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# Tumor Recurrence and Graft Survival in Renal Transplant Recipients with a History of Pretransplant Malignancy: A Matched Pair Analysis

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- J. Clin. Med. J. Clin. Med. **2021**, 10, 2349 **2021**, 10, 2349

# Introduction

- RTx offers superior medical outcomes :
- improved survival
- enhanced quality of life.

- Critical risk balancing between RRT and RTx is mandatory
- One of the few but well-defined contraindications
- for RTx is the presence of active or past malignancy.
- With a few exceptions like :
- NMSC ,small renal incidentaloma.

- Pre-transplant malignancy has been considered a relative contraindication of transplantation until a disease specific minimum remission time has been achieved.

- PTM is a risk factor for occurance of post transplant malignancies.(1)

- Data report an overall incidence of post-transplant recurrence of up to 21.5% in PTM recipients.(2)

1.J. Am. Coll. Surg. **2019**, 229, 568–579

2.Transplantation **2018**, 102, 1156–1164

- In an aging society, including RTx-recipients, incidence of cancer increases.

- Currently,7.0% of all solid organ transplant (SOT) recipients in population-based studies have a PTM.(3)

- Among renal Tx recipients cancer is the second most common cause of death.(4)

3.Transplantation **2018**, 102, 1156–1164
4.Kidney Int. **2020**, 20, 31256–31257

# Material and Methods :

- Study Design :
- A retrospective single center study
- A double case control matched pair analysis
- follow-up period of 60 months after transplantation

- Donor and recipient data were extracted from Eurotransplant Network Information System (ENIS),
- in-house transplant data files and patient charts

# Study Population

- The initial screening included all RTx recipients
- between 1 January 2000 and 31 July 2012,
- with a five-year follow-up ending on 1 July 2017.
- **Exclusion Criteria :**
- *recipient age < 18*
- recipients with a *previous history of transplantation* of any kind.

- RTx recipients with a history of PTM were matched 1:1 in a case control matched Pair analysis to
- corresponding recipients without PTM.

- The data compared in terms of incidence of recurrence and de-novo as well as secondary de-novo malignancy.
- .Matching criteria were:
- age, sex, and duration of immunosuppressive therapy.
- Matching criteria in the second matched pair analysis
: age, sex and underlying cause of ESRD.

# Baseline characteristics of recipients with a history of pretransplant malignancy

| PTM-RTx ($n$ = 65) | | |
|---|---|---|
| Age at PTM diagnosis (mean ± SD) | | 53.5 ± 10.9 |
| Sex (% males) | | 55.4 |
| Age at RTx (mean ± SD) | | 62.6 ± 8.6 |
| Time between PTM and RTx (months, mean ± SD (min–max)) | | 105.6 ± 78.1 (6, 468) |
| Time on RRT (months, mean ± SD) | | 60.6 ± 31.7 |
| PTM during RRT ($n$, %) | | 21, 32.3% |
| PTM before start of RRT ($n$, %) | | 44, 67.7% |
| PTM ($n$, %) | | Time between PTM and RTx (months, mean ± SD, (min–max)) |
| Skin | 13 (20.0) | 76.9 ± 62.4 (9, 169) |
| Urothelial cell | 10 (15.4) | 133.2 ± 129.9 (27, 468) |
| Gynecologic | 7 (10.8) | 178.6 ± 87.6 (34, 301) |
| Kidney | 7 (10.8) | 96.7 ± 31.9 (64, 148) |
| Gastrointestinal | 6 (9.2) | 100.8 ± 62.9 (50, 206) |
| Prostate | 6 (9.2) | 68.7 ± 17.0 (48, 97) |
| Thyroid | 6 (9.2) | 63.7 ± 55.0 (6, 155) |
| Breast | 5 (7.7) | 136.4 ± 50.6 (101, 225) |
| Head & Neck | 2 (3.1) | 109.5 ± 36.1 (84, 135) |
| Lung | 1 (1.5) | 78.0 |
| Hematologic | 1 (1.5) | 129.0 |
| Neuroendocrine | 1 (1.5) | 33.0 |

# Outcome Measures

- Primary outcome for the first matched pair analysis was incidence of post-transplant malignancy
- (de-novo, second de-novo and recurrence).

- Primary outcome for the second matched paired analysis was 5-year-graft and -patient survival.
- Secondary outcome parameters :
- Frequencies of : DGF ,PNF,BPAR within 1 year after TX ,1&5 year Cr and eGFR

# Statistical Analysis

- Normally distributed continuous variables are presented as mean standard deviation(SD) .
- Groups were compared utilizing the student's t-test.
- For continuous variables which are not normally distributed, median an quartiles (interquartile range, IQR, Q0.25–Q0.75) are given.
- A comparison between groups was performed with the Mann-Whitney test.
- . For categorical variables, the Fisher's exact test was used.
- One and five-year patient survival, death-censored graft and overall graf survival were estimated by Kaplan-Meier methodology compared using log-rank tests.

# Statistical Analysis

- p-values 0.05were considered statistically noticeable.
- Cox proportional hazards regression models with univariable and multivariable logistic regression analyses of matched cohorts
- were used to determine independent factors influencing patient, death-censored, and overall graft survival after 5 years.
- .

- Univariable analysis included PTM, recipient age, recipient sex, cold ischemia time, warm ischemia
- time, dialysis vintage, cause of ESRD and number of HLA-mismatches.
- To adjust for multiple variables, a stepwise forward variable selection procedure (including
- variables with p-value less than 0.05 in the likelihood ratio test) was performed for the final
- multivariable model.

# Results

- **Results**
- Between 1 January 2000 and 31 July 2012, 1217 patients received a RTx at our center.
- A total of 838 RTx patients met the inclusion
- criteria and were included in further analysis.
- Of these, 65 (8.0%) patients had a history of PTM.
- Most PTM were detected and treated in TNM-stage T1 (n=17).

- Only one patient was diagnosed with a TNM-stage T4 prostate cancer pre transplantation.
- Majority of malignancy had been diagnosed
- pre RRT (44 before (67.7%); 21 during (32.3%) RRT.

- Induction therapy was given in 54 (83.1%) cases
- (51 times basiliximab, three times thymoglobuline).

- In the matched cohorts without history of PTM
- , induction therapy was given to 54 (83.1%) and
- 55 (83.3) patients, respectively.

Table 3. Baseline donor characteristics for renal transplantation recipients with and without a pretransplant malignancy, matched by age, sex and underlying end stage renal disease.

| | PTM-RTx ($n$ = 65) | RTx ($n$ = 65) | $p$-Value |
|---|---|---|---|
| Deceased donor ($n$, %) | 58 (89.2) | 61 (93.8) | 0.508 [b] |
| Living donor ($n$, %) | 7 (10.8) | 4 (6.2) | 0.461 [b] |
| ABOi ($n$) | 2.0 | 2.0 | 1.00 [b] |
| ESP ($n$, %) | 25 (38.5) | 28 (43.1) | 0.648 [b] |
| Donor age (median, IQR) | 65 (52.5, 71.5) | 64 (52, 70.5) | 0.483 [c] |
| Donor BMI (median, IQR) | 26.2 (24.2, 27.9) | 27.6 (29, 42.1) | 0.927 [c] |
| Donor sex (male, $n$, %) | 28 (43.1) | 39 (60.0) | 0.091 [b] |
| Donor creatinine (median, IQR) | 1 (0.7, 1.3) | 0.9 (0.6, 1.5) | 0.772 [c] |
| KDRI (mean ± SD) | 1.5 ± 0.6 | 1.4 ± 0.5 | 0.546 [a] |
| KDPI (mean ± SD) | 76.8 ± 25.6 | 72.3 ± 27.5 | 0.352 [a] |
| CIT (h) (mean ± SD) | 10 ± 5.0 | 9.8 ± 4.6 | 0.572 [a] |
| WIT (min) (mean ± SD) | 31.8 ± 7.4 | 33.2 ± 7.0 | 0.311 [a] |
| HLA mismatch (mean ± SD) | 3.3 ± 1.6 | 3.2 ± 1.6 | 0.746 [a] |
| HLA-A mismatch (% 0/1/2) | 30.8/53.8/15.4 | 26.2/52.3/21.5 | 0.364 [b] |
| HLA-B mismatch (% 0/1/2) | 13.8/41.5/44.6 | 20/43.1/36.9 | 0.249 [b] |
| HLA-DR mismatch (% 0/1/2) | 23.1/41.5/35.4 | 23.1/50.8/26.2 | 0.429 [b] |

- Results are shown as HR with 95% confidence interval (CI) and p-value of likelihood ratio test

**Table 2.** Oncological outcome for renal transplantation recipients with and without a pretransplant malignancy, matched by age, sex and duration of immunosuppressive therapy.

| | PTM-RTx ($n$ = 65) | RTx ($n$ = 65) | $p$-Value |
|---|---|---|---|
| Post-transplant malignancy ($n$, %) | | | |
| De-novo malignancies | - | 9 (13.9%) | |
| Second de-novo malignancies | 13 (20) | - | |
| Recurrence | 3 (4.6) | - | 0.143 [b] |
| No malignancy | 49 (75.4) | 56 (86.2%) | |
| RTx to post-transplant malignancy (d, mean ± SD) | 973.7 ± 452.4 | 884.2 ± 496.8 | 0.285 [a] |
| RTx to post-transplant tumor recurrence (d, mean ± SD) | 1038 ± 370.9 | - | |
| PNF ($n$, %) | 4 (6.2) | 2 (3.2) | 0.678 [b] |
| DGF ($n$, %) | 15 (23.1) | 12 (18.5) | 0.664 [b] |
| ≥1 BPAR within 1 year after RTx (%) | 7 (10.8) | 6 (9.2) | 1.000 [b] |
| 1-year eGFR (CKD-EPI, mL/min/1.73 $m^2$, mean ± SD) | 43.9 ± 19.4 | 50.5 ± 18.5 | 0.078 [a] |
| 5-year eGFR (CKD-EPI, mL/min/1.73 $m^2$, mean ± SD) | 45.8 ± 19.2 | 46.5 ±19.2 | 0.791 [a] |
| Graft loss within 1 year after RTx ($n$, %, DC) | 9 (13.8) | 7 (10.8) | 0.688 [c] |
| Graft loss within 5 years after RTx ($n$, %, DC) | 15 (23.1) | 9 (13.8) | 0.146 [c] |

**Table 4.** Baseline recipient characteristics stratified PTM-RTx or RTx, matched by age, sex and underlying end stage renal disease.

| | PTM-RTx ($n$ = 65) | RTx ($n$ = 65) | $p$-Value |
|---|---|---|---|
| Age (mean ± SD) | 62.5 ± 8.6 | 61.9 ± 8.6 | 0.156 [a] |
| Sex (% males) | 36 (55.4) | 38 (58.5) | 0.500 [b] |
| BMI (kg/m$^2$, mean ± SD) | 25.4 ± 3.3 | 26.9 ± 3.8 | 0.029 [a] |
| RRT ($n$, % yes) | 64 (98.5) | 64 (98.5) | 1.000 [b] |
| Dialysis vintage (d, mean ± SD) | 1841.9 ± 962.4 | 2007 ± 1093.4 | 0.329 [a] |
| Hypertension ($n$, %) | 59 (90.8) | 56 (86.2) | 0.508 [b] |
| Diabetes ($n$, %) | 11 (16.9) | 10 (15.4) | 1.000 [b] |
| CAD ($n$, %) | 18 (27.7) | 22 (33.8) | 0.541 [b] |
| PNF ($n$, %) | 4 (6.2) | 2 (3.1) | 0.688 [b] |
| DGF ($n$, %) | 15 (23.1) | 13 (20.0) | 0.839 [b] |
| ≥1 BPAR within 1 year after RTx (%) | 7 (10.8) | 8 (12.3) | 1.000 [b] |
| 1-year eGFR (CKD-EPI, mL/min/1.73 m$^2$, mean ± SD) | 43.9 ± 19.4 | 47.2 ± 16.5 | 0.286 [a] |
| 5-year eGFR (CKD-EPI, mL/min/1.73 m$^2$, mean ± SD) | 45.8 ± 19.2 | 45.4 ± 16.6 | 0.446 [a] |
| Graft loss within 1 year after RTx (%) DC | 9 (13.8%) | 2 (3.1) | 0.039 [c] |
| Graft loss within 5 years after RTx (%) DC | 15 (23.1%) | 4 (6.2) | 0.003 [c] |
| Post-transplant malignancy ($n$, %) | | | |
| De-novo malignancies | - | 11 (16.9) | |
| Second de-novo malignancies | 13 (24.6) | - | |
| Recurrence | 3 (4.6) | - | 0.383 [b] |
| No malignancy | 49 (75.4) | 54 (83.1) | |
| RTx to post-transplant malignancy (days, mean ± SD) | 973.7 ± 452.4 | 1058.9 ± 566.4 | 0.593 [a] |

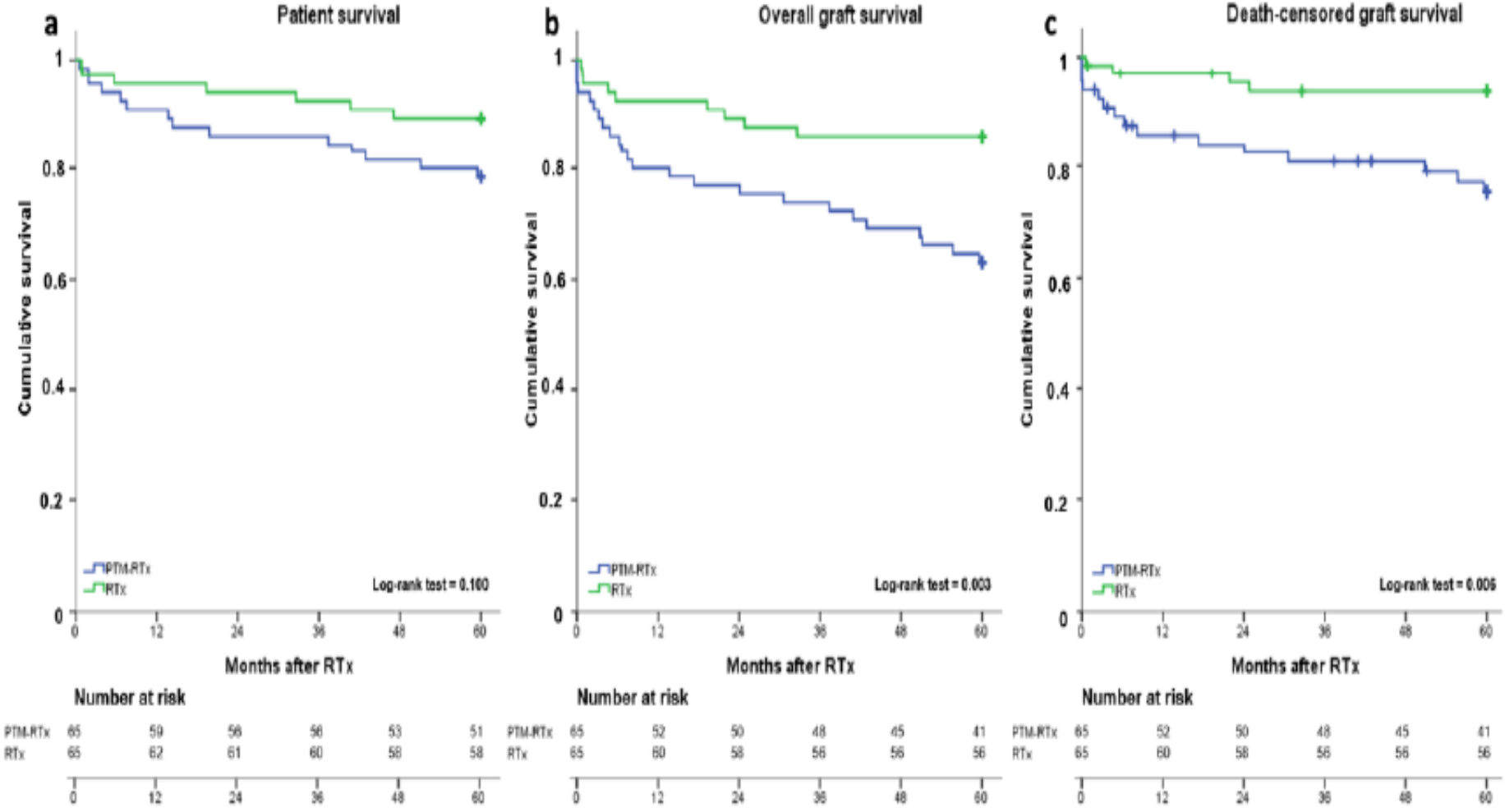
Results are presented as mean ± standard deviation (SD) or relative frequencies. Categorical variables were compared using Fisher's exact

Table 5. Cox proportional hazards regression model with logistic regression analysis of five-year death censored and overall graft survival.

| | Death-Censored Graft Survival | Overall Graft Survival |
|---|---|---|
| Independent Variables | HR (95% CI) *p*-Value | HR (95% CI) *p*-Value |
| PTM (yes vs. no) | 4.198 (1.392–12.657) 0.011 | 2.997 (1.393–6.541) 0.005 |
| Recipient age (years) | 1.060 (0.995–1.130) 0.072 | 1.061 (1.011–1.114) 0.016 |
| Recipient sex (male vs. female) | 0.878 (0.357–2.162) 0.778 | 1.078 (0.541–2.151) 0.830 |
| Cold ischemia time (hours) | 1.049 (0.963–1.143) 0.273 | 1.046 (0.980–1.116) 0.176 |
| Warm ischemia time (minutes) | 1.037 (0.973–1.106) 0.266 | 1.059 (1.009–1.111) 0.021 |
| Dialysis vintage (days) | 1.000 (0.999–1.000) 0.378 | 1.000 (0.999–1.000) 0.223 |
| Cause of ESRD | 0.752 (0.603–0.937) 0.011 | 0.846 (0.728–0.983) 0.029 |
| HLA mismatch | 1.023 (0.776–1.349) 0.872 | 1.041 (0.844–1.285) 0.707 |

HR = hazard ratios, CI = 95% confidence interval. PTM = pre-transplantation malignancy, ESRD = end stage renal disease, HLA = human leukocyte antigen.

- Unadjusted Cox proportional Hazard modeling showed that PTM-RTx patients had a 4.198 (1.392–12.657 95% CI) hazard of death-censored graft loss
- and a 2.997 (1.393–6.541 95% CI) hazard of overall
- graft loss.
- Multivariate Cox regression models adjusted for potential confounders revealed that PTM was still associated with an
- inferior death-censored (HR: 4.535, 95% CI: 1.503–13.680 and p-value = 0.007) as well as overall graft survival (HR: 3.233
- , 95% CI: 1.499–6.973 and p-value = 0.003).




igure 2. Kaplan-Meier curves for five-year patient and graft survival. Longitudinal patient (a), overall graft (b) an
eath-censored graft survival (c) stratified for pretransplant malignancy (PTM) renal transplantation (RTx)-recipients an
Tx-recipients, respectively. Survival rates of RTx-(green lines) and PTM-RTx-recipients (blue lines) were estimated b
aplan-Meier methodology and compared by log-rank test.

# Discussion

- This is the first study to analyze oncological, patient and particularly graft specific outcome in a PTM- TX cohort using a case control matched pair analysis.

- In comparison to the general population, RTx-recipients who suffer from cancer are reported
- to have impaired outcomes. (3,4)


- 3 - J. Am. Coll. Surg. **2019**, 229, 568–579
- 4 - Transplantation **2010**, 90, 1542–1546

- Higher cancer incidence and an increased
- cancer-specific mortality hold true for patients undergoing RRT.(5)

- Cincinnati Tumor Transplant Registry (CTTR)
- , reports recurrence rates of up to 21.0%
- and the development of secondary malignancy in approximately 33.0% of PTM.(6)

5-J. Am. Soc. Nephrol. **2019**.
6-Transplantation **2018**, 102, 1156–1164.

- The current study identified PTM-recurrence
- in three (4.0%) cases, reporting recurrence rates as low as demonstrated by others.

- Possible explanations for the presented difference might be based on varying waiting and follow-up times.

- Battstrom et al, estimated a recurrence rate of 9.4%,
- which is closer to the presented results here.(7)

Transplantation **2013**, 96, 297–305.

- In general, era-dependent refinements in induction
- and maintenance of immunosuppressive therapy could also play a role.

- Differences in tumor recurrence or development of de novo malignancy were not attributable to the use of induction therapy.

- Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement. Am. J. Transplant. **2021**, 21, 460–474.

- The low recurrence rates reported here are also influenced by a comparably small cohort as well
- as relatively short follow-up of five years in combination with a rather strict comply with minimum waiting time to RTx in PTM recipients.

- This study provides further evidence for inferior survival rates in PTM-RTx recipients by reporting worse 5 year overall patient survival.
- Survival rates in Rtx cohort are comparable to larger cohorts.
- This study showed worse outcomes in terms of cancer mortality , all-cause mortality and outcome of post –transplant de novo malignancies in PTM-RTx recipients.

- Brattström et al. identified an **increased rate of death** in PTM-RTx recipients , mainly attributable to **cancer**.(8)
- Acuna et al. further confirmed this trend
- , indicating that PTM-patients had worse overall survival.(9)
- (UNOS) data, Livingston-Rosanoff et al. as well found **inferior long-term outcome in PTM-RTx**
- Recipients.(10)

8-Transplantation **2013**, 96, 297–305
9-JAMA Oncol. **2016**, 2, 463–46903, 581–587
10-J. Am. Coll. Surg. **2019**, 229, 568–579.

- In accordance with our data, Livingstone-rosanoff et al, found increased rates of graft loss and decreased
- overall survival among analyzed US patients with PTM.
- Our data provides evidence of inferior graft survival in PTM-RTx recipients, advocating careful graft
- surveillance and immunological management in PTM-RTx recipients.

- Brattström et al. recommend an adaption of waiting times to tumor aggressiveness in RTx-recipients .

- waiting times >5 years after diagnosis of cancer as the risk of cancer-associated death in their PTM
- patients decreased with a longer waiting time.

- Kaufmann et al.,confirmed these results too.(11)

- Unterrainer et al., looking at global data from 243 transplant centers, **could not find** an increased incidence or recurrence of malignancy after different lengths of follow-up.(12)

- Cancer mortality seems to increase in PTM patients, especially during the first years after diagnosis, and there seems to be
- a link between aggressiveness of PTM and outcome.

11-Transpl. Int. **2006**, 19, 607–620.
12-Transplantation **2019**, 103, 581–587.

- Dahle et al,showed similar graft survival with **waiting time of only one year** and advocated for shorter
- waiting times in order to overcome increased morbidity and mortality during RRT, even though this
- might be in expense of higher cancer-associated
- mortality.
- 1963-2010-n=5867Tx-PTM:337-40-43% autoimmune disease- less than6-10% diabetes.

13-Transplantation **2017**,101, 2599–2605.

- The current study provides evidence of inferior one- and five-year overall and death-censored graft survival for PTM RTx-recipients.
- **No noticeable difference regarding baseline donor characteristics(including KDPI and KDRI) or HLA-**
- **Mismatches**.
- Subtle impairment of recipients caused by previous cancer-specific treatment in combination with the impact of RRT and waiting time.

- However, **waiting times did not differ noticeably between the two cohorts, even though they were**
- **slightly longer for PTM-RTx-recipients**.

- There is potential bias among physicians concerning a restraint against higher immunosuppressive
- regimes in PTM-RTx patients.

- However, data on induction and maintenance regimes revealed no differences.

- In addition, the relatively small number of 65 patients per group involves an inherent bias when conducting sub-analysis.

- The underlying mechanisms for the observed differences remain insufficiently understood.

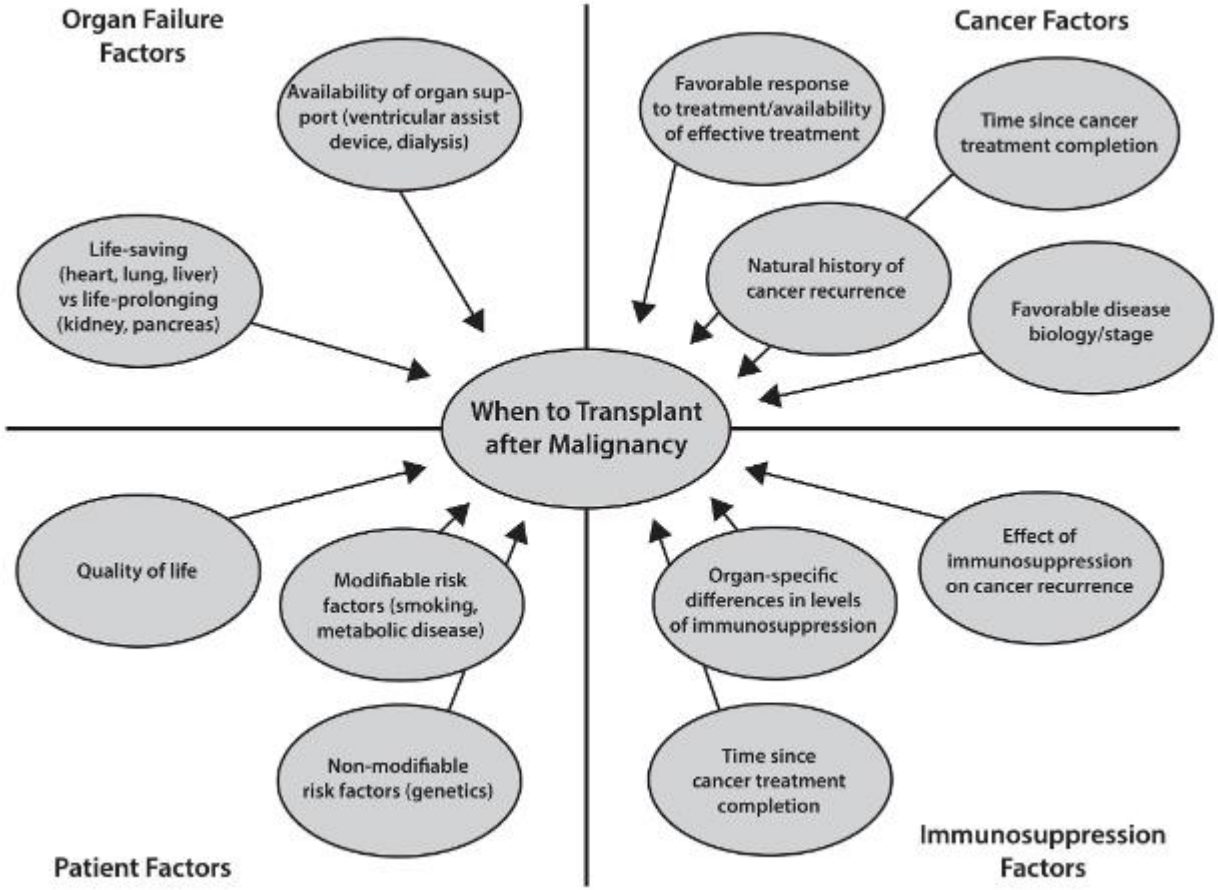



**Figure 1.**
Potential factors to Consider When Evaluating a Patient with a PTM for Transplantation.

Am. J. Transplant**2021**, 21, 460–474**.**

Recommended wait time for SOT candidates with a prior history of breast cancer.

| Risk/Stage | 5-year Disease Specific Survival[18,19] | Time Interval to Transplant | Additional Considerations |
|---|---|---|---|
| **LOW RISK**<br>DCIS<br>Stage I | 97–99% | No wait time necessary * | -Hormone receptor negative disease may have a slightly higher risk of recurrence in the first 2–3 years |
| **INTERMEDIATE RISK**<br>Stage II | 90–99% | **1–2 years**<br>NED * | -Hormone receptor negative disease may have a slightly higher risk of recurrence in the first 2–3 years |
| **HIGH RISK**<br>Stage III | 66–97% | **3–5 years**<br>NED * | -Hormone receptor negative disease may have a slightly higher risk of recurrence in the first 2–3 years<br>-Inflammatory breast cancer likely has a higher risk of recurrence and worse survival |
| **PROHIBITIVE RISK**<br>Stage IV | 32–38% | Not a SOT candidate | |

* After completion of all standard treatments. Endocrine therapy does not need to be completed prior to transplant, as this is an oral medication that is fairly well tolerated with few serious side effects and often continues for 5–10 years.

Standard oncologic treatments are based on those recommended in the NCCN (National Comprehensive Cancer Network) Breast Cancer guidelines (www.nccn.org). Breast cancer stages are based on the *prognostic stage groups* specified in the AJCC's Staging Manual, 8th edition. Anatomic stage groups are not necessarily equivalent to the corresponding prognostic stage groups and should not be applied here. DCIS: ductal carcinoma *in situ*, NED: no evidence of disease

Am. J. Transplant**2021**, 21, 460–474

Recommended wait time for SOT candidates with a prior history of rectal cancer.

| Risk/Stage | Recurrence Free Survival 5-year[41,46] | Time Interval to Transplant | Additional Considerations |
|---|---|---|---|
| **LOW RISK**<br>Stage I<br>(T1 or T2, N0, M0)<br>Full oncologic resection | 85%–88% | 1 year, consider 2 years if high-risk features present | *Low risk features:*<br>- MSI without BRAF mutation<br>- Upper 1/3 rectum or rectosigmoid<br>*High risk features:*<br>- LVI or PNI<br>- Mucinous or Signet Histology<br>- Poorly differentiated histology<br>- Bowel obstruction<br>- Tumor perforation<br>- <12 lymph nodes examined<br>- Lower 1/3 of rectum<br>- Incomplete mesorectal excision<br>*Tumor deposits considered as N+ disease<br>*Patients with stage II & III disease should complete trimodaility treatment (chemoradiotherapy, surgery and chemotherapy) unless elimination of one of these is deemed appropriate after multidisciplinary discussion<br>*For patients who have undergone preoperative radiotherapy, response to treatment is highly prognostic. Complete and nearly complete responders have much lower risk for recurrence than those with poor response |
| **LOW INTERMEDIATE RISK**<br>Stage I<br>(T1, N0, M0)<br>Local Excision | 78%–88% | 2 years | |
| **HIGH INTERMEDIATE RISK**<br>Stage II<br>(T3 or T4, N0, M0)<br>Stage III<br>(Any T, N+, M0) | 70% | 3 years, 5 years if high-risk features present | |
| **HIGH RISK**<br>Stage IV<br>(Any T, Any N, M+) | 14% | 5 years NED | SOT not recommended prior to 5 years; see special consideration regarding resectable CRC metastasis |

RFS: recurrence free survival; LVI: lymphovascular invasion; PVI: perineural invasion; MSI: microsatellite instability; CT: Computed tomography; CAP: chest, abdomen and pelvis; CEA: Carcinoembryonic antigen; NED: no evidence of disease

Recommended wait time for SOT candidates with a prior history of prostate cancer.

| Risk/Stage | Survival[60, 62, 64] | Time Interval to Transplant | Additional Considerations |
|---|---|---|---|
| **VERY LOW RISK**<br>- PSA< 10 ng/ml<br>- 3 or fewer cores of Gleason 6 (grade group 1); no greater than 50% of individual core<br>- T1c-T2a | <1% risk of mets/death over 15 years | None | Surveillance is strongly recommended<br>Extenuating circumstances may require treatment |
| **LOW RISK**<br>- PSA< 10 ng/ml<br>- Gleason 6 (not meeting very low-risk criteria)<br>- T1c-T2a | ~2–3% risk of mets/death over 15 years | None | Surveillance is strongly recommended<br>Extenuating circumstances may require treatment |
| **LOW-VOLUME INTERMEDIATE RISK**<br>- One of the following criteria: PSA > 10 ng/ml, Gleason 7 (grade group 2 or 3), T2b | <5% risk of mets/death over 15 years | If surveillance, no wait time<br>If treatment initiated, and nomogram (www.nomograms.org) predicts cancer-specific death over the next 15 years <10%, no wait time | Surveillance or treatment, depending on patient and cancer characteristics |
| **HIGH-VOLUME INTERMEDIATE RISK, HIGH RISK or VERY HIGH RISK**<br>- PSA >20 ng/ml or high-volume Gleason 7 or any Gleason 8–10, T3 | 20–70% risk of mets/death over 15 years | If treatment initiated, and nomogram predicts cancer-specific death over the next 15 years <10%, no wait time | Treatment |
| **METASTATIC CASTRATION-SENSITIVE** | Median survival ~ 5–6 years | If stable disease for 2 years with prolonged estimated life expectancy, may consider transplant | Best systemic therapy +/– local treatment |
| **METASTATIC CASTRATION-RESISTANT** | Median survival 2–3 years | Not a SOT candidate | Best systemic therapy |

Recommended wait time for SOT candidates with a prior history of renal cell carcinoma.

| Stage | Recurrence free survival 5-year[69,73,74,75] | Time Interval to Transplant |
|---|---|---|
| T1a (≤4cm), N0, M0 | 95–98% | No wait time |
| T1b (>4cm ≤7cm), N0, M0 | 91% for FG 1/2<br>80–82% for FG 3/4 | FG 1–2: no wait time<br>FG 3–4: 1–2 years |
| T2 (7–10cm), N0, M0 | 80% | 2 years |
| T3, N0, M0 | 43–80% | Minimum of 2 years, then reassess |
| T4, N0, M0 | 28–55% | Minimum of 2 years, then reassess |
| Any T, Node positive, Metastatic disease | 0–32% | Not a candidate (if solitary metastasis + resected, tumor board discussion on candidacy) |
| Any T with sarcomatoid and/or rhabdoid histologic features | 15–27% | Not a SOT candidate |
| Collecting duct or Medullary RCC | <10% | Not a SOT candidate |

RCC: renal cell carcinoma; FG: Fuhrman grade (Grade 1: Inconspicuous nucleoli at ×400 magnification and basophilic, Grade 2: Clearly visible nucleoli at ×400 magnification and eosinophilic, Grade 3: Clearly visible nucleoli at ×100 magnification, Grade 4: Extreme pleomorphism or rhabdoid and/or sarcomatoid morphology)

Recommended wait time for SOT candidates with a prior history of bladder cancer.

| Bladder Cancer History | 2-year Local Recurrence from Baseline Trans Urethral Resection of Bladder Tumor[77, 80, 81] | Time Interval to Transp |
|---|---|---|
| NMIBC low risk * | 19% | 6 months |
| Intermediate risk ** | 39% | 6 months |
| high risk *** | 38% *** | 2 years |
| MIBC, post radical cystectomy | 25–37% | 2 years |
| MIBC, post chemoradiation | 25–30% (10 year) | Not a SOT candidate |

NMIBC: non-muscle invasive bladder cancer; MIBC: muscle invasive bladder cancer

Low risk* - solitary, ≤ 3 cm, low grade, Ta tumor, absence of carcinoma in situ (CIS)

Intermediate risk** - solitary tumor > 3 cm, recurrence within 12 months with low grade Ta tumor, multifocal low-grade Ta tumor, low grade tumor, or high-grade tumor < 3 cm

High risk*** - any CIS, high grade Ta tumor > 3 cm, high grade T1 tumor, multifocal high-grade Ta tumor, any recurrent high-grade Ta tumo variant histology, lymphovascular invasion, high grade prostatic urethral involvement, recurrence after BCG intravesical therapy. Although 2- recurrence rate is lower than intermediate risk, the progression rate to muscle invasion is higher.

Recommended wait time for SOT candidates with a prior history of gynecological cancer.

| 5-year Recurrence Risk[92,93,94] | Type and Stage | Time Interval to Transplant |
|---|---|---|
| **LOW RISK**<br><5% risk of recurrence | Stage IA/IB, grade 1–2 endometrial cancer without lymph-vascular space invasion<br>Stage IA/IB/IC Grade 1–2 epithelial ovarian cancer<br>Stage IA1, IA2 squamous/adenocarcinoma of the cervix | No waiting period after completion of primary treatment |
| **INTERMEDIATE RISK**<br>5–15% risk of recurrence | Stage I/II endometrial cancer + risk factors *<br>Stage IB squamous/adenocarcinoma of the cervix | 2–3 years after completion of treatment |
| **HIGH RISK**<br>>30% risk of recurrence | Serous, clear cell, or carcinosarcoma of uterus (All stages)<br>Stage III grade 1–3 endometrioid cancer of the uterus<br>Stage II/III epithelial ovarian cancer<br>Stage II/III squamous cell/adenocarcinoma cervical cancer | 5 years after completion of treatment |
| **VERY HIGH RISK**<br>>80% chance of recurrence | Stage IV endometrial cancer (all grades)<br>Recurrent or metastatic endometrial cancer<br>Stage IV epithelial ovarian cancer (any grade)<br>Recurrent ovarian cancer<br>Stage IV squamous cell/adenocarcinoma of the cervix<br>Metastatic or recurrent cervical cancer | Not a SOT candidate |

* Risk factors: Older age, lymph-vascular space invasion, grade 2 or 3 endometrioid, deeply invasive tumor

Recommended wait time for SOT candidates with a prior history of lung cancer.

| Stage | Tumor and Node | 5-Year Survival (%)[101,102] | Work-up Pre-SOT | Time Interval to Transplantation | Additional Considerations |
|---|---|---|---|---|---|
| I | T1aN0 | 92 | PET-CT; consider biopsy post SBRT | ≥3 years | |
| | T1bN0 | 83 | PET-CT; consider biopsy post SBRT | ≥3 years | |
| | T1cN0 | 77 | PET-CT; consider biopsy post SBRT | 3–5 years | 5-year recurrence-free survival is safest |
| IB | T2aN0 | 68 | PET-CT | 5 years | |
| IIA | T2bN0 | 60 | PET-CT | 5 years | |
| IIB | T3N0 | 53 | PET-CT | 5 years | |
| IIIA | | 36 | PET-CT | 5 years | Special caution with N2 disease |
| IIIB | | 26 | N/A | N/A | Not a SOT candidate |
| IIIC | | 13 | N/A | N/A | Not a SOT candidate |
| IVA | | 10 | N/A | N/A | Not a SOT candidate |
| IVB | | 0 | N/A | N/A | Not a SOT candidate |

SOT: solid organ transplantation; PET-CT: positron emission tomography - computed tomography; SBRT: stereotactic body radiation therapy