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The Diagnosis and Management of Bladder Cancer: A Literature Review

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ABSTRACT

Cancer is still one of the health problems around the world. Cancer is an uncontrolled (abnormal) cell division and can invade surrounding tissues and can also spread to other parts of the body through the blood and lymphatic system known as metastasis. This disease is often diagnosed in men aged 50-80 years with an average age of 73 years. Bladder cancer is divided into transitional cell carcinoma (95%), squamous cell carcinoma (3%), adenocarcinoma (2%), and less than 1% small cell tumors (paraneoplastic syndrome). Risk factors for this disease are smoking, exposure to carcinogenic substances, drugs, infection with the parasite Schistosoma haematobium, chronic irritation (stone disease), physical trauma (in the uroepithelial layer), infectious diseases and those that have not been proven to be the cause are coffee, alcohol, saccharin and cyclamate sweeteners. The prognosis of the disease depends on histologic examination to see the stage of the disease and by tissue biopsy. **Methods:** This paper is based on a literature search of clinical practice guidelines, scientific literature, websites, and textbooks on the topic of bladder cancer. **Results and Discussion**: Hematuria is the main clinical symptom in addition to other symptoms as a complaint of bladder cancer. The disease is divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Non-invasive and invasive cancer conditions play an important role in the treatment and prognosis of the disease. MIBC is a disease condition with high morbidity and mortality. **Conclusion**: Cystoscopy followed by biopsy resection is the diagnostic standard followed by anatomic pathology examination (histology and cytology) for definitive diagnosis of the disease. The prognosis will be better if the disease is still at superficial and non-invasive stage (Ta), so that only transurethral tumor resection followed by chemotherapy drugs, intravesical and results will be more satisfactory.

Keywords: *Bladder Cancer, Hematuria, Cystoscopy, Biopsy*

1. INTRODUCTION

Cancer is still one of the problems in the world of health. Cancer is defined as continuous and uncontrolled (abnormal) cell division and invasion of surrounding tissues. Cancer cells can also spread to other parts of the body through the blood and lymphatic system. This process of spreading is called metastasis.[1,2] Cancer killed 7.6 million people in 2005 and is expected to increase to 11.5 million by 2030d and is the leading cause of death after cardiovascular disease worldwide. It is estimated that the prevalence of cancer will increase from year to year, due to increased life expectancy, worsening socioeconomic conditions, and changes in the pattern of infectious or infectious diseases towards degenerative diseases, neoplasms and injuries.[2]With risk factors such as unhealthy lifestyles of alcohol consumption, unhealthy diet, smoking, and physical inactivity.[1]

The results of the *years of life lost* (YLL) value for men and women when summed up are, the largest value is in lung cancer (19,823 *person years*), followed by colon cancer (19,007 person years), pancreatic cancer (14,155 *person years),* stomach cancer (3,372 person years), bladder cancer (3,251 person *years)* and laryngeal cancer (1,242 *person years).*[3,4]

In the anamnesis, patients complain of hematuria or painless bloody urine is the most frequent symptom, the presence of hematuria needs to be fully evaluated to recognize other symptoms of bladder cancer. Other symptoms are irritative *Lower Urinary Tract Symptoms* (LUTS) and do not disappear with symptomatic therapy and may be symptoms of carcinoma insitu. Other symptoms such as pelvic pain and lower abdominal lumps may be symptoms of advanced bladder cancer. The physical examination includes digital rectal examination, bimanual palpation of the kidneys and palpation of the bladder. The bimanual palpation examination of the bladder is performed when the patient is unconscious due to anesthesia before and after transurethral resection of the tumor.[5]

The TNM classification of bladder cancer according to the *American Joint Committee on Cancer* is TX (Undetermined primary tumor), Tis Intraepithelial (carcinoma insitu), TA Papillar, (only in the mucosa), T1 (subepithelial), T2a (superficial muscle layer), T2b (deep muscle layer), T3a (microscopic perivesical tissue), T3b (macroscopic perivesical tissue), T4a (invasion of surrounding organs such as prostate, uterus, or vagina), T4b (invasion of pelvic or abdominal wall), NX (lymph nodes cannot be determined), N0 (no spread to lymph nodes), N1 (single nodes 2cm-5cm), MX (no distant metastasis), M0 (no distant metastasis), M+ (distant metastasis). [6]

Based on anatomical pathology examination in terms of histologic differentiation, bladder carcinoma can be divided into three classes: class I well-differentiated tumors, class II moderately differentiated tumors, and class III poorly differentiated tumors. Well-differentiated tumors rarely progress to higher stages, while poorly differentiated tumors have a high risk of progressing to worse stages.[7]

Cancer is more common in whites than blacks, with a male to female ratio of 3:1. The location of cancer is only in the bladder as much as 85% and 15% have spread to regional lymphonoduses or can also go to more distant places. The cell types of bladder cancer are transitional cell carcinoma (95%), squamous cell carcinoma (3%), adenocarcinoma (2%), small cell tumors (with paraneoplastic syndrome) only amount to < 1%.[7] 75-80% of tumors cause superficial lesions, 20% have tumor invasion into the muscle, and 5% have metastasized. [8]

Non-invasive bladder tumors are the most common neoplasms at initial diagnosis, tumors can be divided into 2 categories, namely papillary forms and flat forms, and can be found separately or together. The papillary type has variations ranging from reactive proliferation, and papilloma to papillary urothelial neoplasm of low malignant potential, low and high grade papillary carcinoma. These tumors have a high risk of recurrence, and under 15% of patients progress to invasive disease. Low grade papillary urothelial carcinoma is a papillary urothelial neoplasm with low malignant potential (lower grade of malignancy than urothelial cancer), with an incidence rate of 5 per 100,000 individuals per year.[9]

According to the World Health Organization's 2020 epidemiological data on malignancies, the most common urological disease is urothelial bladder cancer (more than 90% of all cases).[10] While bladder cancer (BCa) is the second highest genitourinary cancer after prostate cancer in men. According to GLOBOCAN data (2018) bladder cancer is the tenth most frequent type of cancer worldwide, 3% of all global cancer diagnoses and very frequent in developed countries. In the United States, bladder cancer is the sixth most common incident neoplasm, 90% of diagnoses at age 55 years and older with a median age of 73 years and four times more common in men than women. The average 5-year survival in the US is 77%, and 5% progress to metastasis.[11] In Europe, the incidence of bladder cancer is 27 per 100,000 for men and 6 per 100,000 for women.[5]Every year in the UK 10,000 people develop bladder cancer and almost half of those who do die.[12]

Risk factors for bladder cancer include: estimated tobacco smoking (50-65%) of all cases, exposure to carcinogens (workplace or environmental). Squamous cell bladder cancer is often associated with chronic irritation by foreign bodies such as stones, catheter insertion, and Schistosoma haematobium invasion, while adenocarcinoma often occurs at the top and bottom of the bladder or due to metastasis from disorders in other organs.[7] While clinical factors associated with this disease are preoperative conditions, namely the stage and grading of the tumor there is lymphovascular invasion and carcinoma in situ. [13]

The disease is diagnosed through: anamnesis of clinical symptoms, physical examination and supporting examinations in the form of, laboratory examinations, radiology, ultrasonography, and computed tomography. tissue biopsy accompanied by anatomical pathology examination (histopathology and cytology).

In the supporting examination, the disease is confirmed by cystoscopy and tissue resection biopsy followed by anatomic pathology examination (histology and cytology examination).[14] In addition, there are also laboratory examinations, radiology, ultrasonography, and computed tomography. With tissue biopsy and histopathologic examination, the diagnosis of the disease can be confirmed.[7,5] Removal of the entire tumor is important to establish the diagnosis, as a therapeutic measure, and to determine the presence of tumor invasion through the muscle layer. Transitional cell carcinoma is present in the form of superficial lesions (75%), there is invasion into the muscle (20%), and tumor metastasis (5%).

The best management of bladder cancer depends on the stage of the disease based on anatomical or histopathological pathology examination.[7] Divided into 2, namely based on invasion into the bladder muscle, namely the management of Non Muscle Invasion Bladder Cancer (KKKNIO) or Non Muscle Invasive Bladder Cancer (NMIBC) and KKKIO / MIBC. Management for KKKNIO or NMIBC can be transurethral tumor resection accompanied by intravesical chemotherapy drugs. Treatment for Muscle Invasive Bladder Cancer (MIBC) may include radical cystectomy, external radiation and/or chemotherapy.[5]

Bladder cancer management is based on the TNM system. In superficial bladder cancer (TIS, Ta, T1), transurethral tumor resection is performed and followed by intravesical drug administration (intravesical chemotherapy or immunotherapy). Widely used intravesical drugs are mitomycin C (MMC), doxorubicin, and Bacillus Calmette-Guerin (BCG). Intravesical administration of BCG is immunotherapeutic by suppressing recurrence and progressivity of bladder carcinoma so it is indicated for patients who tend to experience recurrence after transurethral resection surgery.BCG reduces recurrence by 40% - 45%, compared to other intravesical drugs which are only 8-18%. In several studies the use of minimal doses of MMC as intravesical chemotherapy has shown very high effectiveness against bladder carcinoma. MMC is most effective given as soon as possible after surgery, where MMC will coat the bladder mucosal layer and work to stop the growth of stopping the growth and division of cancer cells. The goal of this therapy is to kill the cancer cells so that the bladder mucosa will be free of cancer cells, thereby reducing the recurrence rate by up to 40%.[7] For bladder cancer that is invasive to the muscle (T2, T3) is radical cystectomy which in some countries has been used as the main standard therapy. Radiotherapy at 5000-7000 cGy over a 5-8 week delivery period acts as an alternative treatment with a five-year survival rate of 30- 45%. Metastatic bladder carcinoma (T4) using chemotherapy drugs, usually a combination of M-VAC (Methotrexate, Vinblastin, Adriamycin, and Cisplatin), PT (Ciplastin and Paklitaxel), GTC (Gemsitabine, Paklitaxel, Ciplastin), or CISCA (Cisplatin, Cyclophosphamide, Adriamycin).[5,7]

The disease is treated with surgery, intravesical and chemotherapy, radiation therapy and immunotherapy**.** Radiation therapy for bladder cancer as a single management modality for invasive disease has an average cure rate of 16-30%, lower than cystectomy management, but radiation can be used in patients who are not treated with surgery. External radiation therapy in bladder cancer is performed with several techniques, namely with four fields *(box techniques*), two front and back fields, rotational techniques and three field techniques. In the Radiotherapy Installation at Dr. Moewardi Hospital, external radiation therapy in bladder cancer is performed with external radiation therapy techniques with two anterior and posterior fields, but in the case of metastases in the articulatio coxae the radiation field is made asymmetrical with one side made wider to reach the articulatio coxae and without the installation of a blockade in the articulatio coxae area, then not continued with a booster field in the bladder.[12]

Bladder cancer is a malignancy that is quite frequent in the world, tends to experience progressivity and recurrence and metastasis, and depends on histological examination and disease stage.[8,15]Cancer or carcinoma that has invaded perivesical tissue and metastasized to lymph tissue has a poor prognosis.[7,6] In addition, preoperative pathology, tumor stage and grading, the presence of lymphovascular invasion and carcinoma in situ and the administration of chemotherapy are thought to be associated with postoperative prognosis. [13]

Transurethral Bladder Tumor Resection Therapy (TUR-BT), performed in KKKNIO/NMIBC and KKKIO/MIBC although the same but have different objectives. In KKKNIO/NMIBC, the purpose of TUR-BT is to establish a diagnosis and curative management by removing all visible tumors. Whereas in KKKIO/MIBC, TUR-BT only aims to determine the histopathological diagnosis and staging which must involve the muscle layer at the time of tissue collection. A new technique in performing TUR-BT is using bipolar cautery. The advantage of this method compared to monopolar cautery is that it can reduce the occurrence of complications such as bladder perforation due to stimulation of the obturator nerve block. A

second resection is performed 2-6 weeks after the initial resection if the initial resection is incomplete, no muscle specimen is obtained, T1 tumors, and cancer with a high degree of differentiation. [16]

METHODS

This paper is a literature review that takes from several trusted sources of articles covering knowledge about knowing bladder cancer. The sources of writing in making this literature review include systematic search studies of computerized databases in the form of research journals, review articles and books. The author takes an important part of each article and combines each part of the theme according to the important focus in the article so that the author can make a writing about knowledge of one of the urological malignancies, namely bladder cancer.

RESULTS AND DISCUSSION

In this paper the author seeks and presents knowledge by recognizing one of the urological malignancies known as bladder cancer, through several studies or case reports. As in the case report by Samuel S. Senduk et al in a 66-year-old man. with a farmer's occupation.[7]

In another study conducted by Pandu Putra Anugrah, et al at West Nusa Tenggara General Hospital, the total incidence of bladder cancer cases in the 2017-2018 period was 90 cases. Consisting of 42 cases (2017) and 48 cases (2018). The incidence of this disease is higher in men than women. In 2017 cases in men (27 people) and women (15 people). In 2018 bladder cancer cases in men (38 cases and in women (10 cases). With the age of most cases averaging over 50 years old.[8]

Research conducted by M. Ariful Islam, et al for two years showed the results of a total sample of 73 cases of bladder cancer found as many as 22 cases (30.1%) at the age of 51-60 years, with an average age of 60.85 years. Male gender as many as 58 cases (79.5%) and women as many as 15 cases (20.5%) with a ratio of men and women 3.9: 1.[17] Research conducted by M. Ariful Islam, et al for two years showed the results of a total sample of 73 cases of bladder cancer, where as many as 49 samples (67.1%) were smokers.[17]

Research conducted by Eolia Effend from 2014-2018 with a total sample of 82 people with a diagnosis of bladder cancer, found a male sample (84.1%) with the most age group over the age of 60 years.[18]

In this study, patients who had received chemotherapy or radiotherapy, or had previous cystoscopic resection with intravesical therapy were excluded, resulting in a total of 120 patients. With the characteristics of age < 40 years as many as 12 patients (10.0%), age 40-60 years as many as 36 patients (30.0%) and age > 60 years (60%). The male gender group was 99 patients (82.5%) and female 21 patients (17.5%). The types of work were employees as many as 54 patients (45%), farmers 48 patients (40%), laborers 12 patients (10%), and housewives 6 patients (5%) and the area of residence in urban areas as many as 40 patients (33.8%) and in rural areas as many as 80 patients (66.3%).[19]

A study conducted by Qingwei Wang to look at prognostic risk factors and postoperative bladder cancer recurrence in patients with upper urinary tract urothelial cancer or carcinoma (UTUC). With a total sample of 439 UTUC patients, risk factors such as comorbidities (diabetes mellitus), metformin use, smoking, taking traditional Chinese medicine (containing aristolochic acid), previous history of disease (bladder cancer), age, tumor size, tumor stage, tumor grade, and lymph node metastasis, tumor characteristics (number, location, stage, grade), and open or laparoscopic surgery. The total number of patients was 236 men (53.7%) and 203 women (46.3%). The results of this study showed that the 5-year survival rate of UTUC patients from central China was not high compared to UTUC patients from other regions. Advanced tumor stage and presence of high-grade tumor and preoperative ureteroscopy in DM without metformin consumption give poor prognosis as well as recurrence and suggest preoperative ureteroscopy should not be performed except when preoperative imaging diagnosis is difficult. While postoperative bladder perfusion chemotherapy is a must in bladder cancer.[20]

A case report by Pablo A. Rojas reported on a 31-year-old woman who presented with squamous cell cancer, diagnosed during the second trimester of pregnancy. Bladder cancer in pregnant women is very rare and should be considered in women with recurrent hematuria and/or recurrent urinary tract infections. Case management is done by a multidisciplinary team. Cystectomy can be performed at least 4 weeks after cesarean section and not at the same time as cesarean section.[21]

The study by Rahul Guptadkk was to evaluate the clinico-pathological profile of bladder cancer in female patients in North India from January 2012 - January 2021.There were 56 female patients, found masses

in the bladder, of which 55 patients with a diagnosis of transitional cell carcinoma (TCC), while one patient with a diagnosis of having pheochromocytoma (tumor in the small adrenal gland above the kidney / in the adrenal gland). Patients with painless hematuria (80.3%) were the most common complaint. 5 patients (9.1%) were diagnosed with muscle-invasive bladder cancer (T2-T4), and 50 patients with non-muscle-invasive disease. A total of 31 patients (56.4%) with high-grade stage and 19 patients (34.5%) with low-grade papillary cancer (in the lamina propria). 23 patients (41.8%) had a history of exposure to domestic chulha (open firewood cooking stove), and 11 patients (20%) were smokers, 6 patients (10.9%) were exposed to both chulha and smoking. Patient characteristics of the total 55 patients, with a mean age of 56.9 years (age 25-82) viz: 60-79 years (43%), 40-59 years (31%), 20-39 years (15%) and >80 years (11%).It can be seen that most patients (76.3%) were in the post-menopausal age group.(20%) had a history of smoking/tobacco, while 23 patients (41.8%) had exposure to chulha while cooking.6 patients (10.9%) had a history of smoking as well as exposure to chulha, 27.3% had no exposure to predisposing factors. Out of 55 patients, diabetes mellitus (DM) 12 patients (21.8%), with hypertension 8 patients (14.5%). Painless hematuria was present in 45 patients (81.8%). All patients in this group had transitional cell carcinoma. 5 patients (9.1%) had high-grade muscle-invasive bladder cancer. 50 patients had non-muscle-invasive disease, (31 patients/56.4% of patients had high grade and 19 patients/34.5% of patients with low grade papillary cancer invading the lamina propria).[22]

In the research and case reports above, it is known that some cancers including bladder cancer can be induced by carcinogens that are commonly found around us, thought to be related to several factors that cause bladder cancer, such as 1. Smoking habits (2 to 6 times greater than those who are not (cigarettes contain carcinogens, namely aromatic amines, nitrosamines) or about 50-65% of cases.2. Frequent exposure to chemical plant workers (paints, matches, textile fabrics, cowhides,) and hair salon workers, stylists (due to exposure to aromatic amine carcinogens, such as 2- naphthylamine, bensidine, and 4- aminobifamil). , drugs (intravesical cyclophosphamide, phenacetin, opium, antituberculous INH).[6] 3. Urinary Tract Infection (UTI): in UTI E. coli germs and Proteus spp there are nitrosamines containing carcinogens and chronic irritation due to stone disease.4. Some substances that are thought to be associated with this disease, but have not yet been proven, such as: coffee, alcohol, cyclamate and saccharin sweeteners. [8,17]4.Schistosomiasis infection is one of the most frequent causes of bladder cancer in endemic regions of Africa and the Middle East and is considered the second most dangerous tropical pathogen after malaria. As many as 81% of cases are caused by known risk factors and only 7% by genetics. Preventing risk factors is critical to the onset of the disease, including smoking cessation, the importance of workplace safety, weight loss, exercise, and prevention of schistosomiasis (through water disinfection and mass drug administration).[11] Squamous cell cancers are often associated with chronic irritation by foreign bodies such as stones, catheter insertion, and schistosoma haematobium invasion, while adenocarcinomas often occur at the apex of the dome of the bladder. [7]

In the above studies and case reports, it can be seen that the incidence of bladder cancer is more common in men. Bladder cancer ranks 4th in malignancies in men, and 12th in women. The incidence of this disease is higher in whites than blacks and more often in men (2.5 times more often).than women, and most commonly found at the age of 60-70 years.[7,8]Research by Supit et al (2011) at Cipto Mangunkusumo Hospital with a male presentation of 86.2%, and women 11.8%. Nitrosamine compounds in cigarettes can bind to tryptophan to form mutagenic nitrosamines and if these compounds bind to DNA the process of protein synthesis and enzyme work in the cell cycle is disrupted, especially in proteins or enzymes that play a role in growth signaling factors such as CDK, EGFR, FGF, and MDM25 .[8]In addition there is the factor of nitrite substances in cigarettes, the role of androgen receptors (AR) is also a risk factor for men to suffer more bladder cancer than women, because AR is a receptor that plays a role in the regulation of growth and development of target cells. If AR and the androgen hormone bind, it will form an AR complex which will then bind to the target cell DNA to perform its function as a regulator in DNA formation. Mutations in AR will cause DNA damage so that the process of proliferation and apoptosis is disrupted. Until now there has been no research that can explain the cause of AR mutations in bladder cancer cases.[8]

Other conditions that cause bladder cancer can occur as reported by Rahul Gupta et al that women with bladder cancer are more likely than men. Some literature writes about this disease in women is quite rare. The ratio of male to female bladder cancer patients in our neighborhood (10:1) is much greater than that reported in the literature (3:1) This difference can be attributed to social, economic, and educational factors. Another possible reason is the reduced exposure to carcinogens or industrial chemicals (where men usually work). It is also because the majority of women in our region are housewives who are often exposed to fumes from the stoves where they cook. Rahul Gupta et al. In addition, smoking exposure is the strongest risk factor for the disease in both men and women (up to six-fold higher). This may be due to the secretion of alpha and

beta naphthylamine in the urine of smokers, which has been recognized to be a trigger for this disease. Fear and feeling that this disease is just a symptom of urinary tract infection, especially in post-menopausal women, so they self-medicate by taking antibiotic drugs. In the end they come for treatment with complaints of more severe disease.[22] According to the age group, bladder cancer often occurs at the age of over 50 years, where there is a theory of aging and genetic mutation explaining that there is an accumulation of genetic material that has decreased function with age, especially the inactivation of p5319. In addition, with age there will be DNA mutations that continue to accumulate, telomeres will shorten progressively, mitochondrial damage, and some other DNA damage, so that it can interfere with the control of the cell proliferation process and control of cell damage. This damage is also supported by external factors, namely exposure to carcinogens in our environment including exposure from smoking.[8]

Research conducted by M. Ariful Islam, et al for two years showed the results of a total sample of 73 cases of bladder cancer with the main symptom being hematuria (91.8%).[17] Research conducted by Hisham H. Ragab, et al in Egypt in the period February 2020-March 2021, to see the characteristics of bladder cancer patients, with a total sample of 120 patients, 72% of cases with gross hematuria with clots.[19]

In cases of bladder cancer**, the** most common complaint is hematuria, painless, (a classic sign), recurrent, occurring at the beginning to end of micturition but in cases of extensive infiltration often symptomatic of irritation. 85% of bladder cancer patients with total hematuria can also be microscopic, painless and recurrent, there are symptoms of urgency, polyuria and dysuria (25%), usually patients with carcinoma insitu and buli-buli overactivity, indicating that there has been tumor invasion of the bladder detrusor muscle.... In about 5% of cases there is weight loss, fever, bone pain, and signs and complaints associated with metastasis to the liver and lungs.In geriatric patients recurrent urgency and no obvious cause should be suspected as bladder cancer. [6,7]

The diagnosis of bladder cancer is established through several examinations such as physical examination with bimanual palpation, laboratory, imaging, biopsy and cystoscopy. In the case report by Samuel S. Senduk et al, several examinations were carried out to establish the patient's diagnosis with clinical examination, laboratory, ultrasonography, and cystoscopy which showed a tumor in the bladder.[7]

Research conducted by M. Ariful Islam, et al for two years showed the results of a total sample of 73 cases of bladder cancer with the most frequent location being the lateral wall of the bladder and 75% reported as high-grade urothelial cancer.[17]

Research by Eolia Effendi from 2014-2018 with a total sample of 82 people with bladder cancer had an invasive tumor invasion rate (93.9%), had a history of buli-buli stones (30.5%), and the most histopathological picture results were transitional cell carcinoma (91.5%) and squamous cell carcinoma (8.5%). [18]

In a study conducted by Abubakar Sadiq Muhammad et al, for 12 months with a total of 88 patients, consisting of 52 cases with a diagnosis of squamous cell carcinoma type bladder cancer in schistosomiasis endemic areas and 32 cases with complaints of hematuria due to other diseases and other benign urology. An examination was conducted to see and compare the sensitivity, specificity, and predictive value of the bladder tumor antigen quantitative test (BTA TRAK) and urine cytology. The results obtained BTA TRAK is more sensitive but less specific than urine cytology for the detection of bladder cell carcinoma in schistosoma endemic areas.[23]

Case report by Adi Nur Afif, et al on a man aged 68 years, with complaints of hamaturi accompanied by severe pain. Rectal examination (pinched ani sphincter), no blood or stool was found. Ultrasound examination was found to have an enlarged prostate, mass or tumor in the bladder.[6]

Research conducted by Harfira Mudahar, with a total sample of 36 cases, with an age of 60-69 years, with the most gender in men, examining urothelial infiltrate bladder cancer with EGFR (Epidermal Growth Factor Receptor) expression with immunohistochemical staining of cell membranes and cytoplasm is one that can be useful in determining prognosis and treatment. Here, EGFR was assessed and correlated with histopathologic grade, resulting in a non-meaningful relationship between EGFR expression and histopathologic grade.[15]

Research conducted by Hery Tiera, et al, using Urinary Bladder Cancer Antigen (UBC) examination or rapid UBC is one of the latest non-invasive examinations in detecting buli carcinoma by identifying the expression of cytokeratins 8 and 18 in the urine.Conducted in cases of transitional cell carcinoma (KST) buli patients with a history of total bladder tumor resection who underwent routine cystoscopy follow-up, after which it will be compared with cystoscopy and histopathology examinations. The results showed that Rapid

UBC can be a promising and useful additional supporting examination for rapid evaluation in cases with suspected buli tumors. The role of cystoscopy as the gold standard examination of buli tumor examination has not been replaced.[24]

Research conducted by Hidayu et al, with a total of 130 patients with a diagnosis of bladder cancer with blood test examinations that determine leukocytes, hemoglobin, platelets, and Neutrophil-Lymphocyte Ratio (NLR), with the results of the prognosis getting worse when the disease progresses to an advanced stage. Leukocytosis, thrombocytosis and high NLR results.[25]

Research conducted by Hisham H. Ragab, et al in Egypt in the period February 2020-March 2021, to see the characteristics of bladder cancer patients, with a total sample of 120 patients, by conducting urine cytology sensitivity was 32.5% and increased especially with high degree / stage tumors and histological examination which showed the results of about 78 cases were UCC (urothelial cel carcinoma), 36 were SCC (scamous cel carcinoma) and 6 were ADC (adenocarcinoma).[19]

Huiming Gui conducted a retrospective study of 175 patients with newly diagnosed and hospitalized bladder cancer in China from March 2005 to March 2016. A total of 136 had undergone radical cystectomy (RC). These studies the role of inflammatory biomarkers in BC prognosis remains inconclusive. This study aimed to compare preoperative plasma fibrinogen (PF) and other inflammatory biomarkers such as platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), C-reactive protein (CRP) level, and serum albumin level to predict the prognosis of patients with BC (Bladder Carcinoma). The results showed Preoperative PF level can be a prognostic biomarker and when combined with NLR, it can improve the survival prediction ability of BC patients, especially BC patients undergoing RC**, the** combination of PF and NLR can improve prognostic accuracy and be used as selection criteria for risk factor stratified treatment in patients with BC.[26]

Research by Kadek Agus et al, at the Anatomical Pathology Laboratory of Sanglah General Hospital Denpasar from 2015-2020. The expression of c-MET was examined by immunohistochemical painting of c-MET (receptor tyrosine kinase that binds specifically to its ligand, hepatocyte growth factor / HGF) with a total sample of 42 people. The aim is to determine the relationship between c-MET expression with the degree of histological differentiation and the level of depth of invasion in infiltrating urothelial bladder cancer. The result is that there is a relationship between c-MET expression with the degree of histological differentiation and the level of depth of invasion in infiltrating urothelial bladder carcinoma at Sanglah Hospital, Denpasar. High c-MET expression has a 2 times greater likelihood or risk of becoming a tumor with an advanced level of invasion depth compared to low c-MET expression.[3]

Research by Mahmoudreza Morad, on Primary clear cell carcinoma of urinary bladder (PCCUB) or primary clear cell cancer of the bladder or frequent Mullerian cell type cancer in women. These tumors are solid or sessile papillary (stemless), with symptoms of hematuria and vaginal discharge and pelvic pain. Immunohistochemical (IHC) test has high sensitivity and specificity for the diagnosis of this tumor. Pan cytokeratin, CK7 and CA125 were positive for this tumor. This disease is encountered in the age of 19-80 years and PCCUB is rare and surgery for management.[27]

Case report by Marius Stanimir on a patient aged 3.9-9.8 months. The histologic result was fibrosis and ypT0pN0 classification. There was pain and a solid mass in the penis, so total penectomy (removal of the penis) was performed. Histologic examination showed transitional cancer metastasized to the urothelial bladder. After total panectomy, a positron emission tomography/computed tomography (PET/CT) scan showed that it had metastasized to the lymph nodes.Papillary transitional cancer of the bladder in the specimen is very important and has a serious impact on the management of the disease. In this case it metastasized to the penis (a rare condition). Appropriate management of the patient may include local excision of the tumor, partial or complete penectomy, external beam radiation therapy, brachytherapy, chemotherapy, immunotherapy (Methotrexate, Vinblastine, Doxorubicin (Adriamycin) and Cisplatin /MVAC) followed by cystoprostatectomy or a combination.[28]

Case report by Vika Indriani, et al with a case of infiltrative urothelial carcinoma of squamous differentiation and sarcomatoid variant in buli, in a 44-year-old male patient, with complaints of pain when urinating and redness. Ultrasound and CT scans were performed, and a solid mass was found in the buli. A biopsy was also performed, there was tissue necrosis and then a frozen section showed a picture of spindle-shaped anaplastic cells, heavy nuclear pleomorphia and mitoses that were very easy to find, forming solid, infiltrative islands between the stroma and muscle. The diagnosis was confirmed by paraffin block examination, showing spindle-shaped, round and polygonal anaplastic urothelial cells, with severe nuclear

pleomorphia, hyperchromatic solid and infiltrative papillae between the muscle layers. Clinical, laboratory, radiologic, histopathologic and immunohistochemical examination revealed an infiltrative urothelial carcinoma with squamous differentiation and sarcomatoid variant in the buli with poor prognosis due to the presence of sarcomatoid differentiated component, high grade.[29]

A case report by Youssef Kadouri et al, of six cases of bladder sarcomatoid carcinoma malignancy, collected over 8 years. Five patients were aged 44-70 years, with an average age of 58 years. The main symptom was total hematuria with blood clots, found in all patients (100%), associated with lower urinary tract irritation syndrome (pollakiuria and urine burns) in 4 patients and worsening general condition with anorexia and weight loss in 2 patients. Bone pain in 3 patients and anemia in all patients (100%), all our patients were examined with renovesical ultrasound to see the morphology of the bladder and suspected the diagnosis of bladder tumor by looking at the parietal tissue mass.Management with transurethral resection of the bladder (TURB) was performed in all patients, (complete in 2 patients and incomplete in 3 because the tumor was not endoscopically controlled.) Thoraco-abdomino-pelvic CT scans were performed, and in all patients, a diagnosis of T2N0M0, T3N0M0, a process occupying almost the entire bladder locally associated with bilateral uretero-hydronephrosis and T3N2M0 with lung and lymph node metastasis was found.Total cystectomy associated with bilateral ilio-obturator lymph node dissection (as per tumor classification) was performed in the patient, followed by urinary diversion with enterocystoplasty in the patient (T2N0M0), bricker in the patient (T3N0M0) and cutaneous ureterostomy in the patient who underwent surgery due to deterioration of her general condition.Palliative chemotherapy is recommended in surviving patients.[30]

Research by Aini Nur Syafa'ah, aims to determine the incidence of urothelial carcinoma in the Anatomical Pathology Section of Dr. Mohammad Hoesin Palembang Hospital for the period 2009-2013. There were 66 cases of urothelial carcinoma out of 29,175 cases examined histopathologically. The incidence rate of urothelial carcinoma in the Anatomical Pathology Section of dr. Mohammad Hoesin Hospital Palembang was 0.23%. Men outnumbered women by 80.3% with a male:female ratio of 4:1. Urothelial carcinoma was most commonly diagnosed at the age of 61-70 years. The most common microscopic diagnosis was invasive high grade urothelial carcinoma at 66.7%. The incidence of urothelial carcinoma in the Anatomical Pathology Section of Dr. Mohammad Hoesin Palembang Hospital in 2009-2013 was 0.23% and the most common microscopic diagnosis was invasive high grade urothelial carcinoma.[31]

Research conducted by Imelda Setiana Silitonga to analyze differences in p53 expression in low-grade and high-grade bladder urothelial carcinoma and the relationship of p53 expression with tumor stage. The sample was 47 cases, divided into 22 low-grade cases and 25 high-grade cases at the Department of Anatomic Pathology, Faculty of Medicine, University of Indonesia / Cipto Mangunkusumo Hospital (FKUI / RSCM) in 2009-2017 and p53 immunohistochemistry was performed with a positive cut off of ≥20%. Results Positive p53 expression in 33 samples, 20 cases of high grade urothelial carcinoma, and 13 cases of low grade urothelial carcinoma; 22 cases of Nonmuscle invasive bladder cancer and 11 cases of Muscle invasive bladder cancer. The expression of p53 in low-grade and high-grade urothelial bladder carcinoma and its relationship with tumor stage showed no significant difference.[32]

Case report by Putriyuni, A et al, on a 70-year-old patient with complaints of hematuria and dysuria. no symptoms from the gastrointestinal tract and a history of stones in the urinary tract. A tumor mass in the bladder was found on ultrasonographic examination, and bladder wall thickening in the right latero-superior area. The tumor cells showed negative expression of CK7, positive for CK20, CDX-2 and β-catenin from immunohistochemical smears. The final diagnosis was primary adenocarcinoma of the bladder, enteric type. It is challenging to diagnose enteric-type primary adenocarcinoma of the bladder due to the high mortality rate in this type. [33]Primary enteric-type adenocarcinoma of the bladder is histologically similar to colorectal adenocarcinoma. The tumor cells show classic enteric (intestinal) morphology, but the possibility of urachus or colorectal origin can be clinically ruled out in this case. IHK panel markers consisting of CK7, CK20, CDX-2, and β-catenin have an important role in differentiating primary adenocarcinoma of the bladder from metastatic colorectal adenocarcinoma. [33]

Research by Fitra Hardian P et al, at Dr. Sardjito Hospital Yogyakarta, from January 2015 - December 2020. Data on demographic characteristics, clinical presentation and staging, grading and staging based on pathological examination results, and management of cancer. This study found 282 patients with buli tumors, there were 50 patients who did not meet the inclusion criteria, so the remaining 232 patients consisted of 169 male patients (72.8%) and 62 female patients (27.2%). The tumor stage when the patient first arrived was 46 patients diagnosed T1 (22.7%), 81 patients diagnosed T2 (40%), 11 patients diagnosed T3 (5.4%) and 64 patients diagnosed T4 (31.6%). Patients with secondary bulbous tumors (metastasis or infiltration from other organs) were found in 30 patients. Pathologic anatomy resulted as transitional cell carcinoma in 177 patients

(76.2%) and adenocarcinoma in 33 patients (14.2%). All patients underwent TURBT for diagnosis and staging, followed by definitive treatment, which consisted of TURBT and administration of bladder chemotherapy in 46 patients (19.8%), radical cystectomy in 84 patients (36.2%), partial cystectomy in 4 patients (1.7%), multimodal therapy (EBRT and/or chemotherapy) in 26 patients (11.2%). There were 72 patients (31%) undergoing TURBT alone. From a 5-year study, it was found that most of the buli tumor patients who came to Dr. Sardjito were male with anatomical pathology results of urothelial carcinoma. Some patients with advanced stage refused appropriate definitive therapy especially for radical cystectomy.[34]

In some of the above studies and case reports, supporting examinations were carried out for cancer conditions before treatment. Anatomical pathology (histology and cytology), cystoscopy, intravenous pyelography, pelvic/abdominal computed tomography, magnetic resonance imaging (85-94% accuracy), ultrasonography, bone scans, thoracic photographs, and laboratory tests (whole blood, ureum, creatinine, calcium, and alkaline phosphatase) are necessary to determine the stage of the tumor.[7] Anatomical pathology examination is performed to determine the exact diagnosis, type, degree of differentiation and degree of invasion (whether or not the bladder muscle layer has been involved), the presence of carsinoma in situ (CIS) and lymphovascular invasion. A tumor base biopsy specimen is required to determine the presence of tumor invasion of the muscle layer.[16] The subtype/variant histology (VH) examination may be considered to be performed due to the increased risk of mortality and disease recurrence in patients with urothelial bladder cancer (UCB). This examination independently predicts micropapillary, plasmacytoid and small cell VH subtypes, so this examination can be a pointer for prognosis, and management plan in patients with UCB cases, which are currently still performed with radical cystectomy.[35]

Laboratory examinations are complete blood tests, liver function, kidney function, and complete urinalysis.Urine cytology and cystoscopy, need to be done if hematuria is due to bladder cancer, urine cytology (+ / positive) indicates the presence of transitional cell carcinoma, but in the absence of supporting clinical symptoms, the results of urine cytology are not meaningful, because false positive results are often found.In transitional cell cancer of the bladder based on urine cytology should be confirmed by cystoscopy and transurethral biopsy. In bladder cancer, normochromic normocytic anemia, macroscopic hematuria and urine cytology consisting of erythrocyte cells and some epithelial cells are found, and no malignant cells are seen. [7]

Cystoscopic examination performed in conjunction with resection biopsy can be performed with suspicion of bladder cancer and the location, size, number, and shape of bladder cancer can be determined. Random biopsy is performed in patients with positive urine cytology/molecular markers but no visible tumor mass. A pars prostatic urethral biopsy is done if the tumor mass is in the neck region of the bladder. [16]

Other recommended examinations are thoracic photographs, intravenous pyelography, and abdominal computed tomography.Thoracic photographs can detect tumor metastasis to the lungs. Intravenous pyelography is to look for obstruction in the ureters, local dilation, and tumors in the pelvio-cephalic system or ureters. If radiolucent filling defects are seen in the bladder.[7]

Ultrasound is recommended for detecting tumors larger than 1.5 cm (58-94% of cases), but cannot be used to determine the degree of tumor. Transurethral ultrasonography can improve the accuracy of diagnosis, can see bladder polyps, see intravesical masses, see blood clots, obstruction in the upper urinary tract and monitoring of patients after therapy.For transitional cell carcinoma, examination with cystoscopy and tumor tissue biopsy are performed.[7]

Intravenous urography (IVU), computed tomography (CT), magnetic resonance imaging (MRI) and thoracic photography IVU is used to detect bladder masses (in the form of space occupying lesions (SOL)), determine renal function and view urinary tract obstructions.[16] Abdominal computed tomography is used to detect enlarged lymph nodes in the pelvis and abdomen, but is only sensitive if there is local invasion of the tumor and has limited ability (40-85%) to differentiate deep tumor invasion (T2) from peri-vesical invasion (T3). Intravenous pyelography and abdominal computed tomography should be suspected for bladder cancer.[7]Abdominal computed tomography and bone scans are performed on patients who complain of bone pain, elevated serum alkaline phosphatase, or elevated serum transaminases. [7] Molecular classification provides a new view of therapy in patients with bladder cancer. Supporting data such as degree, stage, and molecular information can be used to help determine molecular classification. The potential of molecular classification is expected to help determine appropriate therapy, which is expected to reduce the recurrence rate and progressivity of bladder cancer. Further research still needs to be done so that the determination of

therapy and prognosis can be more accurate so that the quality of life of patients with urinary cancer can be improved.[36]

Suspect a case of bladder cancer if: 1. Micturition is characterized by painless hematuria, so it should be fully evaluated including cystoscopy. 2. Tumor specimens and tumor base specimens should be examined and sent in separate containers. 3. Cystoscopic examination should describe the location, size, number and shape of the tumor mass. 4. The report from the anatomic pathology department should include the type, degree of differentiation and tumor base whether or not it has reached the bladder muscle layer, the presence of CIS and lymphovascular invasion.[16] The management of bladder cancer can be done in several ways according to the examination of the degree of disease.Some studies or case reports found, among others,

In this paper there are several case reports and studies that show various ways of managing a bladder cancer.In the case report of a 66-year-old male, the histopathological results of the tissue biopsy showed a picture of a grade II papillary transitional cell carcinoma. Based on the TNM Staging System, this patient was treated as a superficial non-invasive bladder carcinoma (Ta), so only transurethral tumor resection was performed which was then followed by intravesical chemotherapy drugs.[7]

In a study conducted by Pandu Putra Anugrah, et al, the results of the total incidence of bladder cancer cases in the 2017-2018 period were 90 cases. TURB is the most common choice of action. A total of 35 cases in 2017 were performed TURB and 7 cases were chemotherapy. In 2018, 39 cases of TURB were performed and 9 cases of chemotherapy were performed.[8]

Case report by Adi Nur Afif, et al on a man aged 68 years, with complaints of hematuria accompanied by severe pain. On rectal examination (pinched ani sphincter), no blood or feces were found. Ultrasound examination was performed and found an enlarged prostate, mass or tumor in the bladder. TURBT (Trans Urethral Resection of Bladder Tumor) was performed on the patient.[6] Case report by Alexander de J. Rafaelano M on a 39-year-old female. With family history: Grandfather with history of gastric cancer, father with systemic arterial hypertension. With complaints of urinary frequency 20 times a day with nocturia 2 times. Performed urethrographic examination with contrast found a solid mass with irregular edges extending above the right posterolateral wall of the bladder.Management with transurethral resection of bladder cancer.[37] Research conducted by Hisham H. Ragab, et al in Egypt in the period February 2020-March 2021, to see the characteristics of patients with bladder cancer, with a total sample of 120 patients. Management with TURBT or complete transurethral bladder tumor resection in 50 cases for masses with a size lower than 3 cm.[19]

A case report by Özgecan Gündoğar, on a 75-year-old male, who was diagnosed with sarcomatoid variant of urothelial carcinoma of the bladder is a rare malignant neoplasm, defined by a biphasic neoplasm with epithelial and mesenchymal components (rare cases only 0,3% of bladder cancer cases), through histopathological and immunohistochemical examination, magnetic resonance imaging (7.5x6.1x1.8 cm ulcer-vegetating tumor mass infiltrating the bladder base,) and diagnosis with sarcomatoid urothelial carcinoma similar to conventional urothelial carcinoma. This disease has a worse prognosis. The most important factor determining survival is the pathologic grade. Multidisciplinary management of this case consisting of surgery, chemotherapy, and radiotherapy should be customized by evaluating the stage of the disease and the general condition of the patient.[38]

Case report by Pablo A. Rojas on a 31-year-old woman with squamous cell carcinoma of the bladder in the second trimester of pregnancy. After cesarean section at 30 weeks, radical cystectomy with bilateral extended lymphadenectomy, hysterectomy and right oophorectomy were performed. Studer's neobladder technique was performed for urinary tract reconstruction. Definitive pathology examination showed invasive bladder squamous cell carcinoma, Grade 2, with microscopic perivesical fat infiltration, negative margins, and 3/28 lymph nodes with carcinoma (pT3aN2M0). The patient underwent 18 months of surveillance after radical cystectomy, with no recurrence by PET-CT.[21]

In the case reports and studies above, it is known that each case is treated according to the degree of disease. Bladder cancer or buli carcinoma is a malignancy that can occur in anyone in women less frequently than in men. In non-aggressive and usually non-invasive tumors can recur and patients must carry out control or continuous observation in the long term, while aggressive and invasive tumors have a high mortality rate that requires multimodal and invasive treatment. The disease causes approximately 500,000 new deaths each year and ranges from superficial, well-differentiated tumors that have a good survival rate, to poorly differentiated tumors that have a poor prognosis.[13]

Bladder cancer management is divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). The disease condition plays an important role in the treatment and

prognosis of the disease. MIBC is a disease with high morbidity and mortality. Bladder cancer with a diagnosis of MIBC type is 30%. The management of this type is neoadjuvant chemotherapy followed by radical cystectomy (RC) and bilateral pelvic lymphadenectomy with a 5-year survival rate (60%). Patients with MIBC currently no longer choose active surgical treatment because patients will need a postoperative urine bag for life, reduced quality of life, high perioperative mortality (1.5-4.2%), and high complication rates (58-67%). So in the last decade, in the treatment of malignancies without extensive surgery. Management without removal of the bladder organ using trimodality treatment (TMT), namely radiotherapy followed by transurethral resection of the bladder tumor (TURBT), chemotherapy followed by TURBT, chemoradiotherapy (CRT), and single modality therapy. TMT which is concurrent TURBT and CRT and is the most studied treatment. The Massachusetts General Hospital (MGH) used the efficacy and safety of TMT for patients with MIBC. Management with RC in single T2 lesions of small volume, no hydronephrosis, and no carcinoma in situ, with complete TURBT, showed no statistically significant difference in prognosis between patients treated with TMT versus RC.[10]These results from several studies have suggested that patients receiving TMT have a higher quality of life and less toxicity than those receiving RC alone. Therefore, TMT is a good alternative strategy to RC in patients with MIBC. In addition, patients who cannot tolerate chemotherapy may choose TURBT combined with radiotherapy. TURBT and RT are alternatives to primary RC for bladder cancer, but have poor remission and survival rates compared with TURBT and CRT. Neoadjuvant chemotherapy therapy has a complete response (CR) rate. Recently, immune checkpoint inhibitors (ICIs) are used as tumor treatment via programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 inhibitor (CTLA-4) in urothelial bladder cancer. Several PD-1/PD-L1 inhibitors are approved as first-line and second-line treatments for advanced bladder cancer.[10] Multimodal therapy has become an alternative for MIBC patients who are unable or unwilling to undergo radical cystectomy. Administration using immune checkpoint inhibitors (ICIs) for MIBC has been investigated. There are three common modes of ICI-based bladder therapy. ICI combined with chemoradiotherapy (most studied), ICI combined with radICI combined with chemotherapy has also been explored in neoadjuvant therapy patients with good clinical outcomes. However, the value of programmed death-ligand 1 (PD-L1) expression, the ability of tumor mutations and gene changes to predict immune-based bladder preservation is still controversial. Further research is needed.[10] Non-muscle-invasive stage bladder cancer, should be resected via transurethral endoscopy whenever possible. The muscle-invasive stage should be given multimodal treatment, including radical cystectomy with urinary diversion and perioperative systemic therapy, or, if metastatic, chemoradiotherapy. Immunotherapy with checkpoint inhibitors (ICIs) has been used for first- and second-line therapy alongside classical cytostatic treatment and has been shown to significantly prolong patient survival. Administration of checkpoint inhibitors (ICIs) can extend the overall survival of patients with metastases to 15-17 months.[39]

Treatment alternatives after TURBT are at stage : 1.Superficial (stage 0 - A): TUR Buli/fulguration, Intravesical instillation, 2. Invasive (stage B-C-D1): TUR Buli Cystectomy or radiation,3. Metastatic (stage D2): Palliative radiation chemotherapy.[5]

Radical cystectomy is the removal of the bladder and surrounding tissue (in men in the form of cystoprostatectomy) and then the urine flow from the ureters is channeled through several ways of diverting urine, including: 1. Ureterosigmoidostomy: which is to anastomose the two ureters into the sigmoid (this method is not widely used anymore because it causes many complications) 2. Intestinal conduit: which is to replace the bladder with the ileum (urine reservoir), while to remove urine a catheter is installed through a stoma. This conduit was introduced by Bricker in 1950 (not widely practiced anymore because it is not practical). 3. Continent urine diversion: replacing the bladder with the ileal segment by creating a continent stoma (can hold urine at a certain volume). Urine is then released through the stoma by performing periodic self-catheterization. Kock pouch and Indiana pouc are well-known methods of urine diversion.[5]

Bladder cancer patients should receive regular check-ups, as well as clinical examination, urine cytology and cystoscopy. Examination schedule: (1) year I is done every 3 months, (2) year II every 4 months, and (3) year III onwards: every 6 months.[5] The disease can spread lymphogenously (perivesical, obturator, external iliac, and common iliac lymph nodes) and hematogenously (to the bones, liver, and lungs). Anemia may occur with metastasis to the bone marrow or chronic blood loss. Edema in both limbs is due to obstruction of venous vessels or lymph channels. Blood clots can cause urethral obstruction with resulting enlargement and pain in the bladder and waist; hydroureter, hydronephrosis, and pyelonephritis can occur. The physical

examination of this case revealed anemic conjunctiva, lower abdominal tenderness, positive ballottement of both kidneys, and no palpable hepatic and regional lymph node enlargement.[7]A case report of urothelial bladder cancer metastasizing to the retro bulbar region infiltrating the lacrimal gland.[40]

In predicting the short-term and long-term risk of bladder cancer recurrence rate and disease progression in patients, the *European Organization for Research and Treatment of Cancer* (EORTC) and the Genito-Urinary Cancer Group (GUCG) have created a grading and risk system table, based on 1. The number of tumors 2. The diameter of the tumor size 3. The tumor category (T) 4. The tumor grade 5. The previous recurrence rate 6.[7]

In recent years it is known that cancer inflammatory cells infiltrate into the tumor environment and hematological markers have been used as determinants of prognosis of malignancies, including urothelial bladder cancer. Examination of biomarkers associated with malignancy is seen in pathologic features and molecular markers (because they are expensive, they are not routinely performed daily). One example of a molecular marker is LMR (Lymphocyte Monocyte Ratio). This examination is one of the cheap and practical inflammatory biomarkers and has been introduced to determine prognosis in urology, if low LMR results are closely related to a worse prognosis, including in various malignancies and this examination is reliable. The examination is based on tumor monocyte infiltration has an important role in neoangiogenesis, invasion, and tumor migration.[13]

Five-year survival rates in invasive cancers (45%-55%.), in solitary grade I recurrence rates (30-35%), and for multiple tumors (65%-75%). In cystectomized bladder cancer with well-differentiated tumors, the five-year survival rate is (70%- 80%,) while those with poorly differentiated tumors are (35%-40%).[7,6]

CONCLUSIONS

Bladder cancer is one of the urological malignancies with a high incidence and mortality rate. The cause of the disease is associated with several risk factors such as smoking, work in contact with carcinogenic chemicals, drugs (cyclophosphamide), parasitic infection with Schistosoma haematobium, chronic irritation (due to stone disease), due to infectious diseases and unproven things are coffee, alcohol, cyclamate sweeteners and saccharin. Histopathologically, the disease was divided into transitional cell carcinoma (95%), squamous cell carcinoma (3%), and adenocarcinoma (2%). Clinical symptoms include hematuria (80-90%) and urgency, frequency, dysuria, and hip pain after urination (25%). If metastasis has occurred, weight loss, fever, bone pain, and symptoms associated with metastases in the lung and liver (5%). Diagnosis is based on clinical symptoms, laboratory examination, radiology, ultrasonography, and computed tomography. Tissue biopsy and histopathologic examination are the definitive diagnosis.Treatment of bladder cancer at all stages requires interdisciplinary collaboration, to prevent its severity, some of the treatments that can be done are 1: Intravesical therapy, performed after TURBT, to kill the remaining cancer cells, by inserting drugs through a catheter from the urethra, divided into intravesical immunotherapy (boosting the immune system to fight cancer cells, for example with the drug Bacillus Calmette Guerin / BCG) and chemotherapy (chemotherapy drugs are inserted orally or injected into a vein).3.Radiotherapy (using radiation energy, for patients who do not want surgery or chemotherapy) or used for supplementation so that no cancer cells remain.Treatment and prognosis of patients are seen from the stage of the disease and from the results of histopathological examination.Knowing, knowing the symptoms and signs of this disease early, and with immediate and appropriate management, makes the prognosis of this disease better.

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