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Skin neoplasia in kidney transplant candidates and recipients — new perspectives

Abstract

Kidney transplantation (KT) in chronic kidney disease is the best method of renal replacement therapy. KT prolongs the patient's life by decades, but the risk of getting cancer is much higher than in the general population. Cancer is listed as the second, after cardiovascular disease, cause of death after KT; it also causes death of many other solid organ transplant recipients (SOTRs). Skin cancers are the most common tumors in SOTRs. Treatment of these patients is very complex due to immunosuppression and requires cooperation of specialists in many fields depending on the transplanted organ and the type of neoplastic disease. The most frequent cancers are squamous cell carcinoma (SCC), basal cell carcinoma (BCC), malignant melanoma (MM), Merkel cell carcinoma (MCC), and much less frequent — skin lymphomas. Common risk factors include chronic exposure to ultraviolet (UV) radiation, HPV, EBV infection, pretransplant skin cancer, older age at transplantation, Caucasian origin, male sex, and type of immunosuppression. Multidisciplinary cooperation of dermatologists, transplant nephrologists, oncologists, hematologists, and other health professionals is needed for appropriate medical care.
This article focuses on epidemiology, risk factors of skin neoplasia, and eligibility of patients with previous skin cancer and lymphoma for kidney transplants. The possibility of administering immunotherapy in transplant recipients with recurrent and de novo neoplasia is also discussed.

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INTRODUCTION

Onco-nephrology is a new field of medicine that requires multidisciplinary cooperation of not only oncologists and nephrologists but also other health professionals. Adequate cancer screening and prophylaxis enables earlier diagnosis and treatment. However, using some novel therapies in patients at different stages of chronic kidney disease and different types of renal replacement therapy requires up-to-date knowledge and cooperation.

Kidney transplantation is the best method of renal replacement therapy; however, the risk of cancer in this population is increased. Cancer is listed as the second, after cardiovascular disease, cause of death in patients after organ transplantation [1].

Treatment of these patients is very complex due to immunosuppression and requires the cooperation of specialists in many fields depending on the transplanted organ and type of neoplastic disease. Skin cancers are the most common tumors in solid organ transplant recipients (SOTRs). The most prevalent are *squamous cell carcinoma* (SCC), *basal cell carcinoma* (BCC), *malignant melanoma* (MM), *Merkel cell carcinoma* (MCC), and also much less frequent *lymphomas* [2–6].

Appropriate prophylaxis allows for a considerable reduction in the risk of skin cancer, while regular dermatological examination allows for

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a diagnosis in the early phase of the disease and improves the prognosis.

This article is the third in the series of articles published after the Scientific and Training Conference "Nephro-oncology" organized in Gdansk, Poland, every two years. These conferences are devoted to complex relationships between kidney disease and cancer [7–8]. This article summarizes the key information provided in a session focused on skin cancer in SOTR during the 3rd conference that took place on October 14–15, 2022, in Gdansk. It has also been updated to include crucial management issues in nephrology relevant to patients with malignancy, published by KDIGO (Kidney Disease: Improving Global Outcomes), and the current status on malignancies in adult kidney transplant candidates and recipients published most recently in Kidney International [9–10].

EPIDEMIOLOGY OF SKIN NEOPLASIA

Skin cancers such as SCC, BCC, MM, and MCC are the most common tumors in SOTRs [2]. In contrast to the general population, an inverted epidemiology of skin cancers can be observed, i.e., SCC occurs more often than BCC (from 1.5:1 to 5:1) [11]. However, in the Polish population, BCC still dominates, which may be due to too short observation periods and lower cumulative UV radiation dosage due to moderate climate [12]. It is estimated that malignant skin cancers develop in 1–6.5% of patients after organ transplantation after 5 years and in 6–35% of patients after 10 years from transplantation [13]. The highest incidence of skin cancers is recorded in Australia, where 20 years after transplantation, this type of cancer is diagnosed in as many as 70% of patients.

In the study by Kang *et al*. (1,671 recipients with pre-transplant skin cancer *vs*. 102,861 recipients without a history of cancer), the presence of skin cancer before transplantation increased the risk of skin cancer after transplantation (31.5% in patients with pre-transplant skin cancer vs. 7.4% in patients without pre-transplant skin cancer; $p < 0.001$). The presence of cancer was also associated with increased risk of post-transplant lymphoproliferative disease (PTLD), solid organ cancer, death, and kidney loss [14]. Therefore, skin cancer can be considered an indicator of predisposition to developing cancer after transplantation.

PTLD is a rare complication. Four subtypes of PTLD [15] are distinguished. PTLD is derived from B-cells and develops most often early after transplantation. PTLDs arising from T-cells are less frequently observed. Anaplastic large cell lymphoma (ALCL) is the most common, other, less common, cancer is peripheral T-cell lymphoma (PTCL). Posttransplant primary cutaneous T-cell lymphomas represent 5% of PTLD cases involving the skin [5, 6].

There were described mycosis fungoides cases with erythroderma and fatal outcomes [5], which could be related to high doses of immunosuppression and aggressive treatment. There were also cases in which 22 posttransplant T-cell lymphomas involving the skin were reported, with posttransplant cutaneous T-cell lymphoma mycosis fungoides type and posttransplant primary cutaneous ALCL with nodular skin lesions. The former had late onset and mild course — only with erythematous patches and plaques or eczema-like skin lesions; the latter had excellent prognosis [6]. In addition to precise histopathological examination of skin biopsy, with immunohistochemical staining, proper staging (PET or computed tomography, peripheral blood immunophenotyping) has to be performed to distinguish primary cutaneous posttransplant lymphomas and lymphoma that has metastasized to the skin (e.g., ALCL or *B-cell lymphoma* with secondary skin involvements has worse prognosis than primary cutaneous ALCL or primary Cutaneous *B-cell Lymphomas*).

SKIN NEOPLASIA RISK FACTORS

Common risk factors for *Squamous cell carcinoma* (SCC), *Basal Cell Carcinoma* (BCC), *Melanoma* (MM), and *Merkel Cell Carcinoma* (MCC) include chronic immunosuppression; however, the type and duration of immunosuppression are also of great importance. Other risk factors associated with a higher incidence of non-melanoma skin cancer (NMSC) are advanced age, older age at transplantation, male sex, fair skin phototype, skin cancer before transplantation, premalignant lesions, UV exposure, infections (HPV, EBV, etc.), pretransplant and also genetic disorders, such as autosomal dominant polycystic kidney disease [16–17].

Risk increases linearly for BCC and exponentially for SCC, and it is particularly related to ultraviolet radiation and immunosuppression. The immunosuppressive treatment causes an increase in virus replication, some of these viruses have been shown to be associated

with the development of skin cancers (e.g., HPV, HHV-8, Merkel cell polyomavirus).

Skin tumors in SOTRs are also more likely to be multiple and more aggressive, with higher risk of relapse, metastasis, and death due to tumor progression.

PTLD RISK FACTORS

There is conflicting data regarding the PTLD risk factors [18]:

1. Primary EBV infection after transplantation is a major risk factor for EBV-associated early-onset PTLD [19].
2. Posttransplant EBV seronegative status has been considered as a risk factor for some late-onset PTLD (that is why the American Society of Transplant and Kidney Disease): Improving Global Outcomes recommend EBV viral monitoring in pretransplant EBV seronegative patients receiving donor organs that are seropositive (weekly or biweekly for 1 year) or seronegative (monthly) [20, 21].
3. Human leukocyte antigen (HLA) class I and II alleles have been reported to be associated with PTLD (HLA-A26, -B18, -B40 — with increased risk, HLA-A3, -DR7 with decreased risk). There is relation between HAL and EBV status (e.g., HLA-B18 risk is increased in EBV-negative PTLD, HLA-A1 is associated with increased risk, and HAL-A2 with decreased risk of EBV-positive Hodgkin lymphoma) [22, 23].
4. Older recipient age is also a risk factor for cancer and PTLD [24].
5. There is a higher risk of PTDL in the case of expanded criteria for donor kidneys — probably because enhanced systemic inflammatory response increases cancer risk. Additionally, those kidneys are most often allocated to older patients [25].
6. The amount of immunosuppression used (cumulative immunosuppression dosage posttransplant but also pretransplant) is very important in relation to PTDL. The immunosuppressive state is an important factor, not a specific immunosuppressive agent [25], but not in every case it is so simple. For example [18]:
   - 6.a. there is no higher risk with current rabbit anti-thymocyte globulin (rATG) dosing in induction therapy. But when rATG is used to treat rejection — the scale of PTLD risk is uncertain [26];
   - 6.b. treatment with tacrolimus has been associated with higher risk of PTLD compared to cyclosporine — in some studies (but not all) [27, 28];
   - 6.c. high doses of azathioprine have been associated with higher PTLD risk [29];
   - 6.d. mycophenolate mofetil does not increase the PTLD risk [30];
   - 6.e. mammalian target of rapamycin (mTOR) inhibitors are not related to a higher risk of PTLD (probably because of a lower immunosuppressive effect than cyclosporine) according to some observations; on the other hand, there is a higher PTLD risk in maintenance therapy with mTOR inhibitors according to other clinical trials. The higher mortality rate in SOTRs receiving mTOR inhibitors is known [31–33];
   - 6.f. PTLD risk on belatacept looks the same as in the case of calcineurin inhibitors, but belatacept is contraindicated in EBV-seropositive recipients [34].

MOST COMMON SKIN CANCERS

Basal cell carcinoma is the most common skin cancer in the general population (GP), and the risk of BCC after transplantation is about 10-fold higher. In SOTRs, the SCC/BCC ratio changes in favor of SCC. BCC may develop at the site of precancerous conditions or in the previously unchanged skin. BCC occurs in younger patients than in the GP and grows more often multifocally and more extensively. The prognosis in early diagnosis and appropriate treatment of BCC is good, and the risk of recurrence is 5–10% [35].

Squamous cell carcinoma is the most common skin cancer in SOTRs, occurring from 65 to 250 times more frequently than in the GP [16, 35]. The majority of cancers arise from precancerous lesions, including actinic keratosis (AK), Bowen's disease (BD), and *Queyrat erythroplasia* (QE). Patients who develop their first focus SCC have an over 60% risk of developing more SCC in the next 5 years. According to Lindelöf *et al*., 25% of patients with a first SCC will have a second lesion within 13 months, and 50% will have a second lesion within 3.5 years [36]. SCC develops in younger patients and has a rapid growth rate. In 50% of cases, it develops multifocally, more often presents deep tissue invasion, and metastasizes (8–12%) [37, 38]. As in

the GP, recipients with a fair skin phototype and high cumulative dose of UV radiation are associated with higher SCC risk. The main location of SCC is the face, backs of hands, forearms, and mucous membranes, mainly the lower lip. Tumors appearing on the skin usually are asymptomatic, but 1/3 of patients experience tenderness, pain, or itching, which is rarely found in GPs. These symptoms constitute an unfavorable prognostic factor that may indicate a perineural invasion [39]. The risk of metastases in the course of SCC in the GP is 3.6% within 3 years, whereas for immunocompromised patients, such as SOTRs, the risk reaches 7%–12%. In SOTRs, SCC may cause distant metastases. Patients who suffer from metastatic SCC have bad prognosis (3-year survival is 56%, and 5-year survival is 34%) [40–42]. SOTRs have a 2 to 8-fold increased risk of developing MM in the posttransplant period [16].

Melanoma in SOTRs can arise in three principal scenarios: an existing MM before transplantation, an MM arising *de novo* after transplantation, and an MM derived from an organ donor [43–44]. Melanoma results from the malignant transformation of melanocytes and has the highest mortality rate among skin tumors. This tumor has high immunogenicity and changes its behavior in the setting of immunosuppression. The incidence of MM in SOTRs is slightly increased compared to SCC and BCC, although its potential morbidity and mortality have to be considered in post-transplant care.

Initial treatment of melanoma appearing in the posttransplant period does not differ from the standard approach in the GP. In addition to that, reduction or change in immunosuppression is suggested to be a reasonable and effective adjuvant strategy. A balance must be struck between the strength of immunosuppression so that it does not prompt tumor spread and, at the same time, prevents rejection of the transplanted organ. Therapeutic management is particularly challenging in advanced MM stages as the use of immune checkpoint inhibitors confers a high risk of organ rejection.

Merkel cell carcinoma (MCC) is a rare neuroendocrine neoplasm that usually fulfills AEIOU features. A is typically asymptomatic, E — expands rapidly, I — presents more frequently in immunosuppressed populations, O — in patients older than 50 years (mean age in immunocompetent individuals is higher than in SOTRs, in whom the mean age at diagnosis is 50 years), and U — appears in sun-exposed areas. SOTRs have a 24-fold higher risk of MCC [45]. Most cases result from malignant transformation secondary to the *Merkel cell polyomavirus* infection, which may be relevant in SOTRs. It was confirmed that immunosuppression is an established risk factor for MCC [46, 47]. Just as with other skin cancers, the highest incidence of MCC was observed in patients receiving a combined regimen of azathioprine and cyclosporine [46]. The key role of immunosuppressants in MCC development is also confirmed by temporary regression of the tumor upon reduction or withdrawal of the immunosuppressive treatment. MCC typically presents as a painless, rapidly expanding cutaneous nodule or plaque. Lesions are often erythematous or violaceous with a smooth and shiny appearance and generally arise on sun-exposed areas, notably the head, neck, and limbs [35, 48]. SOTRs with MCC should be treated with similar modalities as patients without immunosuppression, *i.e.*, wide local excision, radical node dissection, radiation therapy, and chemotherapy. The prognosis is serious because 31% of patients develop tumor recurrence with a mean interval of 58 months after excision of the primary foci. Two-thirds of SOTRs with MCC develop rapid lymphatic metastases to the regional lymph nodes and systemic metastases to the liver, bones, and lung with a high 1-, 3-, and 5-year mortality rate (20%, 51%, and 54%, respectively) [45, 49–50].

Knowledge of the potential clinical course of skin cancers in this patient population is of paramount importance in determining the proper management of these potentially life-threatening skin lesions. In summary, it should be underlined that the risk of all skin cancers in SOTRs is much higher than in the GP. They appear at a younger age, the clinical course is much more serious, and they are more likely to recur, metastasize, and appear *de novo* in another location. Survival of patients is worse than in the GP.

SKIN CANCERS IN CANDIDATES FOR ORGAN TRANSPLANTATION

In most cases, the diagnosis of BCC or SCC after treatment of the primary lesions in the pre-transplantation period is not a contraindication to organ transplantation.

However, there are some exceptions:

— metastatic skin cancer;
— difficulty undergoing radical treatment and low possibility of long-term remission;

— the presence of high-risk skin cancer is defined as cancer that meets one of the following criteria: tumor diameter > 2 cm, presence of multiple tumors, rapid tumor growth, ulceration of the tumor surface, location in the central part of the face, on the eyelids, in the eyebrow area, in the area of the eye sockets, nose, lips, chin, jaw, pre- and post-auricular area, temples and ears, and the area of the genitals and fingers.

In such clinical scenarios, the disease can become active, and the risk of metastasis is high after initiating immunosuppressive therapy. The waiting period for transplantation in the case of MM *in situ* takes 2 years, but in more serious forms of MM, this time is prolonged to 5–10 years.

Table 1 presents the proposed waiting period from radical treatment to kidney transplantation for various skin cancers.

In candidates for Solid Organ Transplantation (SOT) with MM in medical history, such factors as tumor stage, disease control, and the period from diagnosis to transplantation are the most relevant factors to consider. In a study conducted by Penn *et al*., the risk of MM recurrence in SOTRs was 19%, which was similar to the GP, whereas mortality was 30% (50% higher than in the GP) [41, 51].

Recommendations for transplantation eligibility in patients with prior cancer specify that potential candidates should be in complete remission after radical oncological therapy, with no evidence of active disease. Recommended waiting times for particular cancers before listing vary considerably among guidelines [52]. Additionally, some new data suggest waiting time is not a key determinant of disease recurrence after transplantation [53]. Therefore, due to changing patient characteristics and

Table 1. Proposed waiting periods from radical treatment to kidney transplantation for various skin melanomas [11]

Cancer type	Transplantation allowed, no waiting period from radical treatment	Waiting period in years from radical treatment without recurrence
Basal cell carcinoma		
Primary	×	
Primary lesion, high risk	Patient preference to be taken into consideration after precise counselling	2
Metastatic in remission		5
Metastatic not in remission		Re-consideration after treatment
Squamous cell carcinoma		
Primary, low risk	×	
Primary, high risk	Patient preference to be taken into consideration after precise counselling	2
Metastatic in remission		3
Metastatic not in remission		Re-consideration after treatment
Melanoma malignum[1]		
In situ	x	
Stage Ia Stage Ib		2 2–5
Stage IIa, IIb,IIIa		5–10
Stage III b, IIIc		10–15
Stage IV		10–15
Merkel cell carcinoma		
primary		2–3
Metastatic in remission		3–5
Metastatic not in remission		Re-consideration after treatment
Lymphomas		
Primary skin lymphoma		1 year after treatment with remission
Secondary skin lymphoma		2 years after treatment with remission

[1]Disease staging is determined by clinical staging based on the micro staging of the primary melanoma and by clinical and radiological evaluation for metastases. After removal of the primary melanoma (T), the regional lymph nodes (N) and internal organs (M) should be clinically and radiologically evaluated for the presence of metastases.

the advent of new therapies (targeted therapies, ICIs), the criteria for listing should not be fixed, as had been done historically. Rather, the criteria should be dynamic and personalized and should take into consideration patient preferences, quality of life, survival gains with transplantation, the probability of premature death while on dialysis, and the risk of disease recurrence and cancer-related death after transplantation [9, 10].

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE CASES INVOLVING THE SKIN

Posttransplant primary cutaneous T-cell lymphomas represent 5% of PTLD cases involving the skin. There were described mycosis fungoides cases with erythroderma and fatal outcomes [5], which could be related to high doses of immunosuppression and aggressive treatment.

Treatment of PTLD is dependent on its type. Reduction in immunosuppression (e.g., 50% reduction in calcineurin inhibitor dose, discontinuation of antimetabolites, and continuing steroids if possible) can treat some cases of PTLD alone, but in other cases — especially monomorphic PTLD require radiotherapy, surgery, immunochemotherapy, or combination of them.

It is known nowadays that reduction in immunosuppression and skin-directed therapy should be the 1st step in posttransplant mycosis fungoides (topical corticosteroids, topical retinoids, phototherapy, radiotherapy), as well as bexarotene without immunosuppressing activity [6].

Besides the reduction in immunosuppression, no established treatment is recommended by NCCN for CD30-PTLD T-cell origin. Radiotherapy can be administered. Brentuximab vedotin (CD30 monoclonal antibody conjugate with auristatin E) can be used in CD30+ PTLD (including primary cutaneous ALCL) in cases when first-line therapy fails [54].

A detailed description of the clinical course, current methods of treatment of classic mycosis fungoides, and ALCL can be found in the recommendations of the Polish Dermatological Society and the Polish Lymphoma Research Group, published in 2023. Even though there are no posttransplant lymphomas described, the register of non-immunosuppressive treatment can be found there, with methods that should be considered in the course of posttransplant cutaneous lymphomas as first-line treatment in cases when skin is the only organ involved by lymphoma [55].

Since the risk factors in PTLD B-cell origin are known, acyclovir and ganciclovir have been proposed as early PTLD prevention, but a meta-analysis did not confirm their effects [56]. The pre-emptive interventions in patients who are seronegative pretransplant, with a reduction in immunosuppression in the case of increasing EBV load is recommended [20, 21]. Reduction in immunosuppression is preferred to rituximab proposed by some experts.

Antiviral therapy is not helpful because EBV-driven lymphomas do not express EBV thymidine kinase or EBV protein kinase, being targets of nucleoside analogs [57]. CD20-positive B-cell lymphomas have been answered for immunosuppression reduction and rituximab. If there is no response after 4 cycles of rituximab, chemotherapy (e.g., CHOP) should be administered [58].

Checkpoint inhibitors (anti-PD1, anti-PDL1) have to be considered with caution because of the risk of graft rejection [18].

The cause of death in PTLD can be infections, secondary malignancies, and primary lymphoma and its treatment [59]. The risk factors of death in the course of PTLD include:

- older age;
- advanced lymphoma;
- poor performance status;
- increased lactate dehydrogenase (LDH) levels;
- low albumin levels;
- central nervous system invasion [60].

There is also a risk of graft loss after the reduction in immunosuppression (concerning 5% of patients).

PTLD IN CANDIDATES FOR ORGAN TRANSPLANTATION

Repeat transplant after PTLD can be performed after 1 year of remission. It has a higher risk of PTLD compared to patients without a history of PTDL [61].

USING OF CANCER IMMUNOTHERAPY IN TRANSPLANT RECIPIENTS WITH SKIN CANCER

In recent years, immunotherapy with immune checkpoint inhibitors (ICIs) has revolutionized cancer treatment and is becoming a new standard of care for many tumor types, including skin cancers. ICIs are monoclonal

antibodies capable of blocking negative signals for T-cell activation or T-cell effector activity and represent an important therapeutic option in many tumors, including MM, metastatic cutaneous SCC, and MCC.

There are two types of ICIs: anti-CTLA4 and anti-PD-L1 monoclonal antibodies. The anti-CTLA4 monoclonal antibody (e.g., ipilimumab or tremelimumab) binds to the CTLA4 receptor and activates T cells [62]. The anti-PD-L1 (atezolizumab, avelumab, durvalumab) antibody inhibits activation of programmed cell death-1 (PD-1) receptors on the T cell with its ligand PD-L1 or PD-L2, which occurs in cancer cells. It protects T cells from the state of anergy, and so the cells may demonstrate cytotoxicity and destroy cancer cells [63].

The action of ICIs is based on the stimulation of the immune system to recognize antigens, so their use in transplant patients may stimulate the immune system and facilitate rejection. Rejection occurs more often in patients treated with anti-PD-1 antibodies [64]. Immune tolerance on the tissue level in utilizing PD-1, the PD-1/PD-L1 pathways plays a significant role in the preservation of immunotolerance. PD-L1 present in the epithelium of renal tubules represses cytokines' production by T-lymphocytes, regulating T-lymphocytes' activation and energy and providing the immune balance.

Immunotherapy has become an indispensable treatment tool in the management of diverse neoplasms. In the GP, ICIs are the only systemic treatments approved for locally advanced or metastatic cutaneous SCC and MCC [65–66]. In BRAF wild-type melanoma, immunotherapy is also the first-line treatment in both metastatic and adjuvant settings [67–68].

SOTRs and other immunosuppressed patients have been routinely excluded from clinical trials due to the risk of acute allograft rejection reported in 10% to 65% of cases in retrospective studies [69]. Additionally, the reported response rates of patients with cutaneous SCC and MM to ICI therapy are generally lower than those observed in immunocompetent populations [70].

However, Ferrándiz-Pulido *et al*., in their recent review, recommend that ICIs should be offered to KTRs (Kidney Transplant recipients) with advanced cutaneous SCC, MM, or MCC if surgery and/or radiotherapy have failed. For KTRs, this should be the first line ahead of chemotherapy and targeted therapies.

In other SOTRs, ICI use should be carefully considered with the benefits of ICIs versus risks of allograft rejection in particular cases with decision-making involving patients. Modification of immunosuppression should be considered in the context of the risk of allograft rejection and tumor progression. The authors recommend a dual immunosuppressive regimen combining mTOR inhibitors and either corticosteroids or calcineurin inhibitors before ICI initiation [71].

In summary, we would like to stress that kidney transplant candidates with cancer in medical history and recipients with *de novo* skin neoplasia have optimistic perspectives as far as diagnosis and therapy are concerned.

In potential transplant candidates suffering from advanced skin neoplasia, the medical team should take into consideration patient preferences, quality of life, and potential survival gains with transplantation; they should also balance the risk of disease recurrence and cancer-related death after transplantation.

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REFERENCES

1. Serkies K, Dębska-Ślizień A, Kowalczyk A, et al. Malignancies in adult kidney transplant candidates and recipients: current status. Nephrol Dial Transplant. 2023; 38(7): 1591–1602, doi: 10.1093/ndt/gfac239, indexed in Pubmed: 35998321.
2. Au EH, Wong G, Tong A, et al. Cancer in kidney transplant recipients. Nat Rev Nephrol. 2018; 14(8): 508–520, doi: 10.1038/s41581-018-0022-6, indexed in Pubmed: 29802400.
3. Zavos G, Karidis NP, Tsourouflis G, et al. Nonmelanoma skin cancer after renal transplantation: a single-center experience in 1736 transplantations. Int J Dermatol. 2011; 50(12): 1496–1500, doi: 10.1111/j.1365-4632.2011.04939.x, indexed in Pubmed: 21790552.
4. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipi-

ents. J Am Acad Dermatol. 2011; 65(2): 253–261, doi: 10.1016/j.jaad.2010.11.062, indexed in Pubmed: 21763561.
5. Lok C, Viseux V, Denoeux JP, et al. Post-transplant cutaneous T-cell lymphomas. Crit Rev Oncol Hematol. 2005; 56(1): 137–145, doi: 10.1016/j.critrevonc.2004.12.012, indexed in Pubmed: 16046144.
6. Pilkington J, Shalin S, Wong HK. Cutaneous T-Cell Lymphoma (CTCL) Arising Post Kidney Transplant: A Review of Clinical Variants in the Literature. Hematol Rep. 2023; 16(1): 11–21, doi: 10.3390/hematolrep16010002, indexed in Pubmed: 38247992.
7. Bączkowska T, Bissler JJ, BłasińskaPrzerwa K, et al. Problems of nephrooncology. Proceedings from the 1st Scientific and Training Conference Nephrooncology 5-6 October 2018, Gdańsk, Poland. Pol Arch Intern Med. 2019; 129(Spec. Issue 2): 1–74, doi: 10.20452/pamw.14821, indexed in Pubmed: 31046026.
8. Lizakowski S, Dębska-Ślizień A, Kurnatowska I, et al. Nephro-oncology: clinical and biochemical aspects of kidney disease and cancer. Acta Biochim Pol. 2023; 70(2): 347–361, doi: 10.18388/abp.2020_6588, indexed in Pubmed: 37159995.
9. Małyszko J, Bamias A, Danesh FR, et al. Conference Participants. KDIGO Controversies Conference on onco-nephrology: kidney disease in hematological malignancies and the burden of cancer after kidney transplantation. Kidney Int. 2020; 98(6): 1407–1418, doi: 10.1016/j.kint.2020.07.012, indexed in Pubmed: 33276867.
10. Porta C, Bamias A, Danesh FR, et al. Conference Participants. KDIGO Controversies Conference on onco-nephrology: understanding kidney impairment and solid-organ malignancies, and managing kidney cancer. Kidney Int. 2020; 98(5): 1108–1119, doi: 10.1016/j.kint.2020.06.046, indexed in Pubmed: 33126977.
11. Ulrich C, Kanitakis J, Stockfleth E, et al. Skin cancer in organ transplant recipients--where do we stand today? Am J Transplant. 2008; 8(11): 2192–2198, doi: 10.1111/j.1600-6143.2008.02386.x, indexed in Pubmed: 18782290.
12. Imko-Walczuk B, Ankudowicz A, Jaśkiewicz J, et al. Nowotwory skóry u chorych po przeszczepieniu narządów. Przegl Dermatol. 2011; 98: 91–103.
13. Fortina AB, Piaserico S, Alaibac M. et al.. Squamous cell carcinoma C. In: Urlich C, Euvard S, Stockfeth E., et al. ed. Cancer after Renal Transplantation. Springer, New York 2009: 241–261.
14. Kang W, Sampaio MS, Huang E, et al. Association of Pretransplant Skin Cancer With Posttransplant Malignancy, Graft Failure and Death in Kidney Transplant Recipients. Transplantation. 2017; 101(6): 1303–1309, doi: 10.1097/TP.0000000000001286, indexed in Pubmed: 27336396.
15. Swerdlow SH, Campo E, Harris NL. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. IARC Press:, Lyon 2017: 453–462.
16. Mittal A, Colegio OR. Skin Cancers in Organ Transplant Recipients. Am J Transplant. 2017; 17(10): 2509–2530, doi: 10.1111/ajt.14382, indexed in Pubmed: 28556451.
17. Jankowska M, Dębska-Ślizień A, Imko-Walczuk B, et al. Skin cancer in kidney transplant recipients affected with autosomal dominant polycystic kidney disease. Clin Transplant. 2016; 30(4): 339–343, doi: 10.1111/ctr.12707, indexed in Pubmed: 26916353.
18. Sprangers B, Riella LV, Dierickx D. Posttransplant Lymphoproliferative Disorder Following Kidney Transplantation: A Review. Am J Kidney Dis. 2021; 78(2): 272–281, doi: 10.1053/j.ajkd.2021.01.015, indexed in Pubmed: 33774079.
19. Shahinian VB, Muirhead N, Jevnikar AM, et al. Epstein-Barr virus seronegativity is a risk factor for late-onset posttransplant lymphoproliferative disorder in adult renal allograft recipients. Transplantation. 2003; 75(6): 851–856, doi: 10.1097/01.TP.0000055098.96022.F7, indexed in Pubmed: 12660514.
20. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009; 9 Suppl 3: S1–S155, doi: 10.1111/j.1600-6143.2009.02834.x, indexed in Pubmed: 19845597.
21. Allen UD, Preiksaitis JK. AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019; 33(9): e13652, doi: 10.1111/ctr.13652, indexed in Pubmed: 31230381.
22. Subklewe M, Marquis R, Choquet S, et al. Association of human leukocyte antigen haplotypes with posttransplant lymphoproliferative disease after solid organ transplantation. Transplantation. 2006; 82(8): 1093–1100, doi: 10.1097/01.tp.0000235889.05171.12, indexed in Pubmed: 17060859.
23. Kinch A, Sundström C, Tufveson G, et al. Association between HLA-A1 and -A2 types and Epstein-Barr virus status of post-transplant lymphoproliferative disorder. Leuk Lymphoma. 2016; 57(10): 2351–2358, doi: 10.3109/10428194.2016.1173209, indexed in Pubmed: 27104753.
24. Caillard S, Lamy FX, Quelen C, et al. French Transplant Centers. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. Am J Transplant. 2012; 12(3): 682–693, doi: 10.1111/j.1600-6143.2011.03896.x, indexed in Pubmed: 22226336.
25. Ma MKM, Lim WH, Turner RM, et al. The risk of cancer in recipients of living-donor, standard and expanded criteria deceased donor kidney transplants: a registry analysis. Transplantation. 2014; 98(12): 1286–1293, doi: 10.1097/TP.0000000000000375, indexed in Pubmed: 25119131.
26. Marks WH, Ilsley JN, Dharnidharka VR. Posttransplantation lymphoproliferative disorder in kidney and heart transplant recipients receiving thymoglobulin: a systematic review. Transplant Proc. 2011; 43(5): 1395–1404, doi: 10.1016/j.transproceed.2011.03.036, indexed in Pubmed: 21693205.
27. Navarro MD, López-Andréu M, Rodríguez-Benot A, et al. Cancer incidence and survival in kidney transplant patients. Transplant Proc. 2008; 40(9): 2936–2940, doi: 10.1016/j.transproceed.2008.09.025, indexed in Pubmed: 19010153.
28. Pirsch JD. Cytomegalovirus infection and posttransplant lymphoproliferative disease in renal transplant recipients: results of the U.S. multicenter FK506 Kidney Transplant Study Group. Transplantation. 1999; 68(8): 1203–1205, doi: 10.1097/00007890-199910270-00024, indexed in Pubmed: 10551653.
29. Na R, Laaksonen MA, Grulich AE, et al. Iatrogenic immunosuppression and risk of non-Hodgkin lymphoma in solid organ transplantation: A population-based cohort study in Australia. Br J Haematol. 2016; 174(4): 550–562, doi: 10.1111/bjh.14083, indexed in Pubmed: 27136044.

30. Végso G, Sebestyén A, Paku S, et al. Antiproliferative and apoptotic effects of mycophenolic acid in human B-cell non-Hodgkin lymphomas. Leuk Res. 2007; 31(7): 1003–1008, doi: 10.1016/j.leukres.2006.12.019, indexed in Pubmed: 17320952.
31. Hellström VC, Enström Y, von Zur-Mühlen B, et al. Malignancies in transplanted patients: Multidisciplinary evaluation and switch to mTOR inhibitors after kidney transplantation – experiences from a prospective, clinical, observational study. Acta Oncol. 2016; 55(6): 774–781, doi: 10.3109/0284186X.2015.1130855, indexed in Pubmed: 26824275.
32. Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. Clin Transplant. 2004; 18(4): 446–449, doi: 10.1111/j.1399-0012.2004.00188.x, indexed in Pubmed: 15233824.
33. Knoll GA, Kokolo MB, Mallick R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. BMJ. 2014; 349: g6679, doi: 10.1136/bmj.g6679, indexed in Pubmed: 25422259.
34. Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and Long-Term Outcomes in Kidney Transplantation. N Engl J Med. 2016; 374(4): 333–343, doi: 10.1056/NEJMoa1506027, indexed in Pubmed: 26816011.
35. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003; 348(17): 1681–1691, doi: 10.1056/NEJMra022137, indexed in Pubmed: 12711744.
36. Lindelöf B, Sigurgeirsson B, Gäbel H, et al. Incidence of skin cancer in 5356 patients following organ transplantation. Br J Dermatol. 2000; 143(3): 513–519, indexed in Pubmed: 10971322.
37. Liddington M, Richardson AJ, Higgins RM, et al. Skin cancer in renal transplant recipients. Br J Surg. 1989; 76(10): 1002–1005, doi: 10.1002/bjs.1800761005, indexed in Pubmed: 2597939.
38. Berg A, Mauro P, Borensztein E, et al. An Evaluation of Monetary Regime Options for Latin America. IMF Working Papers. 2002; 02(211): 1, doi: 10.5089/9781451874853.001.
39. Oh CC, Hofbauer GFL, Serra AL, et al. Painful skin lesions and squamous cell carcinoma predict overall mortality risk in organ transplant recipients: a cohort study. Br J Dermatol. 2017; 176(5): 1179–1186, doi: 10.1111/bjd.15269, indexed in Pubmed: 28012178.
40. Haug K, Breuninger H, Metzler G, et al. Prognostic Impact of Perineural Invasion in Cutaneous Squamous Cell Carcinoma: Results of a Prospective Study of 1,399 Tumors. J Invest Dermatol. 2020; 140(10): 1968–1975, doi: 10.1016/j.jid.2020.01.035, indexed in Pubmed: 32169476.
41. Imko-Walczuk B, Kiełbowicz M, Dębska-Ślizień A, et al. Skin Cancers as Contraindication to Organ Transplantation. Transplant Proc. 2015; 47(6): 1547–1552, doi: 10.1016/j.transproceed.2015.03.047, indexed in Pubmed: 26293011.
42. de Jong E, Genders R, Harwood CA, et al. Cumulative incidence and risk factors for cutaneous squamous cell carcinoma metastases in organ transplant recipients: The Skin Care in Organ Transplant Patients in Europe-International Transplant Skin Cancer Collaborative metastases study, a prospective multicenter study. J Am Acad Dermatol. 2024; 90(6): 1200–1209, doi: 10.1016/j.jaad.2024.01.040, indexed in Pubmed: 38301923.
43. Imko-Walczuk B, Turner R, Wojnarowska F. Malignant melanoma. Cancer Treat Res. 2009; 146: 311–322, doi: 10.1007/978-0-387-78574-5_25, indexed in Pubmed: 19415212.
44. Matin RN, Mesher D, Proby CM, et al. Skin Care in Organ Transplant Patients, Europe (SCOPE) group. Melanoma in organ transplant recipients: clinicopathological features and outcome in 100 cases. Am J Transplant. 2008; 8(9): 1891–1900, doi: 10.1111/j.1600-6143.2008.02326.x, indexed in Pubmed: 18786232.
45. Rockville Merkel Cell Carcinoma Group. Merkel cell carcinoma: recent progress and current priorities on etiology, pathogenesis, and clinical management. J Clin Oncol. 2009; 27(24): 4021–4026, doi: 10.1200/JCO.2009.22.6605, indexed in Pubmed: 19597021.
46. Hernandez LE, Mohsin N, Frech F, et al. Merkel cell carcinoma: An updated review of pathogenesis, diagnosis, and treatment options. Dermatol Ther. 2022; 35(3): e15292, doi: 10.1111/dth.15292, indexed in Pubmed: 34967084.
47. Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. Transplantation. 1999; 68(11): 1717–1721, doi: 10.1097/00007890-199912150-00015, indexed in Pubmed: 10609948.
48. Kanitakis J. Merkel cell carcinoma. Cancer Treat Res. 2009; 146: 329–341, doi: 10.1007/978-0-387-78574-5_27, indexed in Pubmed: 19415214.
49. Greenberg JN, Zwald FO. Management of Skin Cancer in Solid-organ Transplant Recipients: A Multidisciplinary Approach. Dermatol Clin. 2011; 29(2): 231–41, ix, doi: 10.1016/j.det.2011.02.004, indexed in Pubmed: 21421148.
50. Lewis CW, Qazi J, Hippe DS, et al. Patterns of distant metastases in 215 Merkel cell carcinoma patients: Implications for prognosis and surveillance. Cancer Med. 2020; 9(4): 1374–1382, doi: 10.1002/cam4.2781, indexed in Pubmed: 31883234.
51. Penn I. Malignant melanoma in organ allograft recipients. Transplantation. 1996; 61(2): 274–278, doi: 10.1097/00007890-199601270-00019, indexed in Pubmed: 8600636.
52. Batabyal P, Chapman JR, Wong G, et al. Clinical practice guidelines on wait-listing for kidney transplantation: consistent and equitable? Transplantation. 2012; 94(7): 703–713, doi: 10.1097/TP.0b013e3182637078, indexed in Pubmed: 22948443.
53. Unterrainer C, Opelz G, Döhler B, et al. Collaborative Transplant Study. Pretransplant Cancer in Kidney Recipients in Relation to Recurrent and De Novo Cancer Incidence Posttransplantation and Implications for Graft and Patient Survival. Transplantation. 2019; 103(3): 581–587, doi: 10.1097/TP.0000000000002459, indexed in Pubmed: 30418430.
54. Kinch A, Amini RM, Hollander P, et al. CD30 expression and survival in posttransplant lymphoproliferative disorders. Acta Oncol. 2020; 59(6): 673–680, doi: 10.1080/0284186X.2020.1731924, indexed in Pubmed: 32102582.
55. Sokołowska-Wojdyło M, Olszewska B, Chmielowska E, et al. Primary cutaneous lymphomas. Diagnostic and therapeutic guidelines of the Polish Dermatological Society (PTD) and Polish Lymphoma Research Group (PLRG). Dermatology Review. 2023; 110(6): 647–674, doi: 10.5114/dr.2023.138937.
56. AlDabbagh MA, Gitman MR, Kumar D, et al. The Role of Antiviral Prophylaxis for the Prevention of Epstein-Barr Virus-Associated Posttransplant Lymphoproliferative Disease in Solid Organ Transplant Recipients: A Systematic Review. Am J Transplant. 2017; 17(3): 770–781, doi: 10.1111/ajt.14020, indexed in Pubmed: 27545492.

57. Perrine SP, Hermine O, Small T, et al. A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus-associated lymphoid malignancies. Blood. 2007; 109(6): 2571–2578, doi: 10.1182/blood-2006-01-024703, indexed in Pubmed: 17119113.
58. Trappe R, Oertel S, Leblond V, et al. German PTLD Study Group, European PTLD Network. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol. 2012; 13(2): 196–206, doi: 10.1016/S1470-2045(11)70300-X, indexed in Pubmed: 22173060.
59. Dierickx D, Tousseyn T, Sagaert X, et al. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. Leukemia & Lymphoma. 2013; 54(11): 2433–2440, doi: 10.3109/10428194.2013.78065, indexed in Pubmed: 23442063.
60. Evens AM, David KA, Helenowski I, et al. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J Clin Oncol. 2010; 28(6): 1038–1046, doi: 10.1200/JCO.2009.25.4961, indexed in Pubmed: 20085936.
61. Leeaphorn N, Thongprayoon C, Chewcharat A, et al. Outcomes of kidney retransplantation in recipients with prior posttransplant lymphoproliferative disorders: An analysis of the 2000-2019 UNOS/OPTN database. Am J Transplant. 2021; 21(2): 846–853, doi: 10.1111/ajt.16385, indexed in Pubmed: 33128832.
62. Perazella MA, Shirali AC. Immune checkpoint inhibitor nephrotoxicity: what do we know and what should we do? Kidney Int. 2020; 97(1): 62–74, doi: 10.1016/j.kint.2019.07.022, indexed in Pubmed: 31685311.
63. Perazella MA, Shirali AC. Nephrotoxicity of Cancer Immunotherapies: Past, Present and Future. J Am Soc Nephrol. 2018; 29(8): 2039–2052, doi: 10.1681/ASN.2018050488, indexed in Pubmed: 29959196.
64. Kumar V, Shinagare AB, Rennke HG, et al. The Safety and Efficacy of Checkpoint Inhibitors in Transplant Recipients: A Case Series and Systematic Review of Literature. Oncologist. 2020; 25(6): 505–514, doi: 10.1634/theoncologist.2019-0659, indexed in Pubmed: 32043699.
65. Stratigos AJ, Garbe C, Dessinioti C, et al. European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC). European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 2. Treatment. Eur J Cancer. 2020; 128: 83–102, doi: 10.1016/j.ejca.2020.01.008, indexed in Pubmed: 32113942.
66. Cornejo C, Miller CJ. Merkel Cell Carcinoma: Updates on Staging and Management. Dermatol Clin. 2019; 37(3): 269–277, doi: 10.1016/j.det.2019.03.001, indexed in Pubmed: 31084721.
67. Garbe C, Amaral T, Peris K, et al. European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC), European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – Update 2019. Eur J Cancer. 2020; 126: 159–177, doi: 10.1016/j.ejca.2019.11.015, indexed in Pubmed: 31866016.
68. Garbe C, Amaral T, Peris K, et al. European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – Update 2022. Eur J Cancer. 2022; 170: 256–284, doi: 10.1016/j.ejca.2022.04.018, indexed in Pubmed: 35623961.
69. Alzahrani N, Al Jurdi A, Riella LV. Immune checkpoint inhibitors in kidney transplantation. Curr Opin Organ Transplant. 2023; 28(1): 46–54, doi: 10.1097/MOT.0000000000001036, indexed in Pubmed: 36579684.
70. Rossi E, Schinzari G, Maiorano BA, et al. Immune-checkpoint inhibitors in renal transplanted patients affected by melanoma: a systematic review. Immunotherapy. 2022; 14(1): 65–75, doi: 10.2217/imt-2021-0195, indexed in Pubmed: 34751039.
71. Ferrándiz-Pulido C, Leiter U, Harwood C, et al. Immune Checkpoint Inhibitors in Solid Organ Transplant Recipients With Advanced Skin Cancers-Emerging Strategies for Clinical Management. Transplantation. 2023; 107(7): 1452–1462, doi: 10.1097/TP.0000000000004459, indexed in Pubmed: 36706163.