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 endorsed by the American Society of Transplantation or the American Society of Transplant Surgeons that are summarized in appendices A and B.

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 disovered incidentally	○	○	○			○
	Symptomatic	◌	●	◌		◌	
	Large or Invasive	●		◌			▨
Bladder cancer	In-situor 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.

[a]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.

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	*Low-risk features:* - MSI without BRAF mutation *High-risk features:* - 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	*Low-risk features:* - MSI without BRAF mutation - Upper 1/3 rectum or rectosigmoid *High-risk features:* - 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 trimodaility 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 - 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 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 - 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

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.

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

[b]Intermediate 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.

[c]High 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

[a]Risk 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	2–4 years	Imaging as above
		Adjuvant therapy with CKI		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	At least 5 years	Oncology referral (no consensus was possible for this group)
		Adjuvant therapy with CKI		
Stage IV	15%–20%	Wide excision plus SLNB plus lymph node dissection	At least 5 years	Oncology referral (no consensus was possible for this group)
		Adjuvant therapy with CKI		

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)

Criteria for safe renal transplantation in myeloma
Stringent complete response
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
Criteria for organ transplantation in amyloidosis
Therapeutic response with dFLC of <4 mg/dl
Only one organ involved with amyloidosis
Does not fulfill criteria for symptomatic myeloma
Must be a candidate for stem cell transplantation following organ transplantation

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