

REVIEWS

# The Diagnosis of Urological Neoplasm in Dialysis Patients – a Brief Review

Mircea Merticariu<sup>2</sup>, Andrei Niculae<sup>1,3</sup>, Corina-Ioana Merticariu<sup>4</sup>, Ileana Adela Vacariu<sup>1,3</sup>, Flavia Liliana Turcu<sup>1,3</sup>, Viorel Jinga<sup>1,5</sup>

## Abstract

Despite being closely monitored for their current and more acute pathology, cancer screening and in particular urological cancer screening is often neglected in patients with end stage renal disease undergoing dialysis. This review encompasses the diagnosis of urological malignancies that occur in end-stage renal patients after the initiation of hemodialysis. We conducted a literature search in PubMed and UpToDate databases using the diagnostic criteria for urological malignancies in hemodialysis patients. Based on the existing data in the current literature it seems that patients undergoing dialysis have a higher risk of developing cancer than the general population, with peculiarities in both cancer detection and investigation that need to be addressed. Further studies should be made in order to improve cancer screening and diagnosis in dialysis patients.

**Keywords:** urological cancer, hemodialysis, end-stage renal disease.

## Rezumat

Deși pacienții aflați în program de dializă sunt atent monitorizați pentru patologia lor prezentă și de obicei acută, screeningul pentru cancer și în particular screeningul pentru neoplazii de tract uro-genital este de multe ori neglijat în cazul pacienților cu boală cronică de rinichi în stadiul final. Această revizuire a literaturii de specialitate urmărește studiul neoplaziilor de tract uro-genital ce apar la pacienții cu boală de rinichi în stadiul final după inițierea dializei. Pentru a face acest lucru, am căutat în bazele de date PubMed și UpToDate folosind ca element de căutare particularitățile de diagnostic pentru neoplazii urologice la pacienții dializați. Bazându-ne pe datele existente în momentul de față în literatura de specialitate, se pare că pacienții supuși dializei au un risc mai mare de a dezvolta cancer față de populația generală, cu particularități legate atât de screening cât și de diagnostic de care trebuie ținut cont. Sunt necesare studii ulterioare pentru a îmbunătăți screeningul și diagnosticul cancerelor la pacienții dializați.

**Cuvinte cheie:** cancer uro-genital, hemodializă, boală cronică de rinichi în stadiul final.

<sup>1</sup> "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

<sup>2</sup> "Carol Davila" Hospital of Nephrology, Bucharest, Romania

<sup>3</sup> Department of Nephrology, "St. John" Emergency Clinical Hospital, Bucharest, Romania

<sup>4</sup> "Dr. Victor Gomoiu" Children's Clinical Hospital, Bucharest, Romania

<sup>5</sup> "Prof. Dr. Theodor Burghele" Hospital of Urology, Bucharest, Romania

### Corresponding author:

**Merticariu Mircea**, "Carol Davila" Hospital of Nephrology, 4<sup>th</sup> Grivitei Avenue, 1<sup>st</sup> District, 010731, Bucharest, Romania.  
E-mail: merticarium@gmail.com

## INTRODUCTION

The idea of this review arised from a small lot of patients recently evaluated by a joint team of urologists and nephrologists in one of the largest dialysis departments in Bucharest, Romania. We decided to review the existing medical literature in order to have a better grasp of the peculiarities regarding the incidence, symptoms, tumor markers and imaging studies for urological cancers in end stage renal disease (ESRD) patients undergoing dialysis.

## INCIDENCE

In some available studies it is mentioned that patients with ESRD, undergoing hemodialysis or renal transplantation, have a higher risk of developing cancer, urological cancer being the most frequent type<sup>1,2,3,4</sup>.

One of the largest studies ever published was an international retrospective study conducted on aprox. 800000 patients with ESRD on maintenance dialysis from Europe, Australia, New Zealand and USA for a period of 14 years. The authors noted a 3.6-fold higher risk for kidney cancer and 1.5-fold increased risk for urinary bladder cancer compared to the general population. Furthermore, the authors noted a more pronounced risk in younger and female patients<sup>5</sup>.

Regarding renal cancer, the increased risk was greater for congenital disease, toxic nephropathy and miscellaneous conditions, the last two categories being mostly due to analgesic nephropathy and Balkan nephropathy<sup>6</sup>. The authors state that the increased risk for renal parenchymal cancers is related to the loss of renal function and its duration rather than to the primary renal disease or dialysis modality. Acquired cystic kidney disease (ACKD) alone has been considered a risk factor for cancer in ESRD patients<sup>7</sup>.

Another 7 year prospective nationwide study conducted in Korea followed the incidence of specific cancers in aprox. 5000 patients. Although the incidence of cancer was similar compared to that of the general population, the incidence of urinary tract carcinoma was higher in ESRD patients. Again, the authors note a higher risk for the female gender<sup>8</sup>. A similar Japanese study noted that the risk for Renal Cell Carcinoma (RCC) was higher than Transitional cell Carcinoma (TCC) in ESRD patiens on dialysis<sup>8,9</sup>.

In a 14 years study conducted in USA that observed the incidence of all types of cancer in a large group of over 35000 patients, the authors found that out of the 8 most common site-specific malignancies diagno-

sed within 6 months from the initiation of dialysis, the incidence was highest for cancers of the kidney/renal pelvis and urinary bladder<sup>10</sup>.

Finally, in a large Taiwanese study following cancer incidence in patients on dialysis for at least 3 months, bladder cancer was the most frequent type of malignancy found in ESRD patients. The authors also noted that there was an increased incidence of overall cancers in young patients, particularly in the first year of dialysis<sup>11</sup>.

## SYMPTOMS

Screening of urinary neoplasia in hemodialysis patients is particularly challenging, one of the problems being the lack of signs and symptoms.

In 2012, Ofer Yossepowitch et.al correlated the clinical symptoms of patients diagnosed with bladder cancer which were on hemodialysis with disease outcome. During an 11 year follow-up, a total of 15 patients were included in the study. The most common clinical symptoms associated with urinary bladder carcinoma were hematuria and bloody urethral discharge<sup>12</sup>. The tumors detected were mostly large and multifocal. High grade urothelial tumors were detected in 73% of the patients<sup>12,13</sup>.

The most common symptoms noted in 73 Taiwanese patients with upper urinary tract TCC who underwent chronic dialysis were urethral bloody discharge and painless gross hematuria<sup>14</sup>.

A larger retrospective study reviewed aprox. 1500 hemodialysed patients treated in a single Taiwanese hospital for 9 years; 26 patients presented with TCC. The most frequent symptom reported was gross hematuria (24 patients) followed by disuria (5 patients), flank pain (1 patient) and abdominal pain (1 patient). The most frequent location of the tumors was found in the upper urinary tract (54%), urinary bladder (18%), ureter (11%). Multifocal tumors were found in 27% of the patients<sup>15</sup>.

## MARKERS

Markers are commonly used as screening tools to detect the presence of underlying neoplasia. Three of the most commonly used markers in detecting urological malignancies are the Prostate specific antigen (PSA), the Alpha-Feto Protein (AFP) and the Human Chorionic Gonadotropin (hCG). The authors reviewed the literature in order to find out if dialysis has any effect on these markers.

The conclusion of a 3 year study published in 1995 by Morton et al., which followed the PSA values of 80 hemodialysed patients, was that dialysis does not affect the serum PSA values and that digital rectal examination (DRE) and serum PSA are equally effective in detecting underlying prostate cancer for this category of patients<sup>16</sup>.

Another study compared the stage of cancer at diagnosis in patients with ESRD with the one in the general population. The authors concluded that patients with ESRD were twice as likely to be diagnosed with a more advanced stage of prostate cancer partly due to lower use of PSA screening in this category of patients<sup>17,18,19</sup>. Furthermore, keeping in mind the high morbidity and mortality in dialysis patients it is advisable to reserve PSA screening for patients with a life expectancy of at least 10 years<sup>17</sup>.

Khairullah et. al stated in their study published in 2004 that routine screening using DRE and PSA was not sensitive enough to detect the disease and that PSA doubling-time improved the sensitivity and positive predictive value of prostate cancer detection<sup>20</sup>.

Finally, in a review published in 2014 the authors concluded that total PSA and free PSA serum levels can vary before and after hemodialysis, based on the type of membrane and dialysis modality used and that further studies are needed in order to determine the exact extent of these alterations<sup>21,22</sup>. Regarding AFP levels (commonly used for testicular cancer screening), the same authors concluded that the serum level is not influenced by ESRD or the type of dialysis<sup>23,24</sup>. As for hCG, this marker is excreted in urine, thus in patients with CKD and/or hemodialysis, there should be caution in interpreting its values<sup>25,26,27</sup>.

## IMAGING

Knowing that ESRD patients have a higher risk of developing RCC, regular imaging screening should be performed<sup>28</sup>.

One author recommends a screening protocol with computed tomography (CT) or ultrasound (US) every 3 years for all patients on dialysis and once a year for those with ACKD<sup>29</sup>.

Although ultrasound examination has been one of the most used screening tools for detection of RCC in dialysis patients, its accuracy may be challenged due to the pre-existing changes in ESRD kidneys regarding renal echogenicity, dimensions, contour and possible presence of hypertrophic tissue<sup>28</sup>. Other ultrasound limitations are represented by the possible mass effect

of the hypertrophic tissue on the pyelocalyceal system which can simulate a renal neoplasm and also the inability to clearly distinguish between hemorrhagic cysts and RCC<sup>30,31,32,33</sup>.

ACKD is commonly observed in hemodialysis patients and it is related to the duration of chronic renal failure or dialysis<sup>34,35</sup>. The CT diagnosis of cancer in patients with ACKD can be difficult due to the marked deformation of the renal architecture<sup>30</sup>. One author has demonstrated that early enhanced helical CT is superior to the delayed enhanced CT in the detection of RCC in ACKD patients<sup>36,37</sup>.

Regarding MRI imaging with low dosages of gadolinium, Holley et al. stated that although it is considered safe to use in patients with CKD, there is some concern about the association between sclerosing fibrosis and gadolinium exposure in these patients, particularly when hemodialysis is used for tracer removal<sup>38</sup>.

Another study group raised awareness about the possible association between nephrogenic systemic fibrosis and gadodiamide enhanced MRI imaging in renal failure patients. Based on their 13 case study, the authors decided to avoid its use in ESRD patients until further studies are conducted<sup>39,40,41,42</sup>.

## CONCLUSIONS

Based on published data from current available literature it seems that patients undergoing dialysis have a higher risk of developing cancer than the general population and that urological malignancies (renal and urinary bladder cancers) tend to be more frequent in this group.

The most common symptoms associated with lower urinary tract neoplasia occurring in dialysis patients is gross hematuria and bloody urethral discharge. These symptoms should raise suspicion and should prompt further investigations.

Although most markers used in the diagnosis of urological cancers remain unaltered after dialysis, careful interpretation is essential and most importantly, practitioners should integrate the results in the overall clinical context and adjust the therapy to the life-expectancy of these patients.

Imaging diagnosis of urological malignancies in ESRD patients can be difficult due to the modified renal architecture or the presence of ACKD associated with ESRD and currently there is no 'perfect' imaging tool.

In conclusion, since there is a gross lack of peer reviewed information to clearly guide current clinical

practice in ESRD patients with urological malignancies, further prospective studies should be conducted in

joint settings by teams of urologists and nephrologists in order to improve cancer screening and diagnosis in ESRD patients.

## References

- McCredie M, Stewart JH, Carter JJ, Turner J, Mahony JF. Phenacetin and papillary necrosis: independent risk factors for renal pelvic cancer. *Kidney Int*, 1986; 30: 81–84
- Port FK, Ragheb NE, Schwarz AG, Hawthorne VM. Neoplasm in dialysis patients: a population-based study. *Am J Kidney Dis*. 1989; 14: 119–123.
- Matas AJ, Simmons RL, Kjellstrand CM, Buselmeier TJ. Increased incidence of malignancy during chronic renal failure. *Lancet*. 1975; 1: 883–886.
- Birkeland SA, Lokkegaard H, Storm HH. Cancer risk in patients on dialysis and after renal transplantation. *Lancet*, 2000; 35: 1886–1887.
- Stewart JH, Bucciante G, Agodoa L, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. *J Am Soc Nephrol* 2003; 14:197.
- Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Bucciante G, Lowenfels AB, Wolfe RA, Jones E, Disney AP, Briggs D, McCredie M, Boyle P. Distribution of primary renal diseases leading to end-stage renal failure in the United States, Europe, and Australia/New Zealand: Results from an international comparative study. *Am J Kidney Dis*, 2000; 35: 157–165.
- Chudek J, Herbers J, Wilhelm M, Kenck C, Bugert P, Ritz E, Waldman F, Kovacs G. The genetics of renal tumors in end-stage renal failure differ from those occurring in the general population. *J Am Soc Nephrol*, 1998; 9: 1045–1051.
- Yoo KD, Lee JP, Lee SM, Park JY, Lee H, Kim DK, et al. Cancer in Korean patients with end-stage renal disease: A 7-year follow-up. *PLoS ONE*, 2017; 12(7): e0178649.
- Satoh S, Tsuchiya N, Habuchi T, Ishiyama T, Seimo K, Kato T. Renal cell and transitional cell carcinoma in a Japanese population undergoing maintenance dialysis. *J Urol* 2005; 174: 1749–1753.
- Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996-2009. *Am J Kidney Dis* 2015; 65:763.
- Lin HF, Li YH, Wang CH, et al. Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan. *Nephrol Dial Transplant* 2012; 27:1585.
- Ofer Yossepowitch, Itay Sagy, David Margel, Jack Baniel. Urothelial Carcinoma of the Bladder in Patients on Hemodialysis: Clinical Characteristics and Oncological Outcomes *J Urol*, 2012; 187(4): 1215-9.
- Zhang, Y., Zhu, C., Curado, M.P. et al. Changing patterns of bladder cancer in the USA: evidence of heterogeneous disease. *BJU Int*. 2012; 109: 52.
- Ching-Fang Wu, Phei-Lang Chang, Chih-Shou Chen, Cheng-Keng Chuang, Hsu-Huei Weng, See-Tong Pang The Outcome of Patients on Dialysis With Upper Urinary Tract Transitional Cell Carcinoma, 2006; 176(2): 477–481.
- Chang, C.-H., Yang, C.-M. and Yang, A.-H. Renal diagnosis of chronic hemodialysis patients with urinary tract transitional cell carcinoma in Taiwan. *Cancer*, 2007; 109: 1487–1492.
- Morton JJ, Howe SF, Lowell JA, et al. Influence of end-stage renal disease and renal transplantation on serum prostate-specific antigen. *Br J Urol* 1995; 75:498.
- Taneja S, Mandayam S, Kayani ZZ, et al. Comparison of stage at diagnosis of cancer in patients who are on dialysis versus the general population. *Clin J Am Soc Nephrol* 2007; 2: 1008.
- Winkelmayer WC, Owen W, Glynn RJ, Levin R, Avorn J. Preventive health care measures before and after start of renal replacement therapy. *J Gen Intern Med*. 2002; 17:588–95.
- U.S. Renal Data System, USRDS 2002 Annual Data Report. Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 2002.
- Khairullah QT, Pamatmat SD, Chatha M, et al. Early detection of prostate cancer in the ESRD population. *Clin Nephrol* 2004; 61:308.
- L. Bruun, C. Savage, A. M. Cronin, J. Hugosson, H. Lilja, and A. Christensson. Increase in percent free prostate-specific antigen in men with chronic kidney disease. *Nephrology Dialysis Transplantation*, 2009; 24(4): 1238–1241.
- Coppolino G, Bolignano D, Rivoli L, et al. Tumour markers and kidney function: a systematic review. *Biomed Res Int*, 2014; 2014:647541, 9 pages.
- W. C. Lye, P. Tambyah, S. O. Leong, and E. J. Lee. Serum tumor markers in patients on dialysis and kidney transplantation. *Advances in Peritoneal Dialysis*, 1994; 10: 109–111.
- C. R. Nichols. Testicular cancer, *Current Problems in Cancer*, 1998; 22(4): 187–274.
- E. I. Kohorn. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. *International Journal of Gynecological Cancer*, 2001; 11(1): 73–77.
- B. C. Nisula, D. L. Blithe, A. Akar, G. Lefort, and R. E. Wehmann. Metabolic fate of human chorionic gonadotropin. *Journal of Steroid Biochemistry*, 1989; 33(4B): 733–737.
- R. E. Wehmann and B. C. Nisula. Metabolic and renal clearance rates of purified human chorionic gonadotropin, *Journal of Clinical Investigation*, 1981; 68(1): 184–194.
- Yasukazu Nakanishi, Fumitaka Koga, Hiroshi Fukushima, Toru Motoi and Ken-ichi Tobisu. Renal Cell Carcinoma in End-Stage Renal Disease, *Updates in Hemodialysis*, InTech, 2015; DOI: 10.5772/59378.
- Sarasin, F. P., et al. Screening for acquired cystic kidney disease: a decision analytic perspective. *Kidney Int*, 1995; 48(1): 207–19.
- Cho, C., G. W. Friedland, and R. S. Swenson. Acquired renal cystic disease and renal neoplasms in hemodialysis patients. *Urol Radiol*, 1984; 6(3-4): 153-7.
- Văcăroiu IA, Rădulescu D, Ciocâlțeu A, Peride I, Ardeleanu S, Checheriță IA. Comparative evolution of hemodialysis vs. peritoneal dialysis in elderly. *Rev Med Chir Soc Med Nat Iasi*. 2012; 116(1):22-29.
- Văcăroiu IA, Rădulescu D, Ciocâlțeu A, Peride I, Ardeleanu S, Checheriță IA. Functional status of chronic renal replacement therapy in elderly patients--comparison between hemodialysis and peritoneal dialysis. *Rev Med Chir Soc Med Nat Iasi*. 2012; 116(2):375-382.
- Levine, E. Renal cell carcinoma in uremic acquired renal cystic disease: incidence, detection, and management. *Urol Radiol*, 1992; 13(4): 203-10.
- Chandhoke PS, Torrence RJ, Clayman RV, Rothstein M. Acquired cystic disease of the kidney: a management dilemma, *J Urol* 1992; 147: 969-974
- Matoson MA, Cohen EP. Acquired cystic kidney disease: occurrence, prevalence and renal cancers. *Medicine*, 1990; 69: 217-226
- Geavlete B, Bulai C, Ene C, Checherita I, Geavlete P. The Influence of NBI Vision Over the First Follow-up Cystoscopy Outcomes in Newly Diagnosed NMIBC Patients, *Chirurgia (Bucur)*, 2015; 110(2):157-60.
- Takebayashi, S., et al. Using helical CT to evaluate renal cell carcinoma in patients undergoing hemodialysis: value of early enhanced images, *AJR Am J Roentgenol*, 1999; 172(2): 429-33.

38. Holley JL. Screening, diagnosis, and treatment of cancer in long-term dialysis patients, *Clin J Am Soc Nephrol*, 2007; 2: 604.
39. Spinu D, Rădulescu A, Bratu O, Checheriță IA, Ranetti AE, Mischianu D. Giant condyloma acuminatum - Buschke-Lowenstein disease - a literature review , *Chirurgia (Bucur)*, 2014; 109(4):445-50.
40. Marckmann P, Skov L, Rossen K, Dupont A, Damholt MB, Heaf JG, Thomsen HS. Nephrogenic systemic fibrosis: Suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging, *J Am Soc Nephrol*, 2006; 17: 2359– 2362.
41. Jean L Holley. Cancer screening in patients with end-stage renal disease. UpToDate. 2015; <https://www.uptodate.com/contents/cancer-screening-in-patients-with-end-stage-renal-disease#references>. Accessed 18 Sep 2017.
42. *Chirurgia (Bucur)*. 2015 Mar-Apr;110(2):157-60. Geavlete B, Bulai C, Ene C, Checherita I, Geavlete P; -. The Influence of NBI Vision Over the First Follow-up Cystoscopy Outcomes in Newly Diagnosed NMIBC Patients.