Identification of Some Specific Hematological Indicators as Bladder Cancer Risk Factors

Hind Sadeq Mohammed[1] and Mohammed Mezher Hussein[2]

[1]Assistant lecturer, Department of Medical Instrumentation Engineering Techniques, Electrical Engineering Technical College, Middle Technical University, Iraq.
[2]Lecturer Dr, Department of Optical Technology, College of Health and Medical techniques, Middle Technical University, Iraq.

1 ***Hind_sadeq@mtu.edu.iq*** ***and 2*** ***mohammed.mezhar.h@mtu.edu.iq.***

Abstract

Background: Our study's objectives were measuring the levels of blood glucose, blood pressure, glomerular filtration rate GFR, body mass index BMI and creatinine in the blood of patients with bladder cancer in order to control the development of a relationship between those hematological parameters in the case of bladder cancer.

Methods and Results: Blood samples were collected during the application of this work on 155 participants diagnosed with bladder cancer were admitted to medical –Baghdad city and Al-Kindey teaching hospital. All the participants were with the age ranged (25-70 years).There are many people who have been excluded because of their young age under 20 years old and those who have any type of common cancer, which was outlined as any malignant neoplasm, including those with hematological or lymphoid origin and other tissues associated with them. All the participants wearing light clothing and no shoes in order to measure their height and weight. Blood pressure was recorded using a standard mercury sphygmomanometer after an average of 2 readings taken with a 10 min interval. Creatinine and GFR and DM also were measured meanwhile.

It was noticed through the results that there is a high percentage of patients who are of advanced ages about 67(43.2%) with age ≥65 years, and those with high weights BMI ≥ 30 were 64(41.3%). After conducting pathological analyzes of blood samples, it was found that patients were having high levels of sugar, especially those with long duration of diabetics type 2, as well as high blood pressure, creatinine levels, and low GFR levels, and it was clear that males outperformed females in the height of all measurements, which is the dominant characteristic in this research.

Conclusion: This study concluded that males are more likely to develop the disease with bladder cancer than female. The disease is directly related with an increase the age and obesity, BP, creatinine, low GFR and long duration of DM.

Keyword s: Cancer, Bladder, Creatinine, Glomerular, Filtration.

Abbreviate: BC. Bladder Cancer, GFR: Glomerular Filtration Rate, DM: Diabetes Mellitus.

INTRODACTION

Bladder cancer (BC) is (referred to be) any tumor that develops from the bladder. It is the most prevalent urinary tract tumor, and urothelial carcinoma (UC) is the most prevalent histologic subtype of the tumor. [(1)] Especially in high-income areas, urinary bladder cancer is fairly common. [(2)] There are two different types of bladder cancer as Muscle-invasive and non-muscle-invasive. [(3-5)] Bladder cancer represents 3% of all malignancies and is the tenth most frequent cancer in the world.[(6,7)] In the US, bladder cancer is the sixth most prevalent type of cancer. [(8)] Smoking, drinking water toxins such chlorinated byproducts and arsenic, and other risk factors for bladder cancer have been identified. [(9-12)] and BC connection to metabolic risk factors as blood hypertension (Bp) and obesity According to a

meta-analysis of epidemiological data, diabetes mellitus (DM) was associated with a higher risk of bladder cancer.[13,14] A correlation exists between BC and occupational exposure to paint, rubber, petroleum compounds, and colors. Chemicals linked to BC include arsenic, aryl amine dye, aniline dye, cyclophosphamide (a cytostatic medication) and an analgesic (phenacetin). [15, 16]

Bladder cancer (BC) is one of the most common cancer forms in developed countries. The prevalence of BC rises with age and is twice as common in Caucasians as it is in African Americans. The prevalence of BC is twofold as high in developing nations when compared to developed countries. Squamous cell carcinoma accounts for the majority of BC cases in underdeveloped nations, which is associated with endemic schistosomiasis. [17, 18]

BC is frequently present with the following symptoms: minimal hematuria obstructive or infectious gross hematuria. Painful urination, frequency, constitutional symptoms like weariness and weight loss, and a pelvic mass are some other, less prevalent symptoms. For the early detection of BC, there are no screening tests available. Advanced disease stage is correlated with gross hematuria. [19]

Materials and Methods

Samples were collected from twelve of September to the first of December of the year twenty twenty-one in medical city –Baghdad at the biochemistry Department. 155 samples of participants including (80) males and (75) females diagnosed with bladder cancer were analyzed within three month period. Urea, creatinine, and blood glucose levels were the primary study variables.

Results:

The data in table (1) clarified that there are 155 patients pre-diagnosed bladder cancer were including this study with 80 males and 75 females aged 25 – 70 years. As noted the percentage of patients with advanced ages is more prevalent

67(43.2%) (P=0.123) with age range ≥65, especially in males than in females 36(45%), 31(41.3%) respectively.

Table 1.Ages of the participating patients.

Age (year)	Male n (%)	Female n (%)	Total	p-value
25-34	2(2.5)	2(2.7)	4(2.6)	0.158
35-44	8(10)	9(12)	17(11)	0.124
45-54	14(17.5)	15(20)	29(18.7)	0.10
55-64	20(25)	18(24)	38(24.5)	0.098
≥65	36(45)	31(41.3)	67(43.2)	0.123
Total	80(100)	75(100)	155(100)	0.005

It is noted from the data listed in Table (2) that the majority of patients are of high weight, as the measurements of BMI 64(41.3%) (P=0.0049) at range ≥ 30 Kg/m2 was 34 (42.5%), 30(34.3%) for males and female respectively.

Table 2. BMI of the participant's cohorts.

BMI (Kg/m2)	Male n (%)	Female n (%)	Total	p-value
≤ 20	3 (3.75)	4(5.3)	7(4.5)	0.008
20 - 24.9	14 (17.5)	17(22.7)	31(20)	0.0067
25 – 29.9	29 (36.25)	24(30.0)	53(34.2)	0.0055
≥ 30	34 (42.5)	30(34.3)	64(41.3)	0.0049
Total	80(100)	75(100)	155(100)	0.000

The percentage of participants with diabetes represents 115(74.19%) (P-value = 0.0002), including 64(80%) males and 51 (68%) females, as shown in Table (3). Among the results of this research, according to what is shown in Table (4), is that there is a direct relationship between the risks of developing BC with people with the highest period of diabetes for the period ≥10 years about 59(38.1%) (P= 0.003) represent 31(38.75%) males and 28(37.3%) females.

Table 3.The metabolic factors for the male and female participants.

Parameters	Male n (%)	Female n (%)	Total	p-value
Diabetes Mellitus	**64(80)**	**51 (68)**	**115(74.19)**	**0.0002**
Blood Pressure (mmHg)	**45 (56.25)**	**36 (48)**	**81(52.25)**	**0.000**
Glomerular Filtration Rate ≤ 60 mL/min	**26 (32.5)**	**29 (38.66)**	**55(35.48)**	**0.003**
Creatinine				
≥ 97µmol/l (male)	**46 (57.5)**	**——**	**46(29.67)**	**0.0001**
≥80µmol/l (female)	**——**	**36(48)**	**36(23.22)**	**0.0002**

When observing the data listed in Table (3), the height of each of blood pressure (mmHg) (81(52.25%), Glomerular Filtration Rate ≤ 60 mL/min 55(35.48%) and Creatinine 46(29.67%) for males and 36(23.22%) for females concentration accompanies patients with BC.

Table 4. Comparison of the duration of Diabetes mellitus disease between male and female participants (years).

Duration (year)	Male n (%)	Female n (%)	Total	p-value
< 1	6(7.5)	6(8)	12(7.74)	0.01
1 - <2	10(12.5)	8(10.7)	18(11.61)	0.06
2 - <5	13(16.25)	12(16)	25(16.1)	0.004
5 - <10	20(25)	21(28)	41(26.45)	0.003
≥10	31(38.75)	28(37.3)	59(38.1)	0.003
Total	80(100)	75(100)	155(100)	0.000

Discussion:

This research found that as shown in table (1) older ages over 65 years 67(43.2%) (p=0.123) are at risk for BC 36(45%) among men and 31(41.3%) among women this finding was not statistically significant but it is consistent with previous studies that found the BC affecting persons older than 65 years which postulated the age-related decrease in the immune response and changes in infection-fighting defenses cause prevalence of the disease to rise. Additionally,

this population group has significant comorbidity, instrumentation, and frequent hospitalization, all of which raise the risk of nosocomial infections. [20]

BC is the one of the most prevalent cancer types in developed nations which has a connection to metabolic risk factors like obesity, which is typically assessed using the BMI (Kg/m^2), our results at table (2) demonstrated that a positive correspondence between BMI and BC ≥ 30 64(41.3%) (p=0.0049) especially for man 334(42.5%) more than in women 30(34.3%) this findings are in deep synchronization with research that was previously conducted. [21-23]

In this study, as indicated in table (3), we observed a higher incidence of BC in patients with type2 diabetes in the latter years following diagnosis, as it turns out, the percentage of BC patients with diabetes was 115(74.19%) (p=0.0002) higher in male 64(80%) than that of female51 (68%)

These results are consistent with those that were previously established. Most studies did not consider the possibility of BC in DM type1, which is consistent with the findings in Sweden. [24-26]

In affluent countries, a 69% increase in the proportion of persons with DM is anticipated between 2010 and 2030.Previous investigations have demonstrated a link between type 2 DM and an increased risk of BC. The individuals having the highest BC risk among those who have had diabetes the longest history this is illustrated in table (4) [27-33] .The best explanation for the increased risk of cancer in type 2M adults is insulin, which has been hypothesized to be a cancer growth promoter. In addition, poor glycemic control causes an increase in oxidative stress, upregulation of a number of cell molecules, and inflammation processes, all of which are thought to have a negative impact on cancer prognosis. [34-40]

Additionally, we discovered a stronger positive linear connection between BP and the probability of BC showed in table (3) the percentage of BC patients with high blood pressure 81(52.25%) (p=0.000) for males is higher 45(56.25%) than for women 36(48%). Once more, these results are in line with earlier research that discovered a relationship between BP and BC.

The following are some of the explanations for the connection between BC and hypertension: There is convincing evidence from animal studies supporting a causal role for oxidative stress in the pathogenesis of hypertension, and oxidative stress has been known to play a causal role in the development of cancer. Hypertension is one component of the metabolic syndrome which has been shown to associate with subsequent cancer development.

Participants in the healthcare system who are being treated for hypertension are undoubtedly subjected to extra tests that could lead to the early diagnosis of BC, which could affect the relationship between BP and BC. [41-43]

It is well recognized that a significant percentage of BC patients have impaired renal function. Attributable to a variety of causes, including concomitant conditions, aging-related reduction in glomerular filtration rate, and ureteral blockage. [44, 45]

As shown in the data of table (3). Glomerular Filtration Rate ≤ 60 mL/min 55(35.48%) (p=0.003) for male was 26(32.5%) and for female was 29(38.66%), which are agreed with other researches. As illustrated below: Bladder cancer is the most frequent solid tumor and the most common malignancy affecting the urinary system. About 40% of patients with bladder cancer diagnosed with renal impairment measured by a creatinine clearance ≤60ml/min. There are several possible causes of renal insufficiency, including age-related decreased glomerular filtration rate, ureteral obstruction, previous nephrectomy, and illness. Creatinine is

the most often utilized endogenous marker for the evaluation of glomerular function. [46, 47]. From table (3) the Creatinine levels ≥ 97µmol/l (male) was 46(57.5%) (p=0.0001) and ≥80µmol/l (female) was 36(48%) (p=0.0002), also this results are deeply consistent with what was found in previous studies, which can be explained as follows, the body at a constant rate produces creatinine, which is a by-product of the chemical of creatine phosphate in muscle. Creatinine is primarily removed from the blood totally by the kidney. Creatinine levels in the blood rise as a result of decreased renal clearance by the kidney. The daily production of creatinine is influenced by muscle mass. Raised creatinine levels are a sign of renal failure, which is negatively effects the body. [48-51] Hydronephrosis is frequently caused by advanced bladder cancer that has infiltrating the ureter's bladder orifices. Due to the kidney's impaired ability to filter urine, there is a rise in the concentration of creatinine when the kidney obstructed outflow of urine from the body. [52-58]

References

1.Kaseb H, Aeddula NR. Bladder Cancer. 2022 Oct 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 30725608.

2. Ploeg M, Aben KKH, Kiemeney LA. The Present and Future Burden of Urinary Bladder Cancer in the World. World J Urol (2009) 27:289–93. doi: 10.1007/s00345-009-0383-3

3. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. Med Sci Basel Switz (2020) 8:15. doi: 10.3390/medsci8010015

4. Leliveld AM, Bastiaannet E, Doornweerd BHJ, Schaapveld M, de Jong IJ. High Risk Bladder Cancer: Current Management and Survival. Int Braz J Urol Off J Braz Soc Urol (2011) 37:203–210; discussion 210-212. doi: 10.1590/s1677-55382011000200007

5. Isharwal S, Konety B. Non-Muscle Invasive Bladder Cancer Risk Stratification. Indian J Urol IJU J Urol Soc India (2015) 31:289–96.

6. U.S. Cancer Statistics Working Group: United States Cancer Statistics: 1999–2006 Incidence and Mortality Web-Based Report. Atlanta: Centers for Disease Control and Prevention, Department of Health and Human Services, and National Cancer Institute, 2010.

7.Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

8. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2006 Incidence and Mortality Web-based Report. 2010.

9. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC: Association between smoking and risk of bladder cancer among men and women. JAMA 2011;306:737–745.

10. Neumann A, Weill A, Ricordeau P, Faqot JP, Alla F, Allemand H: Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. Diabetologia 2012;55:1953–1962.

11.Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. Eur Urol. 2016 Jul;70(1):106-119. [PubMed: 26996659]

12.Hinotsu S, Akaza H, Miki T, Fujimoto H, Shinohara N, Kikuchi E, Mizutani Y, Koga H, Okajima E, Okuyama A., Japanese Urological Association. Bladder cancer develops 6 years earlier in current smokers: analysis of bladder cancer registry data collected by the cancer registration committee of the Japanese Urological Association. Int J Urol. 2009 Jan;16(1):64- 9. [PubMed: 19054170]

13. Tseng CH: Diabetes and risk of bladder cancer: a study using the National Health Insurance database in Taiwan. Diabetologia 2011;54:2009–2015.

14.Zhu ZW, Zhang XH, Shen ZJ, Zhong Shan, Wang XJ, Lu YL: Diabetes mellitus and risk of bladder cancer: a metaAnalysis of cohort studies. PLOS One 2013;8:e56662.

15.Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks. Eur Urol. 2016 Sep;70(3):458-66. [PubMed: 26149669]

16. Gaertner RR, Trpeski L, Johnson KC., Canadian Cancer Registries Epidemiology Research Group. A case-control study of occupational risk factors for bladder cancer in Canada. Cancer Causes Control. 2004 Dec; 15(10):1007-19. [PubMed: 15801485]

17.Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, Lotan Y, Meeks JJ, Michalski JM, Morgan TM, Quale DZ, Rosenberg JE, Zietman AL, Holzbeierlein JM. Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol. 2017 Sep; 198(3):552-559. [PMC free article: PMC5626446] [PubMed: 28456635]

18. Abern MR, Dude AM, Tsivian M, Coogan CL. The characteristics of bladder cancer after radiotherapy for prostate cancer. Urol Oncol. 2013 Nov; 31(8):1628-34. [PubMed: 22575239]

19.Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, Hernández V, Kaasinen E, Palou J, Rouprêt M, van Rhijn BWG, Shariat SF, Soukup V, Sylvester RJ, Zigeuner R. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol. 2017 Mar; 71(3):447-461. [PubMed: 27324428]

20. Charlton ME, Adamo MP, Sun L, Deorah S. Bladder cancer collaborative stage variables and their data quality, usage, and clinical implications: a review of SEER data, 2004–2010. Cancer. 2014; 120(Suppl 23):3815–25.

21.Lu Y, Tao J. Diabetes Mellitus and Obesity as Risk Factors for Bladder Cancer Prognosis: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2021 Oct 7;12:699732. doi: 10.3389/fendo.2021.699732. PMID: 34690923; PMCID: PMC8529220.

22. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al.. Global and Regional Diabetes Prevalence Estimates for 2019 and Projections for 2030 and 2045: Results From the International Diabetes Federation Diabetes Atlas, 9th Edition. Diabetes Res Clin Pract (2019) 157:107843.

23. GBD 2015 Obesity Collaborators. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al.. Health Effects of Overweight and Obesity in 195 Countries Over 25 Years. N Engl J Med (2017) 377:13–27.

24.Goossens ME, Zeegers MP, Bazelier MT, De Bruin ML, Buntinx F, de Vries F. Risk of bladder cancer in patients with diabetes: a retrospective cohort study. BMJ Open. 2015 Jun 1;5(6):e007470. doi: 10.1136/bmjopen-2014-007470. PMID: 26033947; PMCID: PMC4458630.

25. Shu X, Ji J, Li X, et al. Cancer risk among patients hospitalized for type 1 diabetes mellitus: a population-based cohort study in Sweden. Diabet Med 2010;27:791–7.

26.Swerdlow AJ, Laing SP, Qiao Z, et al. Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study. Br J Cancer 2005;92:2070–5.

27.Xu X, Wu J, Mao Y, et al. Diabetes mellitus and risk of bladder cancer: a meta-analysis of cohort studies. PLoS ONE 2013;8: e58079.

28. Starup-Linde J, Karlstad O, Eriksen SA, et al. CARING (CAncer Risk and INsulin analoGues): the association of diabetes mellitus and cancer risk with focus on possible determinants—a systematic review and a meta-analysis. Curr Drug Saf 2013;8:296–332.

29. Jiang X, et al. Urinary tract infections and reduced risk of bladder cancer in Los Angeles. Br J Cancer. 2009; 100(5):834–9. [PubMed: 19174821]

30. MacKenzie T, Zens MS, Ferrara A, Schned A, Karagas MR. Diabetes and risk of bladder cancer: evidence from a case-control study in New England. Cancer. 2011 Apr 1;117(7):1552-6. doi: 10.1002/cncr.25641. Epub 2010 Nov 8. PMID: 21425156; PMCID: PMC3117102

31.Huang, WL., Huang, KH., Huang, CY. et al. Effect of diabetes mellitus and glycemic control on the prognosis of non-muscle invasive bladder cancer: a retrospective study. BMC Urol 20, 117 (2020). https://doi.org/10.1186/s12894-020-00684-5.

32.Rieken M, Xylinas E, Kluth L, Crivelli JJ, Chrystal J, Faison T, et al. Association of diabetes mellitus and metformin use with oncological outcomes of patients with non-muscle-invasive bladder cancer. BJU Int. 2013;112(8): 1105–12. https://doi.org/10.1111/bju.12448.

33. Ahn JH, Jung SI, Yim SU, Kim SW, Hwang EC, Kwon DD. Impact of glycemic control and metformin use on the recurrence and progression of nonmuscle invasive bladder Cancer in patients with diabetes mellitus. J Korean Med Sci. 2016;31(9):1464–71. https://doi.org/10.3346/jkms.2016.31.9.1464.

34. Chen Y, Wu F, Saito E, Lin Y, Song M, Luu HN, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia cohort consortium. Diabetologia. 2017;60(6): 1022–32. https://doi.org/10.1007/s00125-017-4229-z.

35. Chang SC, Yang WV. Hyperglycemia, tumorigenesis, and chronic inflammation. Crit Rev Oncol Hematol. 2016;108:146–53. https://doi.org/10. 1016/j.critrevonc.2016.11.003.

36. Gonzalez-Roibon N, Kim JJ, Faraj SF, Chaux A, Bezerra SM, Munari E, et al. Insulin-like growth factor-1 receptor overexpression is associated with outcome in invasive urothelial carcinoma of urinary bladder: a retrospective study of patients treated using radical cystectomy. Urology. 2014;83(6):1444 e1–6. https://doi.org/10.1016/j.urology.2014.01.028.

37. Leiter A, Doucette J, Krege S, Lin C-C, Hahn N, Ecke T, et al. Obesity and Outcomes in Patients With Metastatic Urothelial Carcinoma. Bladder Cancer Amst Neth (2016) 2:341–9. doi: 10.3233/BLC-160047

38. Li W, Zhang X, Sang H, Zhou Y, Shang C, Wang Y, et al. Effects of Hyperglycemia on the Progression of Tumor Diseases. J Exp Clin Cancer Res CR (2019) 38:327. doi: 10.1186/s13046-019-1309-6

39. Lu C-C, Chu P-Y, Hsia S-M, Wu C-H, Tung Y-T, Yen G-C. Insulin Induction Instigates Cell Proliferation and Metastasis in Human Colorectal Cancer Cells. Int J Oncol (2017) 50:736–44. doi: 10.3892/ijo.2017.3844

40. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and Inflammation: The Linking Mechanism and the Complications. Arch Med Sci AMS (2017) 13:851–63. doi: 10.5114/aoms.2016.58928

41. Kashiwagi E, Abe T, Kinoshita F, Ushijima M, Masaoka H, Shiota M, et al. The Role of Adipocytokines and Their Receptors in Bladder Cancer: Expression of Adiponectin or Leptin Is an Independent Prognosticator. Am J Transl Res (2020) 12:3033–45.

42. Cespedes Feliciano EM, Prentice RL, Aragaki AK, et al. Methodological considerations for disentangling a risk factor's influence on disease incidence versus postdiagnosis survival: the example of obesity and breast and colorectal cancer mortality in the Women's Health Initiative. Int J Cancer. 2017;141(11): 2281-2290.

43. Lajous M, Bijon A, Fagherazzi G, et al. Body mass index, diabetes, and mortality in French women: explaining away a "paradox". Epidemiology. 2014; 25(1):10-14.

44.Teleka S, Jochems SHJ, Häggström C, Wood AM, Järvholm B, Orho-Melander M, Liedberg F, Stocks T. Association between blood pressure and BMI with bladder cancer risk and mortality in 340,000 men in three Swedish cohorts. Cancer Med. 2021 Feb;10(4):1431-1438. doi: 10.1002/cam4.3721. Epub 2021 Jan 16. PMID: 33455057; PMCID: PMC7926028.

45. Rosenberg JE, Carroll PR, Small EJ. Update on chemotherapy for advanced bladder cancer. J Urol 2005; 174:14-20.

46.Nerli, R. and Ghagane, Shridhar. and Musale, Abhijit. and Deole, Sushant. and Mohan, Shyam. and Dixit, Neeraj. and Hiremath, Murigendra.}, Chemotherapy in a patient with advanced carcinoma of the bladder with renal insufficiency

Journal of the Scientific Society},2018. 45(3): {139-142},doi = {10.4103/jss.JSS_55_18}.

47. Vaughn DJ. Chemotherapeutic options for cisplatin-ineligible patients with advanced carcinoma of the urothelium. Cancer Treat. Rev. 34, 328–338 (2008). • Comprehensive review of the current options in patients unfit for cisplatin.
48. Dash A, Galsky MD, Vickers AJ, Serio AM, Koppie TM, Dalbagni G, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer 2006;107:506-13.
49. Odden MC, Shlipak MG, Tager IB. Serum creatinine and functional limitation in elderly persons. J Gerontol A Biol Sci Med Sci. 2009;64A(3): 370–376. doi:10.1093/gerona/gln037
50. Mansour SG, Verma G, Pata RW, Martin TG, Perazella MA, Parikh CR. Kidney injury and repair biomarkers in marathon runners. Am J Kidney Dis. 2017;70(2):252–261. doi:10.1053/j.ajkd.2017.01.045
51. Liu M, Li X, Lu L, et al. Cardiovascular disease and its relationship with chronic kidney disease. Eur Rev Med Pharmacol Sci. 2014;18(19): 2918–2926
52. Hackemer P, Małkiewicz B, Menzel F, Drabik A, Tupikowski K, Zdrojowy R. Determinants of survival in patients with bladder cancer undergoing radical cystectomy: The impact of serum creatinine level. Adv Clin Exp Med. 2021 Jan;30(1):77-82. doi: 10.17219/acem/130597. PMID: 33529510.
53. Gershman B, Eisenberg MS, Thompson RH, et al. Comparative impact of continent and incontinent urinary diversion on long-term renal function after radical cystectomy in patients with preoperative chronic kidney disease 2 and chronic kidney disease 3a. Int J Urol. 2015;22:651–656.

54. Yu J, Hong B, Park JY, et al. Comparison of a significant decline in the glomerular filtration rate between ileal conduit and ileal neobladder urinary diversions after radical cystectomy: a propensity score-matched analysis. J Clin Med. 2020;9:2236. 55. Faraj KS, Mi L, Eversman S, et al. The effect of urinary diversion on long-term kidney function

56. Eisenberg MS, Thompson RH, Frank I, et al. Long-term renal function outcomes after radical cystectomy. J Urol. 2014;191:619–625.

57. Baba M, Shimbo T, Horio M, et al. Longitudinal study of the decline in renal function in healthy subjects. PLoS One. 2015;10:1–18.

58. Vejlgaard M, Maibom SL, Stroomberg HV, Poulsen AM, Thind PO, Røder MA, Joensen UN. Long-Term Renal Function Following Radical Cystectomy for Bladder Cancer. Urology. 2022 Feb;160:147-153. doi: 10.1016/j.urology.2021.11.015. Epub 2021 Nov 24. PMID: 34838541.