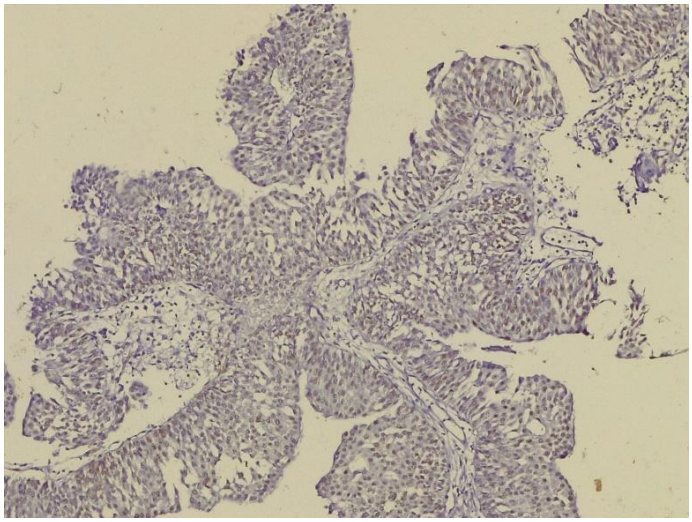

Fig 4.11: Photomicrograph showing low grade papillary type urothelial carcinoma, with positive IHC with P53 score (+1), 10x.

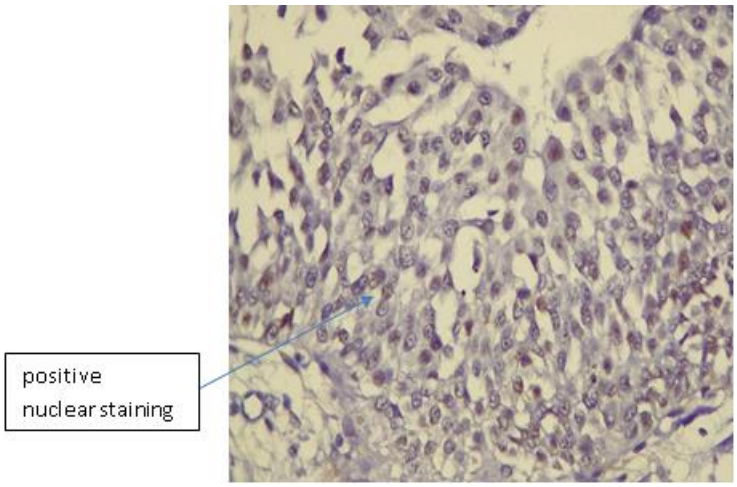

Fig 4.12: Photomicrograph showing low grade papillary type urothelial carcinoma, with positive IHC with P53 score (+1), 40x.

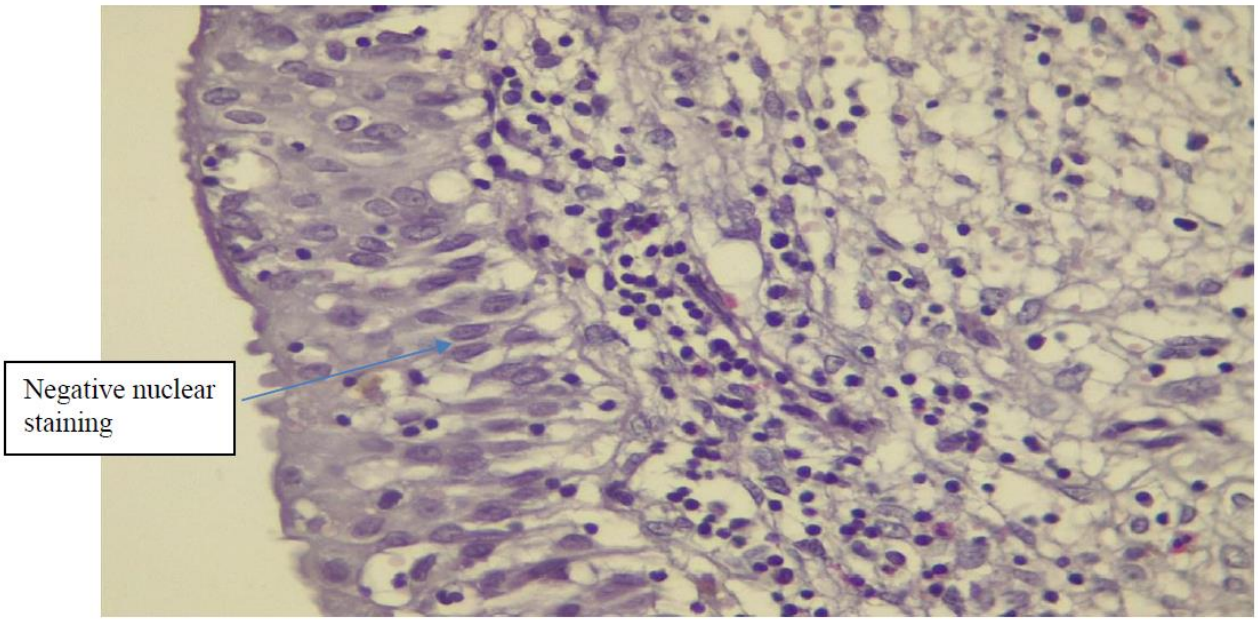

Fig 4.13: Photomicrograph showing Cystitis, with negative IHC for p53 staining, 40x.

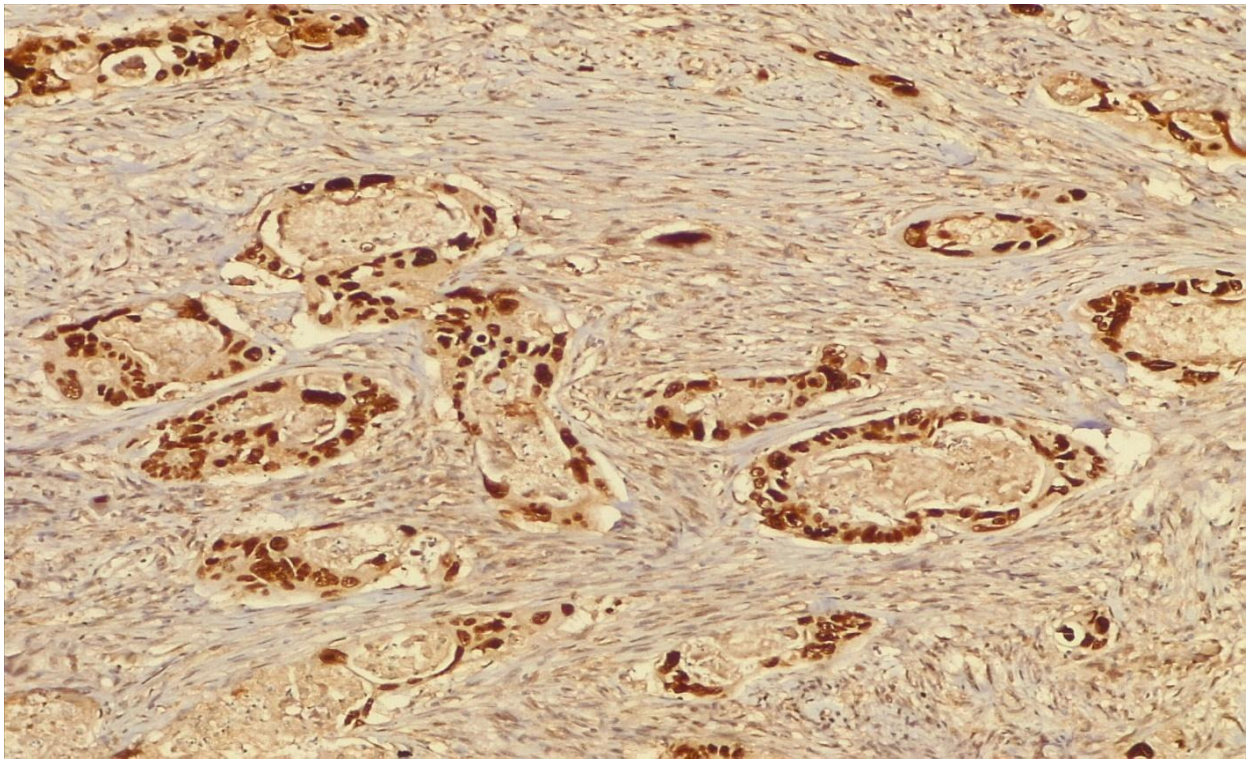

Fig 4.14: Photomicrograph Showing Well differentiated colorectal adenocarcinoma , as a positive control for p53 staining, 40x.

DISCUSSION

Among the 50 patients, 20% were diagnosed with cystitis, a benign condition, while 80% had malignant lesions. Of the malignant cases, 76% were diagnosed with Papillary type urothelial carcinoma, and 4% with solid type Urothelial Carcinoma. This finding emphasizes the higher prevalence of malignant lesions, particularly Papillary type, in the studied group.

In comparison to similar studies, it has been frequently observed that Papillary type is the most common type of bladder cancer, which aligns with current findings. For instance, a study by Chang et al. (2014) found that Papillary type accounted for approximately 70- 75% of bladder cancer cases[64], comparable to current observation of 76%. Solid type, though less common, still represents a significant risk, as noted in current 4% of cases. Studies by Sylvester et al. (2020) highlight the aggressive nature of solid type, often correlated with poor prognosis.[65] Another study by Amin et al. (2014) highlighted similar findings.[66]

Regarding the P53 scoring system P53 shown in figure 4.2, 50% of the patients scored (+3), 18% scored (+2), and 6% scored (+1). Negative scoring, represented 26% of the patients. This distribution reflects a predominant higher scoring trend among malignant cases, as indicated by studies focusing on P53 scoring systems like the Bladder Cancer Recurrence Risk Score (BCRRS), which also found higher scores associated with invasive cancer types and poorer outcomes. These results, particularly the significant presence of Papillary type and high scoring among patients, align with international trends in urothelial cancers, where histopathological features and P53 scoring systems play critical roles in diagnosis, prognosis, and treatment decisions.[67,68]

The results from the current study demonstrate important associations between histopathological findings and sociodemographic variables such as age, gender, and P53 scoring systems. These findings provide insight into how these factors influence the occurrence and severity of cystitis and Urothelial Carcinomas.

Age Group Associations:

In current study, patients aged 60 years and above had the highest rates of malignancy, with 100% of those with solid type UC and 57.9% with Papillary type UC. This supports the well-documented link between advanced age and the increased risk of malignant bladder conditions, particularly Urothelial Carcinoma. For instance, A study by Babjuk et al. (2019) also noted that bladder cancer incidence rises significantly in individuals aged over 60, particularly in relation to aggressive forms like solid type UC.[67] Current patients (aged 20-29 years) had a lower prevalence of Urothelial Carcinoma, which is consistent with broader findings showing that bladder cancer is rare in current populations. Current study shows only 2.6% of Papillary type in this age group, which corresponds to previous research indicating a very low incidence of bladder cancer in current adults.[69]

Gender Differences

A significant difference in cancer prevalence between genders was found in current study, with 100% of males having solid type UC and 92.1% having Papillary type UC. In comparison, 60% of females had cystitis and none had solid type UC. This is in line with existing research that demonstrates bladder cancer is more common in males than females, likely due to factors like occupational exposures and smoking.[70,71] The male-to-female ratio in bladder cancer incidence is approximately 3:1, which reflects current study's gender distribution.

The absence of solid type UC in females is also a notable finding, suggesting gender- based biological differences in cancer progression, which has been similarly documented in studies indicating a better prognosis for females with bladder cancer.

P53 scoring system:

The significant association between higher scores and malignant findings in current study (P-value 0.0001) supports the utility of P53 scoring systems in distinguishing between benign and malignant lesions. All patients with scores (+3) had either Papillary type UC or solid type UC, whereas patients with cystitis had negative scores. The P53 scoring system in this study shows that 50% of patients had scores (+3), indicating a higher risk profile for recurrence or progression. This aligns with established risk stratification models like the EORTC and CUETO, which highlight that patients with higher scores tend to present with more aggressive disease and are more likely to experience worse outcomes, including increased recurrence rates and decreased survival. The EORTC risk tables, for example, predict similar risk stratification where patients with higher scores have a significantly elevated risk of tumor recurrence and progression.[72]

Furthermore, 18% of patients scored (+2), representing an intermediate risk group. This group typically requires close surveillance and, in some cases, more aggressive treatment depending on other factors like tumor grade and stage. Studies, such as those by Fernandez-Gomez et al. (2009), have shown that intermediate scores are associated with a moderate risk of recurrence but may still have favorable outcomes with appropriate treatment.[73] In contrast, only 6% of patients had scores (+1), which corresponds to a low- risk category. These patients are often expected to have a lower risk of recurrence or progression, consistent with findings from CUETO and other risk models, which suggest that lower scores correlate with better long-term outcomes and a reduced need for aggressive intervention.[74] Interestingly, 26% of patients had negative scores. Studies have similarly indicated that benign conditions or low-risk non-muscle-invasive bladder cancers (NMIBC) often have negative or very low-risk scores, and these patients generally do not require extensive treatment beyond routine monitoring.[75]

Thus, the P53 scoring system used in this study effectively mirrors the stratification seen in the literature, where higher scores predict worse outcomes, intermediate scores represent moderate risk, and lower or negative scores indicate favorable prognosis. Current findings are consistent with international studies that highlight the influence of sociodemographic variables on bladder cancer occurrence and progression. The detailed association between histopathological findings and variables such as tumor grade, lymphovascular invasion (LVI), muscularis propria invasion (MPI), and stages in patients with malignant urothelial carcinoma provides important insights into the biological behavior of the disease.

Lymphovascular Invasion (LVI)

A 85% of the patients did not exhibit lymphovascular invasion (LVI), while 15% of the patients showed evidence of LVI. LVI is considered a poor prognostic factor in bladder cancer, as it indicates that the cancer has begun to spread through the lymphatic system, increasing the risk of metastasis. Similar studies also confirm that LVI is linked with more aggressive tumor behavior and worse survival outcomes.[76]

LVI was observed in 100% of patients with solid type UC, which is indicative of the aggressive nature of this subtype. In contrast, only 10.5% of patients with Papillary type UC had LVI. The significant association (P-value = 0.019) highlights the fact that solid type is much more likely to spread through the lymphovascular system, reinforcing its poor prognosis compared to the Papillary invasive type.

Mari A et al. (2018) conducted a large-scale study that confirmed LVI as a significant predictor of poor outcomes in bladder cancer. They found that LVI was present in approximately 30% of bladder cancer patients and was strongly associated with recurrence and reduced survival. The presence of LVI in 100% of solid type in current study aligns with this, highlighting its role as a poor prognostic factor.[77]

Muscularis propria invasion (MPI)

In the current study 75 % of patients did not have muscularis propria invasion (MPI), while 25% did. MPI is a significant marker for advanced-stage urothelial carcinoma. Tumor invasion into the muscularis propria (T2 stage) signals a more advanced and potentially aggressive cancer that often requires radical treatment approaches. This aligns with studies such as Fahoum I et al. (2024) and Hassan O (2020), where muscularis invasion is a critical factor in determining the treatment strategy, often leading to cystectomy or aggressive chemotherapy.[78,79]

A 21.1% of patients with Papillary type had muscularis propria invasion, whereas 100% of patients with solid type exhibited MPI. This is critical because once a tumor invades the muscle layer, it significantly worsens the

prognosis and necessitates more aggressive treatment. There is significant association (P-value = 0.04), Gakis et al. (2019) emphasized that MPI is a key determinant in choosing between bladder-sparing treatments and radical cystectomy. In their analysis, patients with muscle-invasive bladder cancer (T2 and beyond) had significantly lower survival rates, underscoring the importance of early detection and treatment before muscle invasion occurs. Current finding of 100% MPI in solid type supports the critical need for aggressive treatment once muscle invasion is confirmed.[80]

Tumor Grade

A large proportion of patients (77.5%) had high-grade tumors, while 22.5% had low-grade tumors. High-grade tumors are generally associated with a higher likelihood of progression and recurrence, requiring more intensive surveillance and treatment.

Studies, including those by Garg T et al. (2021) and Mesfin FB et al. 2024, highlight the importance of tumor grade as a predictor of prognosis in bladder cancer, where high-grade tumors typically indicate a more aggressive disease course.[81,82]

In the current study all patients with solid type UC had high-grade tumors (100%). This is a key finding, as high-grade tumors are more likely to exhibit aggressive behavior and have a higher risk of progression and metastasis. Papillary type UC showed a mix of high and low-grade tumors: 76.3% of patients had high-grade tumors, while 23.7% had low- grade tumors. Low-grade tumors are typically less aggressive, with a lower risk of progression, which is consistent with current findings. The lack of a statistically significant association between tumor type and grade (P-value = 1.000) might reflect the inherent variation in tumor aggressiveness within Papillary types, where both low- and high-grade variants can coexist.

A recent study by Mehra et al. (2021) found that high-grade tumors were more prevalent among solid type UC patients, with 95% of invasive tumors being classified as high-grade, similar to current finding of 100%. This supports the view that solid type tumors are almost exclusively high-grade, in line with modern grading systems that prioritize aggressive features.[83]

For Papillary type UC, Shariat et al. (2020) emphasized the importance of distinguishing between low-grade and high-grade tumors, noting that high-grade papillary carcinomas often show progression to solid type Urothelial Carcinoma, consistent with current observation of 76.3% high-grade cases.[84]

Tumor Staging

The majority of the patients in current study were diagnosed at stage T1 (75%), with a smaller proportion at stage T2 (25%). Stage T1 indicates tumor invasion into the lamina propria but not into the muscle layer, while stage T2 suggests deeper invasion into the muscularis propria. In line with other studies, such as Krishna SR et al. (2017) and Lawless M et al. 2017, stage T1 tumors, while not yet muscle-invasive, are at risk of progression to more advanced stages if not treated promptly. Stage T2 disease is more serious and often requires aggressive interventions.[85,86]

Most patients with Papillary type were in stage T1 (78.9%), the remaining (21.1%) were in stage T2. In contrast, all patients with solid type were in stage T2 (100%), reinforcing the aggressive nature of this subtype. The significant association (P-value = 0.04) underlines the critical role of tumor stage in determining treatment strategies and prognosis. current study is consistent with recent literature. For example, Soukup et al. (2020) found that the majority of Papillary type cases were diagnosed at T1, while solid type was predominantly diagnosed at T2 or higher stages. Their findings suggest that while Papillary type is often detected early, solid type tends to be diagnosed at more advanced stages, reflecting its aggressive behavior and poorer prognosis.[87]

Urothelial Carcinoma with squamous differentiation (UCSD) is a more aggressive variant of bladder cancer, often presenting at advanced stages and associated with poor prognosis. It is linked to higher rates of recurrence, metastasis, and resistance to standard chemotherapy. UCSD patients typically experience worse survival outcomes compared to those with pure urothelial carcinoma. Molecular differences, such as the upregulation of EMT pathways, contribute to its increased invasiveness and poor treatment response. Radical cystectomy is often required due to its aggressive nature.[88]

Association between P53 scoring system and tumor grade, tumor stage

The results show that higher P53 scores (+2 and +3) are more common in high-grade and T1 stage tumors, suggesting a possible association between P53 expression and tumor aggressiveness. However, the lack of statistical significance (P-values of 0.5 for grade and 0.7 for stage) indicates that P53 scoring may not be a reliable standalone marker for predicting tumor grade or stage in this study. These findings are consistent with recent studies, such as those by. Ali, B. Sadeq et al. (2012) and Leroy et al. (2014), which emphasize the heterogeneous nature of P53 mutations and their variable impact across different cancer types. Additionally, Donehower et al. (2019) found that while P53 alterations are prevalent in many cancers, their correlation with clinical outcomes is context-dependent.[89-91]

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CONCLUSION

- This study highlights the demographic and clinical characteristics of bladder cancer patients, predominantly older males, consistent with global trends.
- Papillary type urothelial carcinoma was the most common histopathological finding, with solid type Urothelial Carcinoma associated with high-grade tumors, lymphovascular invasion (LVI), muscularis propria invasion (MPI), and advanced tumor stages.
- The significant association between higher scores and malignant findings in current study supports the utility of P53 scoring systems in distinguishing between benign and malignant lesions.
- These associations emphasize the aggressive nature of invasive carcinoma and the importance of early detection and accurate staging. The findings align with regional and global studies, underscoring the need for targeted screening and tailored treatment strategies to improve patient outcomes, particularly in high-risk populations.
- There is a significant association between the P53 scoring system and histological type (P-value 0.0001). Negative P53 scoring (100%) correlated with cystitis, while (+3) scoring was linked to papillary type (60.5%) and solid type (100%) Urothelial Carcinoma types.
- Higher P53 scores (+2 and +3) are more common in high-grade and T1 stage tumors, but the associations are not statistically significant based on the provided P-values.

RECOMMENDATIONS

- **Larger population size.**
- **Targeted Screening:** Focus on early detection in high-risk groups, especially older males.
- **Early Diagnosis:** Arrange accurate staging and early diagnosis using advanced techniques.
- **Multidisciplinary Care:** Adopt a collaborative approach involving various specialists for comprehensive cancer management.
- **Patient Education:** Educate the public on risk factors like smoking and chemical exposure.
- **Research Support:** Promote research and establish a regional cancer registry to improve data collection.
- **Personalized Treatment:** Tailor treatment plans based on individual tumor characteristics for better outcomes.

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