

Kidney transplantation in patients with history of malignancy: Time to rethink the guidelines?

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1. ABSTRACT

A history of malignancy is often considered a contraindication for kidney transplantation. While the desire to transplant a 'cancer-free' patient is understandable, the current approach neglects the heterogeneity in the natural history of cancers, even within a given tumor type. The information used to formulate current guidelines are dated and fail to reflect the vast resource of modern oncology clinical trials data that should more accurately predict the expected overall survival and recurrence risk of cancer patients. The expected survival for many cancer patients excluded by current guidelines compares favorably with other conditions considered acceptable for transplantation. This review will suggest that close collaboration between transplant teams and oncologists can increase the appropriate use of renal transplantation in cancer patients.

2. INTRODUCTION

Patients maintained on dialysis have considerably shorter survival compared with those who receive a cadaveric transplant. Many patients with a history of cancer are considered ineligible for transplant, because the risk of malignancy recurrence in transplant patients is felt to be high. One to four percent of patients on dialysis and 9-12% percent of renal transplant recipients die of cancer (1). The increased risk of malignancies in patients with end stage renal disease (ESRD) and organ transplant recipients may be related to the uremic milieu, oncogenic viral infections, or immunosuppression (2). The

immunosuppressive agents themselves are associated an increased risk of a variety of malignancies (3), some of which are associated with viral infection (4), including lymphomas (Epstein-Barr virus), cervical cancer (human papilloma virus), and Kaposi's sarcoma (human herpes virus 8).

While it is important to acknowledge the risk of relapse in patients who have been successfully treated for cancer, advances have been made in cancer detection, treatment and risk stratification that should facilitate the safe transplantation of patients previously excluded. Even in advanced stages, some cancer patients have multiple treatment options and long life expectancy. Several previously lethal malignancies have multiple therapeutic targets and can be considered a chronic condition. In addition to chemotherapy, the evolving treatment options of solid and hematologic malignancies include molecular targeted therapy, vaccines, immunotherapy and other tumor-specific targets that improve survival. Furthermore, advances in staging and molecular characterization of tumors have resulted in more accurate predictions of progression free and overall survival for individual patients. Withholding or delaying organ transplantation in patients who are at risk of recurrence of a treatable malignancy requires careful consideration of cancer and patient-specific factors.

Adequate pre-transplant screening and evaluation for recurrence of malignancy should reduce

post-transplant mortality. The risk of malignancy recurrence depends on multiple variables, most importantly the stage of the cancer and characteristics of the tumor. Prior studies report aggressive and advanced stage at initial diagnosis of malignancy in organ transplant recipients. With better modalities for early detection of some cancers these observations may not apply to present standards of surveillance. The data describing the risk of malignancy recurrence in the post organ transplant population is mostly obtained from the Israel Penn International Transplant Tumor registry (IPTTR). This unique registry was established in 1968 and collected data on malignancies in transplant recipients for over three decades and has provided a wealth of information (5). The data in this registry, however, often groups patients with different stages of disease together for the purposes of reporting outcome. It also does not reflect the substantial changes in the treatment of cancer and immunosuppression in recent years.

After the introduction of cyclosporine in 1984 medications used for immunosuppression changed from azathioprine and prednisone to triple therapy with cyclosporine, azathioprine, and prednisone. In 1997, mycophenolate mofetil largely replaced azathioprine. Since 1996 tacrolimus has been increasingly used in place of cyclosporine, and use of sirolimus has become common. Compared to calcineurin inhibitors, patients on sirolimus have a lower incidence of cutaneous squamous cell carcinoma (6). Over the last decade, the newer immunosuppressives decreased the rate of acute rejection but did not increase the incidence of skin cancer, solid tumors and post transplant lymphoproliferative disorder (PTLD) when compared to older agents including cyclosporine and azathioprine-based regimens (7). There are not enough data on these new regimens to determine their effect on tumor recurrence in patients with a history of malignancy.

In the IPTTR, the risk of cancer recurrence was 21% overall in patients with malignancies treated before transplant. Fifty four percent of recurrences occurred in patients treated less than 2 years before transplant, 33% in those treated 2-5 years before transplantation, and 13% among those treated greater than 5 years pre-transplantation (8). This data is used to justify the importance of an adequate wait period between successful treatment of malignancy and transplant in this group of patients. Surprisingly the ANZDATA (Australian and New Zealand Dialysis And Transplantation) registry database reported a recurrence rate of only 5% for cancers other than skin cancer between 1963 and 1999. This drastic difference in recurrence rates could be related to the variation in data collection (9).

Obtaining a detailed patient history including details of presenting stage, pathology of cancer, prognostic factors and treatment received is paramount

in evaluating cancer survivors before organ transplant. Prior guidelines generally recommend patients with a history of malignancy to be tumor free for about 2-5 years before transplantation, depending on the type and stage of the tumor. Active malignancy is a contraindication for renal transplantation. Tumors with high recurrence rates at >5 years of diagnosis pre-transplant according to the Israel Penn tumor registry include: breast cancer, symptomatic renal cell cancer, bladder cancer, sarcomas, non-melanoma skin cancers and myeloma. Those with lower recurrence rates include: thyroid, testicular, incidental renal carcinoma, carcinoma of the cervix and uterus. It is important to note that the most commonly quoted Israel Penn tumor registry data published on risk of cancer recurrence in patients post kidney transplant only included data collected till 2000 and do not reflect many modern advances in cancer therapy. Using this data to predict risk of tumor recurrence will result in overly conservative restriction of kidney transplants. While general guidelines may be developed for specific tumor types, the evaluation of patients with a history malignancy must be individualized. This should be done in close coordination with the patient's oncologist. Below we provide a brief review of the common malignancies as they pertain to kidney transplantation. A table of the existing guidelines is provided. (See table 1).

3. BREAST CANCER

Patients with early breast cancer have an overall 20-30% risk of recurrence (10). Tumor size, nodal involvement, tumor grade, lymphovascular invasion, estrogen receptor (ER) and human epidermal growth factor receptor2 (HER2) status are all independent risk factors for relapse. For this reason, assigning a mandatory duration of cancer free survival to be eligible for transplantation in hormone sensitive breast cancer patients will not improve outcomes. Almost all relapses for triple negative (ER, PR and HER2 negative) and HER2 positive cancers occur within the first 5 years while the ER positive cancers experience continued late relapse between years 5 and 15 (Figure 1) (10). Several factors, such as extensive nodal involvement and inflammatory carcinomas, predict for relapse and should be considered. The 21-gene Oncotype Dx recurrence score accurately predicts the likelihood of distant recurrence in patients with node negative or node positive ER+ and Her2-breast cancers. This information is also useful in determining which patients will benefit from adjuvant chemotherapy (11). Patients with stage I disease have a lower risk of recurrence and should need a shorter wait period (2 years or less). Patients with DCIS (ductal carcinoma *in situ*) may be considered separately as this entity is not an actual carcinoma, and has no implications for mortality risk (12). Given the relapse pattern of hormone positive tumors and the availability of long-term preventive anti hormonal treatments, special consideration should be given to this group of patients.

Table 1. Summary of guidelines and comments

Cancer type	Recurrence rates	Recommended wait period based on prior guidelines	Reason for suggested change in guidelines
Lung cancer	Incidence ratio in dialysis population 0.9- 1.4.	No clear recommendations	-Advances in adjuvant treatment and surgery techniques
RCC	30%	≥2 yrs for tumors ≤ 5cm >5 yrs for tumors >5 cm	- Advances in prognostic models and stratification by histology
Bladder cancer	18-26%	>2 yrs for invasive bladder cancer Shorter for pTa, unifocal or grade 1 disease	- Improved surgical technique - New adjuvant treatment strategies
Breast cancer	5.4.-63.6.%	DCIS and early stage <2 yrs >5 yrs for other successfully treated stages	-Improved survival with better neoadjuvant/adjuvant treatment - Better targeted therapy - Better understanding of pathology
Prostate cancer	18%	a) >2 yrs	- Better understanding of the natural history of early stage disease - More treatment options for advanced disease
Colorectal cancer	12-21%	>5 y stage yrs 2-5 yrs for Duke stage A+B1 disease	- Improved surgery approach - Better neoadjuvant/adjuvant treatment (chemotherapy/radiation)
Melanoma	0-21%	≥2 y thin <1 mm melanoma ≥5 yrs for other successfully treated stages	- More knowledge of prognostic markers - Improved surgical techniques/adjuvant treatment
Non melanomatous skin cancers	48-62%	≥2 yrs	- Use of sirolimus
Lymphoma (NHL/HL)	11%	>2 yrs after successful treatment with curative intent	- Better survival due to advances made in surveillance and staging (PET CT), treatment regimens including immunotherapy

Abbreviations: NHL: Yr: years, cm: centimeters, DCIS: ductal carcinoma in situ, Non Hodgkin's lymphoma, HL: Hodgkin's lymphoma, PET CT: positron emission tomography- computer tomography

Carefully selected patients with stage III and even stage IV disease with a surgically removed single metastatic lesion could still be considered for kidney transplant after a wait period of 5 years. Patients with a high risk of recurrence based on hereditary factors should be evaluated separately.

4. KIDNEY CANCER

Previously renal cell cancers were classified by cell type and growth pattern. Several distinct subtypes of RCC have been identified: clear cell, non- clear cell (chromophobe, papillary type I and II) among others. This classification reflects the morphology, growth pattern, and cell of origin, histochemical and molecular basis of the different subtypes. Prior studies did not report on these different entities separately. They have different pathogenesis, natural history and response to therapy. For instance early stage chromophobe renal cell cancers rarely metastasize with a low 8% risk of disease recurrence (14). Furthermore new prognostic models like the UCLA integrated staging system (UISS) incorporates the ECOG performance status and the Fuhrman's histology grade into the TNM staging to

produce 5 prognostic categories that correlate with post nephrectomy outcome (15). Patients with low risk (LR) have a 5-year recurrence free rate of 90%, intermediated risk (IR) 61% and high risk (HR) 42% (15) (Figure 2). The pathology, prognostic factors and stage of renal cell cancer play an important role in determining which patients with treated kidney cancer are candidates for renal transplant and the advisable wait period after treatment for malignancy to be eligible for kidney transplant.

5. LUNG CANCER

There are limited data available about the recurrence rate of lung cancer after kidney transplant. The incidence of lung cancer in kidney transplant recipients compared to the general population varies in the literature; from less frequent (16) to a hazard ratio of 1.5 (17). There is a clear and more consistent increase in lung cancer risk in lung transplant recipients (17). Although some studies show that screening patients at risk for lung cancer with computed tomography (CT) may be beneficial, this modality has not been studied in transplant patients. Over the years the survival of

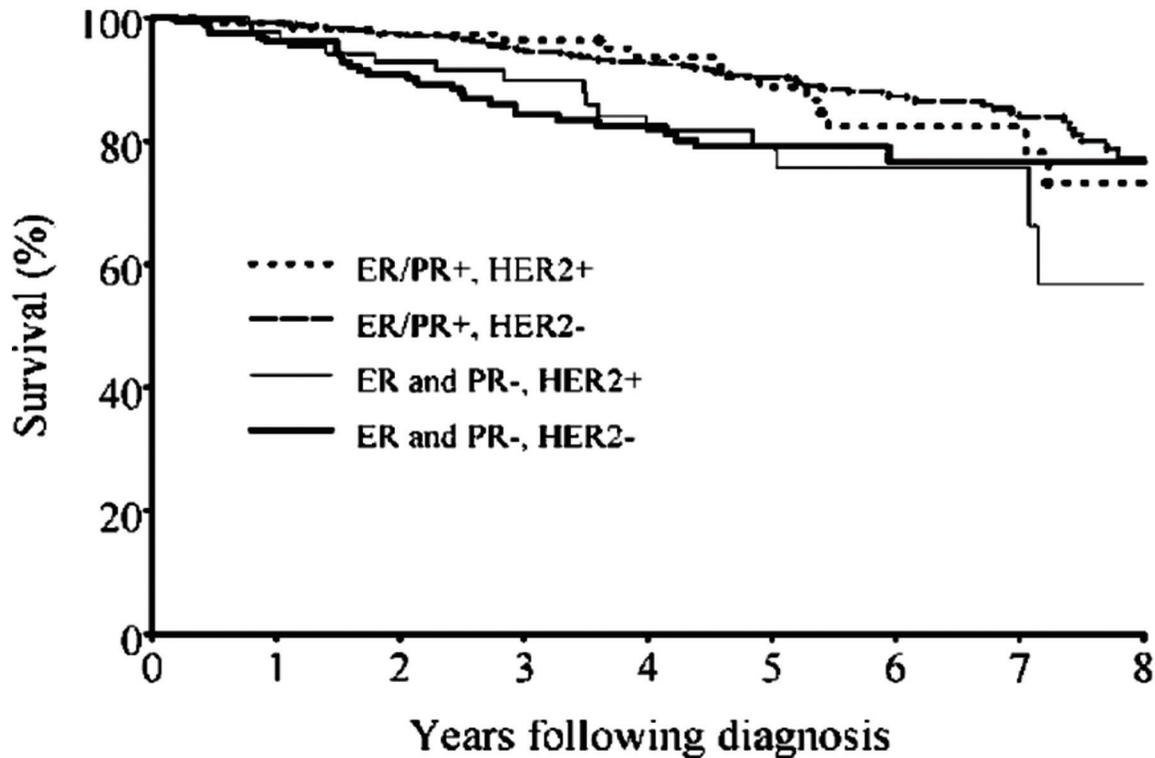


Figure 1. Overall Survival curves for breast cancer subtypes. "Triple negative" (ER-/PR-/Her2-), and Her2+/ER+ subtypes have a poorer clinical prognosis with more early relapses while ER/PR+ subtypes have a better survival but have late relapses. For ER/PR+ patients, the risk of recurrence does not 'plateau'; therefore a finite post-diagnosis moratorium in eligibility for kidney transplant is not consistent with the natural history of this disease. For the triple negative group, there are few relapses after 5 years, suggesting that this may be an appropriate waiting period for this subgroup. Reproduced with permission from, Marschfield Clinic.

patients with lung cancer has improved with a 5-year survival of pathological stage IA disease of ~73% and 13% for stage IV disease (18). With recent advances in both surgical and medical therapy for lung cancer, and with the increasing use of CT imaging for screening, the number of survivors of early-stage lung cancer will likely increase. In a retrospective study of 1294 patients with stage I-II lung cancer by Lou *et al*, the risk of recurrence during the first 4 years after surgery ranged from 6% to 10% per person-year but decreased thereafter to 2%. Furthermore, the risk of second primary lung cancer ranged from 3% to 6% per person-year and did not diminish over time. (Figure 3) The majority of these patients had stage IA adenocarcinoma (19).

6. BLADDER CANCER

Patients in the IPTTR with a history of successfully treated invasive bladder cancer had a recurrence rate of 29 % (20). Most recurrences occurred in patients who underwent transplant less than 2 years after cancer treatment. Patients with superficial cancer (stage 0-I) have a significant risk of local recurrence with a lower risk of invasive/metastatic disease. Patients with carcinoma in-situ have a 5-years survival of 96.4% based on SEER (Surveillance, Epidemiology, and End

Results) database 2003-2009. Patients with carcinoma *in situ* do not require a waiting period prior to transplant. Among patients with muscle invasive pT2 disease the 10-year recurrence-free and overall survival rates were 72% and 47%, respectively after treatment with radical cystectomy (21).

7. MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS

Multiple myeloma is not currently considered a curable disease, so it is not surprising that relapse rates after kidney transplantation are high. Attempts have been made to treat these patients aggressively including combined kidney/bone marrow transplants to induce mixed chimerism and spare immunosuppression (22). Monoclonal gammopathy of undetermined significance (MGUS) is a precursor to multiple myeloma and is prevalent in the population. Progress has been made in identifying MGUS patients at high risk for progression; these factors may be useful when weighing the benefits of kidney transplantation. (23). Because plasma cell dyscrasias cause kidney damage from multiple mechanisms, patients with less malignant forms of plasma cell dyscrasias, such as AL amyloidosis, are often considered for kidney transplantation.

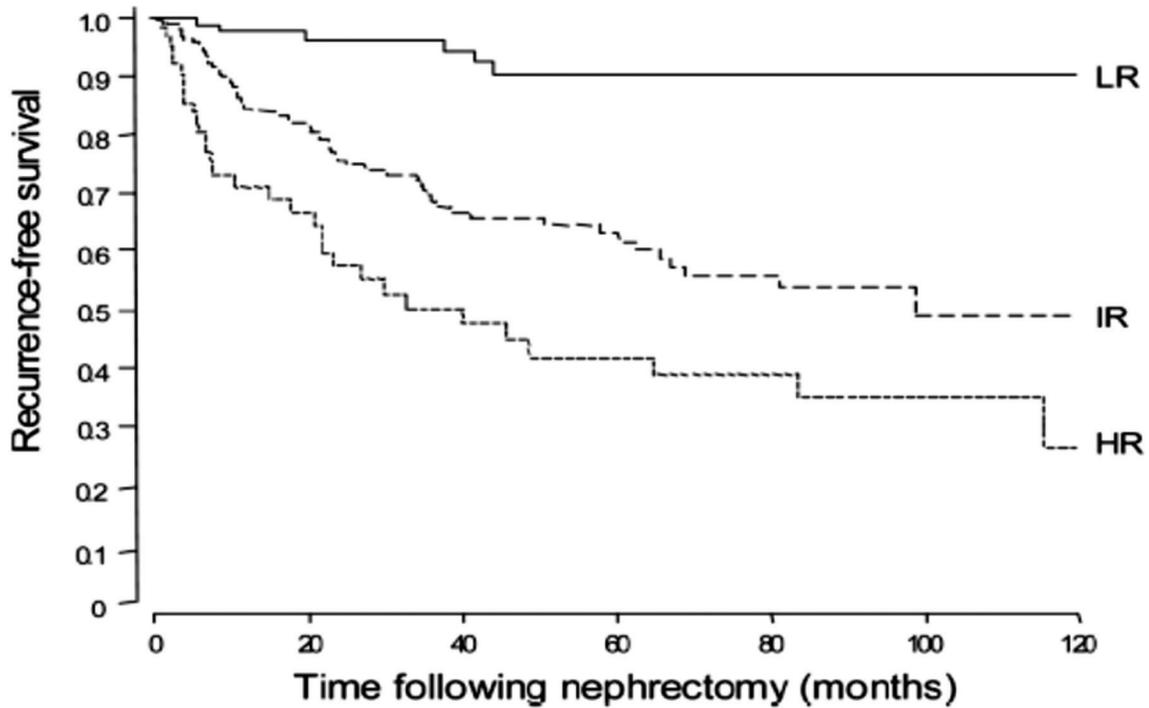


Figure 2. Kaplan-Meier estimates of recurrence-free survival following nephrectomy among UISS risk groups. The low risk group has superb disease free survival and immediate kidney transplant eligibility may be reasonable. Recurrences in this group are rare and tend to occur in the first 40 months. The IR and HR groups continue to have recurrence 100 months after. Reproduced with permission from Elsevier health science journal. (GB 494 6272 12).

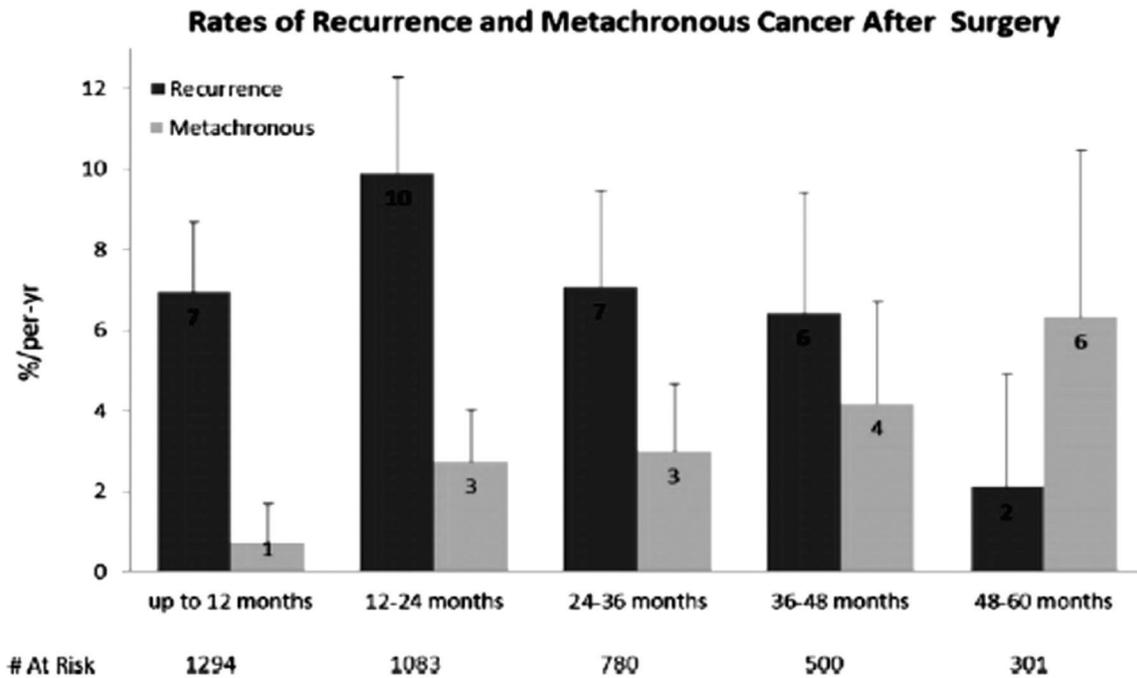


Figure 3. Hazard rates of lung cancer after resection over time decreases for recurrences and increases for metachronous types (ie second primary lung cancers). Reproduced with permission from MOSBY INC (Reference number 1097-685X).

8. LYMPHOMAS

Hodgkin lymphoma (HL) is often seen in younger patients and is highly curable even at an advanced stage. Relapse 3-5 years after treatment is unlikely and effective salvage regimens are available. Non-Hodgkin Lymphoma (NHL) is an umbrella term for a large number of distinct lymphomas, each with a specific natural history. Grouping lymphomas together for the purpose of reporting relapse rates is of limited utility. Trofe *et al* in a retrospective review of U.S. patients between 1968 and 2001 with a history of HL or NHL before solid-organ transplant had a recurrence incidence of 9% for HL and 11% for NHL (24). Aggressive lymphomas, most notably diffuse large B cell lymphoma (DLBCL) are treated with intent to cure using multi-agent chemoimmunotherapy. Expected long-term survival can be predicted using patient characteristics at the time of diagnosis. The revised IPI (international prognostic index) score remains one of the most reliable tools in predicting patient outcomes (25). Patients at high risk for relapse should be observed for several years before being considered for kidney transplant, while it may be reasonable to transplant patients with favorable disease at an earlier time point.

Indolent lymphomas, such as follicular lymphoma, are cancers with a long natural history. These cancers typically present with diffuse disease at the time of diagnosis. While these cancers are typically considered incurable without allogeneic stem cell transplant, their indolent nature often allows for long periods of observation without requiring therapy. Treatment in the form of gentle chemo immunotherapy is effective at shrinking the tumor and alleviating symptoms, typically allowing for another long period of observation. There are no studies describing the outcome of kidney transplant in patients with indolent lymphoma. Prognostic indices for patients with indolent lymphoma can be helpful. The FLIPI2 (Follicular lymphoma international index) score incorporates clinical and pathological features to predict OS, PFS and risk of disease progression (26).

9. PROSTATE CANCERS

With advances made in precision of radiation, hormone and chemotherapy some experts predict that prostate cancer would become a chronic disease even at an advance stage. A high proportion of patients are now treated with active surveillance as many of these patients have indolent disease and never require treatment for their cancer. Additionally, recent studies suggest no overall survival benefit with radical prostatectomy (27). Patients with advanced disease, although incurable, have much longer life expectancies with the variety of new agents. Most patients with localized disease can still be considered eligible for kidney transplant.

10. COLORECTAL CANCER

Chapman *et al* followed 23 renal transplant patients previously treated for colorectal cancer for 7 years, with no reported recurrences (9). This result is contrary to the IPTTR data which reported higher recurrence rates. Over the past few years new targeted therapies have been developed for advanced colorectal cancer. Substantial progress has been made in the treatment of advanced disease and in a small proportion of patients there is a possibility of curing stage IV disease after single metastectomy. Chemoprevention in patients at risk for colorectal cancer is being studied. COX-2 inhibitors and aspirin have shown promising effects in reducing recurrence and incidence of adenomas (28). The addition of oxaliplatin to 5FU leucovorin significantly improved 5-year DFS and 6-year OS in the adjuvant treatment of stage II or III colon cancer (29).

11. MELANOMA

The published data for melanoma in immunocompromised hosts is limited to small single institution studies and retrospective reviews. Beginning with the smaller studies, the IPTTR reported a 21% recurrence rate for melanoma in 29 melanoma patients who had also received a kidney transplant, resulting in 100% mortality in these patients (20). In a retrospective review of 638 patients who underwent solid organ transplantation, there were 59 patients with an antecedent diagnosis of melanoma. None of these patients developed a melanoma recurrence (30). In a retrospective European multicenter study of 100 organ transplant recipients with melanoma, 91 were diagnosed after transplant and 9 before. The overall 2-, 5-, and 10-year survivals were 77%, 54.2%, and 40.6%, respectively, compared with 95.6 %, 82.1 %, and 75.2 % (P= 0.0019) in controls matched for age-, sex-, tumor thickness-, and ulceration using the American Joint Committee on Cancer (AJCC) melanoma database. In a subset analysis, outcomes were not significantly different among the T1 and T2 (≤ 2 mm) post transplant melanoma patients compared with the AJCC control subjects (see figure 1). On the other hand, the patients with melanoma thicker than 2 mm (T3 and T4) had a significantly worse overall survival. Among the 9 organ transplant recipients with melanoma diagnosed pretransplant, the median period between melanoma diagnosis and transplant was 7.8 years and none subsequently recurred or died from melanoma with mean follow up of 5 years (31). Patients with thin primary melanomas (<1mm) can undergo subsequent transplantation since the vast majority of these patients were cured at time of surgery. A high mitotic index or ulceration could portend future recurrence in a small subset of thin melanomas which should be grouped with intermediate and thick primaries

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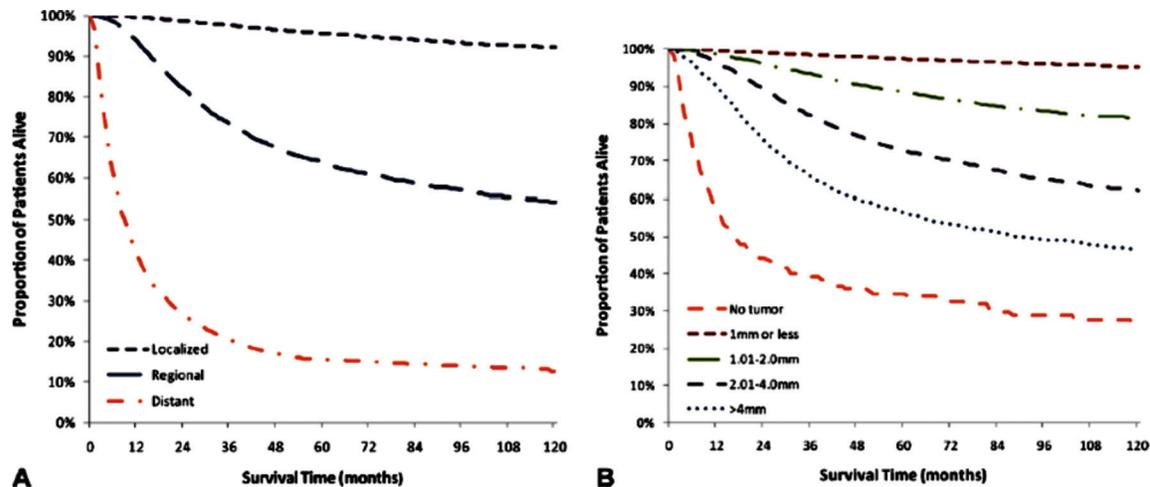


Figure 4. The disease free survival for regional and distant disease decreases rapidly until year 3 then stabilizes from year 5. The deeper the invasion by melanoma, the worse the survival. Reproduced with permission from Elsevier health science journal (32).

with higher probability of recurrence. The Matin study provided the strongest evidence that transplantation can adversely impact prognosis in patients destined to recur from their melanoma, presumably as a result of immunosuppression. It is important to educate survivors of melanoma about the need for close follow up and avoidance of high-risk behaviors. Although there have been impressive advances made in treatment of advanced melanoma (targeting MAPK/ERK pathway and immunomodulatory agents) these agents are still being studied in patients with early stage disease to prevent recurrence. Melanoma survival curves below. (Figure 4)

12. NON-MELANOMA SKIN CANCERS

Organ transplant recipients have an increased risk of NMSC. The incidence rates increase from 10-27% at 10 years post transplant to 40-60% twenty years after (33). Renal transplant recipients have a high rate of recurrence of skin cancers 48-62% with low mortality (5). Most recurrences occur with waiting periods of less than 2 years. The overall prognosis for patients with a primary cutaneous SCC is excellent, with an overall five-year cure rate of greater than 90 percent (34). Patients with basal cell cancers do not require any waiting period after removal of the lesion. Organ transplant patients need close follow up with dermatology for skin exams. Ottley *et al* reported a decrease in cutaneous carcinogenesis after the reduction of immunosuppression (35). The effect of decreased immunosuppression on skin cancer recurrence post transplant in patients with history of cutaneous malignancy has not been studied. In a study involving kidney-transplant recipients with at least one previous cutaneous squamous-cell carcinoma Euvrard *et al* showed that switching from calcineurin inhibitors to sirolimus was associated with a lower risk of subsequent skin cancers (6).

13. CONCLUSIONS

In this review we wish to highlight the importance of an individualized approach in determining which patients with a history of malignancy should be considered for kidney transplant. Existing guidelines do not reflect recent changes in screening, treatment and prevention of malignancy. The oncologist and the transplant team should work closely to formulate a plan appropriate for each specific patient. The pre-transplant evaluation of these patients should include a careful review of initial staging, recent surveillance, expected timing of possible relapse, prognostic factors, relapse pattern of the type of malignancy, tumor markers and pertinent details of the pathology. The IPTTR consultation service is a great resource which should be incorporated in deciding which patients with a history of malignancy are eligible for kidney transplant.

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- Abbreviations:** NHL: Yr: Years, cm: centimeters, DCIS: ductal carcinoma in situ, Non Hodgkin's lymphoma, HL: Hodgkin's lymphoma, PET CT: positron emission tomography- computer tomography

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