

**Maine Medical Center
Maine Transplant Program
Policies and Procedures
Malignancy Prior to Transplantation**

Purpose

Outline policy and procedure regarding candidacy, risk assessment and duration of waiting time for transplant aspirants pertaining to malignancy and kidney transplantation.

Background

Kidney Transplantation is the treatment of choice for end-stage renal disease. However, transplant recipients in general have standardized incident rates of all types of malignancy that is 2 to 3 times higher than the general population consequent on need for immunotherapy. Candidates with a history of prior malignancy who receive a transplant have a 30% higher risk of metastatic malignancy compared with candidates who are cancer free.

Policy & Procedure

1. Age appropriate cancer screening is required for all transplant candidates prior to transplantation
 - a. Colonoscopy to those older than 45 years or younger according to family history. Either colonoscopy or high sensitivity stool based test may be utilized. All positive stool based tests need to be further evaluated by endoscopy.
 - b. Prostate cancer screening for men older than 60 years
 - c. PAP for all women age 21 and older
 - d. Mammogram for all women over 40 years old or according to family risk
 - e. Chest CT to evaluate for lung cancer in potential donors with long- term and current smoking history for those who meet US Preventative Task Force Guidelines:
 - i. Annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years with
 - ii. 30 pack-year smoking history and
 - iii. Currently smoke or have quit within the past 15 years.
 - iv. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.
2. Metastatic Malignancy constitutes an absolute contraindication for transplantation
3. For patients with a history of prior malignancy now deemed in remission, the suggested cancer-free interval prior to transplantation is individualized based on patient and tumor characteristics. Maine Transplant Program follows published guidelines summarized in the appendix. When there is variability between published guidelines, MTP will follow those previously recommended by the American Society of Transplantation.
4. For all other individual tumors not listed on prior addendum figure 1, the proposed waiting time recommendation will be made based on the following:
 - a. Medical Oncology consultation to specifically estimate 5 year tumor recurrence rate and patient survival
 - b. An online consultation may be obtained through the Israel Penn International Transplant tumor Registry for malignancies not referenced in the appendix

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Appendix A: Summary of published guidelines for the minimum time interval between cancer diagnosis and treatment and transplantation

Key: AST, American Society of Transplantation; B&D, Bunnapradist and Danovitch; CARI, Caring for Australasians with Renal Impairment; CST, Canadian Society of Nephrology; EBPG, European Best Practice Guidelines; MMOH, Malaysia Ministry of Health.

| Type | Stage | AST | CARI | B&D | CST | EBPG | MMOH |
|----------------------------------|--|-----|------|-----|-----|------|------|
| Renal cell carcinoma | Small or discovered incidentally | ○ | ○ | ○ | | | ○ |
| | Symptomatic | ⊗ | ● | ⊗ | | ⊗ | |
| | Large or Invasive | ● | | ⊗ | | | ⊗ |
| Bladder cancer | In-situ or non-invasive papilloma | ○ | ○ | ○ | ○ | ⊗ | ○ |
| | Invasive | ⊗ | ⊗ | ⊗ | ⊗ | | ⊗ |
| Breast Cancer | Stage 0-2 (including early stage) | ⊗ | ⊗ | ⊗ | ⊗ | ● | ⊗ |
| | Stage 3-4 (advanced/invasive) | ● | ● | ⊗ | ● | ● | ⊗ |
| Colorectal Cancer | Duke A or B1 | ⊗ | ⊗ | | ⊗ | ⊗ | ⊗ |
| | Duke C | | ● | | | ⊗ | ⊗ |
| | Duke D | | ● | | | ⊗ | ⊗ |
| | Patients with a history of colorectal cancer | ● | | | ● | | |
| Uterine Cancer | Cancer of the uterine body | ⊗ | ⊗ | | | ⊗ | ⊗ |
| | Cervical cancer in-situ | ⊗ | ○ | ○ | ⊗ | ⊗ | ○ |
| | Invasive cervical cancer | | ● | ⊗ | | ● | ● |
| Prostate Cancer | Localised | ○ | ○ | | | | |
| | Invasive | ⊗ | ⊗ | ⊗ | | ⊗ | ⊗ |
| Melanoma | In-situ | ⊗ | ⊗ | ● | ⊗ | | ● |
| | Invasive | ● | ● | ● | ● | ⊗ | ● |
| Non-melanoma skin cancers | Basal Cell Carcinoma | | | | | ⊗ | |
| | Squamous Cell Carcinoma | | | | | | ⊗ |
| Leukemia | | ⊗ | | | ⊗ | | |
| Lung Cancer | | ⊗ | | | ⊗ | | |
| Lymphoma | | ⊗ | ⊗ | ⊗ | ⊗ | | ⊗ |
| Multiple Myeloma | | | ● | | ● | | |
| Testicular Cancer | | ⊗ | ⊗ | | | | ⊗ |
| Thyroid Cancer | | ⊗ | ⊗ | | | | ⊗ |
| Wilms Tumour | | ⊗ | ⊗ | ⊗ | | | ⊗ |

| Symbol | Recommendation |
|---|--|
|  | 0 years |
|  | Minimum 2 years |
|  | 2-5 years |
|  | Minimum 5 years |
|  | Contraindicated |
| | No recommendation (or insufficient evidence) |

Reference: Batabyal et al. Transplantation 2012; 94: 703

Appendix B: Summary of published guidelines for the minimum time interval between cancer diagnosis and treatment and transplantation

Source: *Am. J. Transplant.* 2021;21:460-474.

TABLE 1 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 DCIS Stage I | 97%-99% | No wait time necessary ^a | -Hormone receptor negative disease may have a slightly higher risk of recurrence in the first 2-3 years |
| INTERMEDIATE RISK Stage II | 90%-99% | 1-2 years NED ^a | -Hormone receptor negative disease may have a slightly higher risk of recurrence in the first 2-3 years |
| HIGH RISK Stage III | 66%-97% | 3-5 years NED ^a | -Hormone receptor negative disease may have a slightly higher risk of recurrence in the first 2-3 years -Inflammatory breast cancer likely has a higher risk of recurrence and worse survival |
| PROHIBITIVE RISK Stage IV | 32%-38% | Not a SOT candidate | |

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.

^aAfter 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.

TABLE 2 Recommended wait time for SOT candidates with a prior history of colon cancer

| Risk/stage | Recurrence-free survival 5 years ^{41,46} | Time interval to transplant | Additional considerations |
|--|---|--|--|
| LOW RISK Stage I (T1 or T2, N0, M0) | 91% | 1 year | <i>Low-risk features:</i> - MSI without BRAF mutation <i>High-risk features:</i> - LVI or PNI - Mucinous or Signet Histology - Poorly differentiated histology - Bowel obstruction - Tumor perforation - <12 lymph nodes examined *Tumor deposits considered as N+ disease *Consider chemotherapy prior to transplantation for high-risk stage II disease *Patients with stage III disease should complete chemotherapy |
| LOW INTERMEDIATE RISK Stage II (T3, N0, M0) | 72% | 2 years, consider longer if high-risk features present | |
| HIGH INTERMEDIATE RISK Stage II (T4, N0, M0) Stage III (Any T, N+, M0) | | 3 years, 5 years if high-risk features present | |
| HIGH RISK Stage IV (Any T, Any N, M+) | 13% | 5 years NED | SOT not recommended prior to 5 years; see special consideration regarding resectable CRC metastasis |

Abbreviations: 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.

TABLE 3 Recommended wait time for SOT candidates with a prior history of rectal cancer

| Risk/stage | Recurrence-free survival 5 years ^{41,46} | Time interval to transplant | Additional considerations |
|--|---|--|--|
| LOW RISK Stage I (T1 or T2, N0, M0) Full oncologic resection | 85%-88% | 1 year, consider 2 years if high-risk features present | <i>Low-risk features:</i> - MSI without BRAF mutation - Upper 1/3 rectum or rectosigmoid <i>High-risk features:</i> - LVI or PNI - Mucinous or Signet Histology - Poorly differentiated histology - Bowel obstruction - Tumor perforation - <12 lymph nodes examined - Lower 1/3 of rectum - Incomplete mesorectal excision *Tumor deposits considered as N+ disease *Patients with stage II and III disease should complete trimodality treatment (chemoradiotherapy, surgery and chemotherapy) unless elimination of one of these is deemed appropriate after multidisciplinary discussion *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 Stage I (T1, N0, M0) Local Excision | 78%-88% | 2 years | |
| HIGH INTERMEDIATE RISK Stage II (T3 or T4, N0, M0) Stage III (Any T, N+, M0) | 70% | 3 years, 5 years if high-risk features present | |
| HIGH RISK Stage IV (Any T, Any N, M+) | 14% | 5 years NED | SOT not recommended prior to 5 years; see special consideration regarding resectable CRC metastasis |

Abbreviations: 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.

TABLE 4 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 | <1% risk of mets/death over 15 years | None | Surveillance is strongly recommended |
| - PSA<10 ng/ml | | | |
| - 3 or fewer cores of Gleason 6 (grade group 1); no greater than 50% of individual core | | | Extenuating circumstances may require treatment |
| - T1c-T2a | | | |
| LOW RISK | ~2-3% risk of mets/death over 15 years | None | Surveillance is strongly recommended |
| - PSA<10 ng/ml | | | |
| - Gleason 6 (not meeting very low-risk criteria) | | | Extenuating circumstances may require treatment |
| - T1c-T2a | | | |
| LOW-VOLUME INTERMEDIATE RISK | <5% risk of mets/death over 15 years | If surveillance, no wait time | Surveillance or treatment, depending on patient and cancer characteristics |
| - One of the following criteria: PSA >10 ng/ml, Gleason 7 (grade group 2 or 3), T2b | | If treatment initiated, and nomogram (www.nomograms.org) predicts cancer-specific death over the next 15 years <10%, no wait time | |
| HIGH-VOLUME INTERMEDIATE RISK, HIGH RISK or VERY HIGH RISK | 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 |
| - PSA >20 ng/ml or high-volume Gleason 7 or any Gleason 8-10, T3 | | | |
| 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 |

Abbreviation: PSA, prostate specific antigen.

TABLE 5 Recommended wait time for SOT candidates with a prior history of renal cell carcinoma

| Stage | Recurrence-free survival 5 years ^{69,73-75} | Time interval to transplant |
|--|--|---|
| T1a (≤4 cm), N0, M0 | 95%-98% | No wait time |
| T1b (>4 cm ≤7 cm), N0, M0 | 91% for FG 1/2 80%-82% for FG 3/4 | FG 1-2: no wait time FG 3-4: 1-2 years |
| T2 (7-10 cm), 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 |

Abbreviations: 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).

| Bladder cancer history | 2-Year local recurrence from baseline trans urethral resection of bladder tumor ^{77,80,81} | Time interval to transplant |
|--------------------------------|---|-----------------------------|
| NMIBC low risk ^a | 19% | 6 months |
| Intermediate risk ^b | 39% | 6 months |
| High risk ^c | 38% | 2 years |
| MIBC, postradical cystectomy | 25%-37% | 2 years |
| MIBC, postchemoradiation | 25%-30% (10 year) | Not a SOT candidate |

Abbreviations: NMIBC, nonmuscle invasive bladder cancer; MIBC, muscle invasive bladder cancer.

^aLow risk - solitary, ≤3 cm, low grade, Ta tumor, absence of carcinoma in situ (CIS).

^bIntermediate risk - solitary tumor >3 cm, recurrence within 12 months with low-grade Ta tumor, multifocal low-grade Ta tumor, low-grade T1 tumor, or high-grade tumor <3 cm.

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

TABLE 7 Recommended wait time for SOT candidates with a prior history of gynecological cancer

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

^aRisk factors: Older age, lymph-vascular space invasion, grade 2 or 3 endometrioid, deeply invasive tumor.

TABLE 8 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 | T3 N0 | 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 |

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

Appendix C: Summary of published guidelines for the minimum time interval between cancer diagnosis and treatment and transplantation

Source: *Am. J. Transplant.* 2021;21:475-483.

TABLE 1 Recommended wait time for SOT candidates with a prior history of melanoma

| Pathological stage | 5-year MSS ¹² | Appropriate treatment pretransplantation | Time interval to transplant | Additional considerations |
|---------------------------------------|--------------------------|--|-----------------------------|--|
| In situ | 99% | Wide local excision | No wait time necessary | Follow-up 3 months post-SOT |
| Stage IA (T1a) | 99% | Wide local excision | 1 year | |
| Stage IB (T1b or T2a) | 97% | Wide local excision plus SLNB | 1 year | If positive SLNB at time of diagnosis, imaging as for Stage IIA disease |
| Stage IIA (T2b or T3a) | 94% | Wide local excision plus SLNB | 1 year | Imaging of the brain, CAP Imaging of the neck for those with head/neck melanoma primary |
| Stage IIB (T3b or T4a) | 87% | Wide local excision plus SLNB | 2-4 years | Imaging as above |
| Stage IIC (T4b) | 82% | Wide local excision plus SLNB | 2-4 years | Imaging as above |
| Stage IIIA (T1-2a, N1a or 2a) | 93% | Wide excision plus SLNB plus lymph node dissection | 1-2 years | Imaging as above Oncology referral |
| Stage IIIB (T0-3a and N1a/b/c, N2a/b) | 83% | Wide excision plus SLNB plus lymph node dissection Adjuvant therapy with CKI | 2-4 years | Imaging as above Oncology referral |
| Stage IIIC (T3b-4b and N2b/c-N3b/c) | 69% | Wide excision plus SLNB plus lymph node dissection, Adjuvant therapy with CKI | At least 5 years | Imaging as above Oncology referral (no consensus was possible for this group) |
| Stage IIID (T4b and N3a-3c) | 32% | Wide excision plus SLNB plus lymph node dissection Adjuvant therapy with CKI | At least 5 years | Oncology referral (no consensus was possible for this group) |
| Stage IV | 15%-20% | Wide excision plus SLNB plus lymph node dissection Adjuvant therapy with CKI | At least 5 years | Oncology referral (no consensus was possible for this group) |

Abbreviations: MSS, melanoma-specific survival; SLNB, sentinel lymph node biopsy; CKI, checkpoint inhibitor; CAP, chest, abdomen, and pelvis.

TABLE 2 Recommended wait time for SOT candidates with a prior history of hematological malignancies

| Histology | Survival/relapse data | Time interval to transplant | Additional considerations |
|---------------------------------|---|-----------------------------|---|
| Diffuse large B cell lymphoma | Survival is equivalent to age- and sex-matched general population after EFS24 and PFS24 achieved ^{27,28} | 2 years | |
| Follicular lymphoma | No added mortality when compared to age- and sex-matched general population after EFS24 achieved ^{29,30} | 2 years | |
| Peripheral T cell lymphoma, NOS | 23% relapse within 5 years of EFS24, 78% 5-year survival after EFS24 achieved ³² | 2 years | |
| Burkitt lymphoma | 0.6% relapse after EFS24 achieved ³³ | 2 years | |
| Hodgkin lymphoma | 10% relapse at 10 years after EFS24 achieved ³¹ | 2 years | PET scan negative patients after initial treatment have a low rate of relapse |
| Monoclonal B cell lymphocytosis | N/A | No wait time | |
| Chronic lymphocytic leukemia | 83% 5-year survival untreated ³⁶ | 2-3 years after treatment | Consider if in remission with no CLL-IPI scores >4 |

Abbreviations: EFS24, event-free survival at 24 months; PFS24, progression-free survival at 24 months.

TABLE 3 Criteria for safe SOT candidates with a prior history of myeloma (top) or amyloidosis (bottom)

| |
|--|
| <p>Criteria for safe renal transplantation in myeloma</p> <ul style="list-style-type: none"> Stringent complete response <ul style="list-style-type: none"> No monoclonal protein in serum or urine by immunofixation Normal free light chain ratio Bone marrow plasma cells <1% by flow or immunohistochemistry Performance status 0 or 1 FISH at diagnosis fail to demonstrate deletion (17p), t(4;14), t(14;16) Hematologic remission >6 months <p>Criteria for organ transplantation in amyloidosis</p> <ul style="list-style-type: none"> Therapeutic response with dFLC of <4 mg/dl Only one organ involved with amyloidosis Does not fulfill criteria for symptomatic myeloma <p>Must be a candidate for stem cell transplantation following organ transplantation</p> |
|--|

Abbreviations: dFLC, difference between involved minus uninvolved serum free light chains.

