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Review

In 1975 Matas and co-workers were the first in the world literature to show an increased risk of malignant tumor occurrence in the group of hemodialyzed patients and kidney transplant recipients. The report is an analysis of world literature from the last 35 years in reference to epidemiology as well as the profile of screening tests and diagnostic methods related to malignant tumors in the population with end stage renal disease, especially hemodialyzed patients.

Key words: neoplastic disease, end stage renal disease, hemodialysis, peritoneal dialysis.

Malignant tumors in patients with end stage renal failure undergoing renal replacement therapy

Grzegorz Kade[1], Arkadiusz Lubas[1], Lubomir Bodnar[2], Cezary Szczylik[2], Zofia Wańkowicz[1]

[1]Department of Internal Disease, Nephrology and Dialysis Therapy, Central Clinical Hospital, Ministry of the Interior and Administration, Military Institute of Medicine, Warsaw, Poland
[2]Oncology Department, Central Clinical Hospital, Ministry of the Interior and Administration, Military Institute of Medicine, Warsaw, Poland

Introduction

An increase in incidence and morbidity of chronic kidney disease has been observed in Poland within the last ten years [1]. This results in an increasing number of patients who both suffer from end stage renal disease (ESRD) and require renal replacement therapy. Chronic kidney disease in both pre-hemodialysis patients and renal replacement therapy patients is connected with an increased risk of death, mainly due to cardiovascular diseases (56%), infections (11.2%) and neoplastic diseases (8%) [1].

The current study is an analysis of world literature from the last 35 years with reference to epidemiology as well as the profile of screening tests and diagnostic methods related to malignant tumors in the population with ESRD, especially hemodialyzed individuals.

Epidemiology of neoplastic diseases in patients with irreversible renal failure: has anything changed within the last 35 years? If yes – what?

In 1975 Matas *et al*. were the first in the world literature to publish data on increased risk of malignant tumor occurrence in the group of patients on a hemodialysis program as well as renal transplant recipients. The study included a group of 646 patients. The risk of developing a malignant tumor in dialyzed individuals was estimated as seven-fold higher than in comparable age groups without renal failure [2]. According to the reports from the 1970s, the vast majority of authors confirmed these observations. In 1979 Kjellstrand *et al.* analyzed studies published in the 1970s on carcinogenesis in the dialyzed population. Most of the studies indicated a cause and effect relation between hemodialysis therapy and frequent occurrence of malignant tumor compared to the general population. The analysis considered the more frequent occurrence of urinary tract cancer and kidney cancer, especially in the course of polycystic kidney disease and analgesic nephropathy [3]. Kinlen *et al.* published in 1980 outcomes of a 10-year observation of 1651 patients from Great Britain on hemodialysis, peritoneal dialysis or who received kidney transplant. A greater frequency of non-Hodgkin lymphoma was observed compared to the general population [4]. Slifkin *et al.* did not confirm these observations in material which included 712 hemodialyzed patients observed for 10 years [5]. The greatest multicenter study in the 1980s was conducted by Jacobs *et al.* and involved 39 386 hemodialyzed patients and renal transplant recipients. According to the study, malignant tumors were present in 1.3% of these patients. Among them, the most frequent was lung cancer, observed in 10% of this population [6].

According to the study of Lindner *et al.*, which included 148 dialyzed patients, malignant tumor occurred in 9.5% of the individuals. Similarly to the study of Jacobs *et al.*, the most frequently diagnosed neoplasm was lung cancer, which amounted to 50% of all the diagnosed tumors [7].

However, in the study of Bush *et al.* published in 1984 on 834 ESRD patients the percentage of diagnosed malignant tumors was as low as 0.6% of the examined population and was lower than the expected statistical significance level $p < 0.05$ [8].

In the study conducted in 1989 on 4161 dialyzed patients, Port *et al.* attempted to evaluate the risk of developing malignant tumor considering race, gender and age of the patients. Malignant tumors occurred considerably more frequently in dialyzed patients compared to the general population and all tumors *in situ* as well as kidney, endometrial, cervical and prostatic cancers [9].

One of the carcinogenesis risk factors is chronic immunosuppressive therapy. In the study of Pecqueux *et al.* from 1990 the authors compared a group of 709 kidney transplant recipients with a group of 317 dialyzed patients. Malignant tumor developed in 3% of transplant recipients and in 10% of dialyzed individuals [10].

In the 1990s a few large epidemiologic studies were reported. In the study on 23 209 patients dialyzed in 589 centers in Japan, Inamoto *et al.* observed an increased risk of developing malignant tumor and mortality compared to the general population. The most frequently diagnosed disease was cancer of digestive and urinary tracts. Also, malignant tumors occurred in men much more frequently than in women. In this study, diagnosis of malignant tumor was most often made within the first 6 months of hemodialysis therapy [11]. Similarly, according to the study conducted in Serbia by Čučković *et al.* on 923 hemodialyzed patients between 1983 and 1993, 40% of malignant tumors were diagnosed within the first year of hemodialysis therapy. Mean age of the patients was approximately 59 years [12].

The largest study on malignant tumor occurrence in hemodialyzed patients was a multicenter study in 1999 conducted by Maisonneuve *et al.* on 831 804 patients from North America, Europe, Australia and New Zeeland (the study was based on USRDS, EDTA and ANZDTR data). In the course of a 30-month observation, malignant tumors were diagnosed in 25 044 patients, which amounted to 3% of the examined population. This result considerably exceeded the expected malignant tumor detectability in the general population. Malignant tumors occurred more frequently in patients under 35 years compared to older persons. Also, cervical cancer as well as cancer of the urinary bladder, kidney and thyroid glands were diagnosed more frequently compared to the general population [13].

During the first decade of the 21st century some epidemiologic data confirming previous findings were published in the world literature. In the study by Teschner *et al.*, which was published in 2002 and included analysis of the medical records of 1727 hemodialyzed patients in Bavaria, malignant tumors were diagnosed in 7.2% of these patients. Similarly to previous studies, the diagnosis was made mainly within the first year of dialysis therapy and considerably less frequently in further years of renal replacement therapy. According to this study, the greatest tumor incidence referred to patients aged 35–50 years. Most frequently, malignant tumor developed in kidneys, urinary bladder, prostatic gland, the liver, nasopharynx and lymphatic system. Compared to the general population, an increase in frequency was observed with respect to cancer of the mammary gland, stomach, colon, anus and bronchi. Since the number of patients with diagnosed malignant tumor in their material was very high, the authors suggested a necessity of running regular screening tests in hemodialyzed patients, especially in younger age groups, for the purpose of early diagnosis, particularly of cancer in the kidney, urinary bladder or the liver [14].

In the study by Lee *et al.* published in 2009 on 4562 patients dialyzed by hemodialysis or peritoneal dialysis in Korea and observed for 9 years, malignant tumors were observed in 106 patients, which amounted to 2.3% of the examined group. Most frequently, the sites of malignant tumors were as follows: digestive tract, urinary tract, lungs and thyroid gland. Mean time from dialysis therapy commencement to diagnosis of cancer was 75.2 ±63.9 months. Mean time from cancer diagnosis to patient's death was two times shorter, approximately 36 ±30 months. Similarly to other authors, Lee *et al.* recommended monitoring of cancer occurrence in dialyzed patients, especially with respect to digestive and respiratory tracts [15].

The only Polish study in this field was published by Antoni Sydor *et al.* in 2006 and involved a population of 5648 dialyzed patients including 5260 individuals receiving hemodialysis and 388 peritoneal dialysis. Malignant tumor was diagnosed in 9.5% of the patients in total. The most frequently diagnosed malignant tumors in women were mammary carcinoma and renal cell carcinoma (RCC), while in men they were renal cell carcinoma and lung cancer. Mean age of the examined group was 54 years, while the dialysis therapy period from cancer diagnosis was approximately 4 years [16].

Table 1 presents the most significant epidemiologic studies connected with occurrence of malignant tumors in the population of renal replacement therapy patients in the years 1975–2009.

The prevalence of RCC in patients with end-stage renal disease (ESRD) on dialysis is reported to be higher than in the general population, with a standardized incidence ratio (SIR) of 3.60 (3.45–3.76) [13]. The higher risk is probably attributed to the nature of the primary kidney disease, associated urological abnormalities or the development of renal acquired cystic kidney disease (ACKD) in dialyzed patients [17]. Within the first 3 years of dialysis therapy approximately 10–20% of patients develop ACKD, by 5 years 40–60% have ACKD and by ten years more than 90% exhibit ACKD [18]. Furthermore, ACKD is often associated with several pathological features, e.g. papillary tufts, cribriform lesions, atypical cysts and adenomas, which are morphologically and cytogenetically considered to be early neoplastic lesions [19].

The incidence of RCC in ACKD is reported to be three to six times higher than in the general population [20]. Historically, most tumors arising in the background of ACKD have been considered to be papillary RCC, accounting for 42–71% of cases [21, 22]. Contrary to this belief, Tickoo *et al.* have recently reported a wide spectrum of renal cell tumors aris-

Table 1. The most significant epidemiologic studies connected with occurrence of malignant tumor in the population of renal replacement therapy patients in the years 1975–2009

Authors	Work title	Population	Neoplasm detectability in the examined population	The most common primary site of malignant tumor
Matas *et al.* 1975	Increased incidence of malignancy during chronic renal failure	646 HD, TN	1.6%	respiratory system, urinary system
Slifkin *et al.* 1977	Malignancy in end-stage renal disease	712 HD	3.1%	respiratory system, prostate gland
Kinlen *et al.* 1980	Cancer in patients receiving dialysis	1651 HD, DO, TN	0.9%	lymphatic system
Bush *et al.* 1984	Cancer in uremic patients	834 D	0.8%	non-specific
Port *et al.* 1989	Neoplasms in dialysis patients: a population-based study	4161 D		urinary system, uterine body, prostate gland
Pecqueux *et al.* 1990	Cancer incidence in patients on chronic dialysis and in renal transplant recipients	317 D	0.4% 1	urinary system
Inamoto *et al.* 1991	Incidence and mortality pattern of malignancy and factors affecting the risk of malignancy in dialysis patients	23 209 D	0.48%	digestive system, urinary system
Čučković *et al.* 1996	Malignant tumors in hemodialysis patients	923 HD	4.9%	urinary system
Maisonneuve *et al.* 1999	Cancer in patients on dialysis for end-stage renal disease: an international collaborative study	831 804 HD, DO	3%	urinary system
Tischner *et al.* 2002	Incidence and spectrum of malignant disease among dialysis patients in North Bavaria	1727 HD	7.2%	urinary system
Lee *et al.* 2009	Cancer in patients on chronic dialysis in Korea	4562 3011/1551 HD, DO	2.3%	digestive system, urinary system, respiratory system, thyroid
Sydor *et al.* 2006	*Malignant tumors in chronic kidney disease patients*	5648 5260/388 HD, DO	9.5%	urinary tract, lung, breast

HD – hemodialysis; DO – peritoneal dialysis; TN – transplantation; D – dialyzed (with no method specified)

ing in ESRD, with a majority, particularly those arising in ACKD, showing morphologic features that are not seen in renal tumors in a sporadic setting [23]. The authors tentatively designate such tumors as ACKD-associated RCC. The reasons for their not considering ACKD-associated RCC as a papillary RCC are primarily based on the combination of morphologic features in these tumors, which include:

1) the unique cribriform architecture almost invariably present, either focally or diffusely (in 96% of tumors),
2) the consistent presence of eosinophilic cells in each tumor with grade 3 nuclei,
3) the frequent presence of intratumoral oxalate crystals.

The biologic behavior of RCCs in ESRD is reported to be less aggressive than the RCCs in a sporadic or non-ESRD setting [17, 24–28]. However, rare cases have been reported to behave aggressively and metastasize. One of the possible reasons for this less aggressive behavior may be that these patients are usually under constant medical care, and radiologic evaluations may identify most tumors quite early [23].

Table 2 presents the clinicopathologic characteristics of renal cell carcinoma in patients with end-stage renal disease on dialysis.

To conclude, the described outcomes of epidemiologic studies indicate that routine screening tests for neoplastic disease are justified at least in particular groups of patients who receive renal replacement therapy, especially hemodialyzed individuals.

Screening and diagnostic tests for malignant tumor in dialyzed patients: if and when?

In 2008 Mandayam *et al.* suggested that regular screening tests be performed for neoplastic disease in the population of dialyzed patients. In the case of men the tests would refer to prostatic gland and kidney, in women to digestive tract and mammary glands [29]. Table 3 presents the usefulness of neoplastic markers used in patients on renal replacement therapy.

As the table suggests, very few markers have similar diagnostic value to the ones used for the general population. The other markers either have high false positive rates or should be interpreted very carefully.

Rao *et al.* recommend careful interpretation of neoplastic markers excreted by kidneys. The markers are proteins of a rel-

Table 2. The clinicopathologic characteristics of renal cell carcinoma in patients with end-stage renal disease on dialysis

Authors	Population	Number of patients with RCC (male : female)	Median age (range)	Time on dialysis to diagnosis of RCC mean (range)	Treatment	Histology	Follow-up 2 years (survival)	Conclusion
Hora *et al.*	NR	13 : 1	53 (41–78)	78 mos. (0–154)	13 unilateral nephrectomy, 6 bilateral nephrectomy	multifocal 68.4% (13/19), solitary 31.6% (6/19), PRCC – 68.4% (13/19), CRCC – 47.4% (9/19), PR/CR – 21.0% (4/19)	74%	There is a high risk for bilateral RCC Patients who undergo unilateral nephrectomy must be regularly followed and contralateral nephrectomy carefully considered
Nouh *et al.*	1200	31 : 3	56 (32–82)	116.5 mos. (1–390)	34 nephre-ctomy	multifocal 27% (9/34), CRCC – 37% (10/27), PRCC – 7.4% (2/27), PR/CR – 7.4% (2/27), ACD – associated, RCC – 27% (8/27)	88.9%	The spectrum of histological types of RCCs arising in ESRD is distinct from that of sporadic RCC ACKD in patients with ESRD and on dialysis is a potential risk factor for the development of RCCs
Tickoo *et al.*	NR	34 : 18	56.5 (30–78)	8 yr (1–17)	37 unilateral nephrectomy, bilateral 15	multifocal 54.5% (36/66), PRCC – 18% (12/66), ACD-RCC – 36% (24/66), CRCC (25/66)	34 mos. (range 9–94 mos.)	Acquired cystic disease-associated RCC is the commonest tumor subtype in ESRD
Hurst *et al.*	495.604	3875 : 2257	NR	NR	NR	ACD-RCC – 12.1% (742/6132)	follow--up 8 yr	Among long-term incident US dialysis patients over an 8-year period, most cases of RCC diagnosed were not associated with documented acquired renal cystic disease
Kojima *et al.*	2624	31 : 13	55.5 ±11.1	11.2 yr ± 7.2 yr	44 unilateral nephrectomy, 5 bilateral	CRCC – 47% (23/49), PRCC – 8.2% (4/49), ChCC – 8.2% (4/49), ACD-RCC – 36.7% (18/49)	follow-up 36 mos. range, 6–121	Dialysis in patients showed a higher incidence of RCC than the general population
Satoh *et al.*	6201	30 : 8	56.5	143.2 mos.	33 nephrectomy	NR	88.9% (5 yr survival)	Long-term dialysis is a risk factor for RCC

RCC – renal cell carcinoma; PRCC – papillary renal cell carcinoma; CRCC – clear cell renal cell carcinoma; PR/CC – clear cell/papillary renal cell carcinoma; ACD-RCC – renal cell carcinoma associated with acquired cystic kidney disease; NR – not reported; yr – year; mos. – months

atively high molecular weight and are not necessarily removed by dialysis, leading to false test results. These observations referred to Ca 125 neoplastic antigen, carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC) and neuron-specific enolase (NSE) [30].

The following problem has been discussed in recent years: should dialyzed patients undergo screening diagnostics similar to the general population or should these tests be limited to the groups with particular risk of developing neoplastic diseases. Such groups would include:

- hemodialyzed patients, especially in the 3rd–4th decade of life;
- individuals with genetic predisposition for developing neoplastic disease;
- individuals on hemodialysis, peritoneal dialysis and patients prepared for kidney transplantation;
- individuals with longer life expectancy.

Table 3. Specificity and sensitivity of particular markers of neoplastic diseases in dialyzed patients

Usefulness	Marker
Infallible in dialyzed patients	α-fetoprotein β-chorionic gonadotropin PSA
Interpret carefully	Ca 125 CA 50 CA 19.9
High false positive rate in dialyzed patients	Carcinoembryonic antigen – CEA Squamous cell carcinoma antigen Neuron specific enolase – NSE

Table 4 presents our modification of suggested screening tests for neoplastic disease in dialyzed patients [31].

Table 4. Suggestions of screening test in dialyzed patients with consideration of carcinogenesis risk factors, life expectancy and transplant status (*own modification)

Malignant tumor	Suggested procedure
Breast cancer	Annual mammogram in women over 40 years of age Annual clinical breast test at the age of 40 and more; every 3 years self check for women aged 20–39 years In women from families with high risk of hereditary breast cancer consider intensification of screening tests
Colorectal cancer	Screening tests in patients over 50 years of age based on annual fecal occult blood test or immunochemical fecal test for patients waiting for kidney transplant Sigmoidoscopy, colonoscopy or double contrast barium enema is needed Consider intensification of screening test in patients with family-related higher risk of hereditary colorectal cancer and at the same time long life expectancy
Cervical cancer	Papanicolaou test once a year; the first no later than at the age of 21 years For consideration: vaccination against HPV, especially in women waiting for transplant; annual Papanicolaou test in women waiting for transplant and with risk factors and at the same time long life expectancy
Prostatic cancer	PSA and rectal exam once a year starting from the age of 50 years in men waiting for transplant Consider screening tests in men with high risk of developing disease and at the same time long life expectancy
Kidney cancer	Once a year computed tomography (*carefully in the case of contrast tests due to negative impact on residual diuresis) or MRI (*risk of nephrogenic systemic fibrosis after gadolinium or Magnevist) in patients dialyzed for over 3 years or waiting for transplant

When deciding on indications for various diagnostic tests, their limitations should be taken into consideration. Detection of calcification in chest vessels in women with chronic mineral kidney disease (CMKD) might give false mammography results. Suspected digestive tract neoplasm based on presence of fecal occult blood might be false positive due to frequent occurrence of digestive tract mucosa inflammation or vascular malformation that promotes bleeding in this group of patients. Computed tomography with contrast medium, especially in dehydrated patients, might cause a decline in kidney function in pre-dialysis patients (eGFR > 15 ml/min/1.73 m^2) or a decrease in residual diuresis in dialyzed patients. Magnetic resonance with the use of paramagnetic agents listed in Table 3 is related to the risk of nephrogenic systemic fibrosis [30].

Considering the indisputable fact that malignant tumors occur frequently in renal replacement therapy patients, especially hemodialyzed individuals, particular groups of patients should undergo regular screening tests, especially for the most common neoplasms such as renal or urinary bladder cancer. When deciding whether to run the tests, the patient's life expectancy should also be taken into consideration.

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Address for correspondence

Grzegorz Kade
Klinika Chorób Wewnętrznych, Nefrologii i Dializoterapii
Wojskowy Instytut Medyczny, CSK MON
Szaserów 128
00-909 Warszawa
tel./fax +48 22 681 68 11
e-mail: gkade@wim.mil.pl

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