Richtlijn screening ontvanger niertransplantatie

Gebaseerd op

KDIGO 2020 Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation

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Werkgroep leden:

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De richtlijn bevat aanbevelingen van algemene aard. Het is mogelijk dat in een individueel geval deze aanbevelingen niet van toepassing zijn. Het is de verantwoordelijkheid van de behandelend arts te beoordelen of de richtlijn in de praktijk toepasbaar is. Er kunnen zich feiten of omstandigheden voordoen waardoor, in het belang van een goede zorg voor de patiënt, van een richtlijn moet worden afgeweken. De richtlijn is in eerste instantie als concept becommentarieerd en geaccordeerd door het LONT, de NVN en door de richtlijnencommissie NFN. Vervolgens is het concept ter becommentariëring voorgelegd aan de klinische leden van de NFN. De definitieve richtlijn is uiteindelijk tot stand gekomen na eventuele aanpassing n.a.v. het binnengekomen commentaar.

Colofon

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Inleiding

Deze richtlijn is overgenomen uit de KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. In dit document is de samenvatting van de aanbevelingen overgenomen. Daarnaast wordt in het Nederlands commentaar gegeven wanneer dit van toepassing is op de Nederlandse situatie.

Voor een uitgebreide onderbouwing van de richtlijn wordt verwezen naar de volledige richtlijn, gepubliceerd in Kidney International Suppl (2020 apr); 104: S11–S103, en op de website van KDIGO, www.kdigo.org.

Met uitzondering van:

Hoofdstuk 9:

Bij aHUS wordt verwezen naar de Richtlijn voor behandeling van patiënten met trombotische microangiopathie 2021.

Hoofstuk 10:

Voor screening en behandeling van latente tuberculose (TBC) wordt verwezen naar de Nederlandse richtlijn Tuberculosescreening voorafgaand aan immunosuppressieve medicatie.

Voor vaccinaties pretransplantatie wordt verwezen naar de NTV-richtlijn, LONT Vaccinatie pre-niertransplantatie voor volwassenen, NTV 2022.

Hoofdstuk 11:

In plaats van het hoofdstuk in KDIGO wordt verwezen naar 2 reviews: Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement. A. J. Transplant. 2021;21:460-474) en Preexisting melanoma and hematological malignancies, prognosis, and timing to solid organ transplantation: A consensus expert opinion statement. A. J. Transplant. 2021;21(2): 475 - 483)

Hoofdstuk 15:

Voor het beleid MRA bij patienten met ADPKD wordt verwezen naar de NFN richtlijn: Screening op intracraniële aneurysma bij patiënten met Autosomaal Dominante Polycysteuze Nierziekte (ADPKD), 2022

Hoofdstuk 18:

Voor de behandeling van hyperparathyreoidie bij chronische nierschade verwijzen we naar hoofdstuk 4.2 van de NFN-richtlijn Mineraal- en botstoornis bij chronische nierschade, 2020.

De hoofdstukken uit KDIGO bevatten aanbevelingen die gegradeerd zijn als 'level 1' of 'level 2' (zie onderstaande tabel). De kwaliteit van de ondersteunende bewijsvoering is weergegeven in letter A, B, C, of D.

	Implications		
Grade*	**Patients**	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not	Most patients should receive the recommended course of action	The recommendation can be evaluated as a candidate for developing a policy or a performance measure
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined

*The additional category "Not Graded" is used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. Ungraded recommendations are generally written as simple declarative statements, but not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	The true effect may be substantially different from the estimate of the effect
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth

In deze NFN-richtlijn is de nummering van de hoofdstukken en paragrafen van de KDIGO-richtlijn aangehouden.

SECTION 1: ACCESS TO TRANSPLANTATION

1.1: We recommend that all patients with chronic kidney disease (CKD) G4-G5 (glomerular filtration rate [GFR] < 30 ml/min/1.73 m 2) who are expected to reach end-stage kidney disease (ESKD) (excluding those listed in Rec 1.1.3) be informed of, educated about, and considered for kidney transplantation regardless of socioeconomic status, sex, gender identity, or race/ethnicity (1D).

1.1.1: Refer potential kidney transplant candidates for evaluation at least 6 to 12 months before anticipated dialysis initiation to facilitate identification/ work-up of living donors and plan for possible pre-emptive transplantation (Not Graded).

Commentaar:

Dit geldt ook voor ontvangers van postmortale niertransplantatie. Ook een aantal van de postmortale niertransplantaties in Nederland wordt pre-emptief getransplanteerd.

1.1.2: Refer potential candidates already on dialysis when medically stable and kidney failure deemed irreversible (Not Graded).

1.1.3: We recommend not referring patients for kidney alone transplant evaluation with the following conditions (1D):

• Multiple myeloma (Rec 9.13.1.1), light chain deposition disease or heavy chain deposition disease (Recs 9.13.2.1, 9.13.2.2 and 9.13.2.3) unless they have received a potentially curative treatment regimen and are in stable remission;

• AL amyloidosis with significant extrarenal involvement (Recs 9.13.3.1 and 13.8);

• Decompensated cirrhosis (consider for combined liver-kidney transplant; Recs 10.5.2.4.2, 16.7.2);

• Severe irreversible obstructive or restrictive lung disease (Rec 12.5);

• Severe uncorrectable and symptomatic cardiac disease that is deemed by a cardiologist to preclude transplantation (Rec 13.7);

• Progressive central neurodegenerative disease (Rec 15.4).

1.1.3.1: Document the reason(s) for not referring patients for transplant evaluation (Not Graded).

1.1.3.2: Inform patients about the reason(s) for not referring for transplant evaluation (Not Graded).

Commentaar:

Bij patiënten met een ander falend orgaan waarvoor transplantatie mogelijk is (bijvoorbeeld levercirrose, pulmonaal of cardiaal falen, multipel myeloom) wordt geadviseerd hen niet alleen voor een niertransplantatie te verwijzen, maar een dubbel transplantatie te overwegen. Afhankelijk van de combinatie van organen zal dit gelijktijdig of opeenvolgend plaatsvinden.

1.1.4 We recommend delaying transplant evaluation in patients with the following conditions until properly managed (1D):

Commentaar:

Bij onderstaande condities moet transplantatie worden uitgesteld, maar afhankelijk van de situatie kan de voorbereiding al (deels) plaatsvinden.

• An unstable psychiatric disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk (Rec 4.2);

• Ongoing substance use disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk (Rec 4.3);

• Ongoing, health-compromising nonadherent behavior despite education and adherence-based counseling (Rec 5.4);

• Active infection (excluding hepatitis C virus infection) that is not properly treated (Rec 10.1.1);

• Active malignancy except for those with indolent and low-grade cancers such as prostate cancer (Gleason score ≤ 6), and incidentally detected renal tumors (≤ 1cm in maximum diameter) (Rec 11.2.1);

Commentaar:

Zoals ook in hoofdstuk 11 wordt besproken, verwijzen we voor maligniteiten naar het AJT review: Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement. A. J. Transplant. 2021; 21:460-474. Dit betekent voor de Nederlandse praktijk een afkapwaarde van ≤ 4cm bij niet gemetastaseerde renaalcel carcinomen.

• Active symptomatic cardiac disease (eg, angina, arrhythmia, heart failure, valvular heart disease) that has not been evaluated by a cardiologist (Rec 13.2);

• Active symptomatic peripheral arterial disease (Rec 14.5);

• Recent stroke or transient ischemic attack (Rec 15.1);

• Active symptomatic: peptic ulcer disease (Rec 16.2.2); diverticulitis (Rec 16.3.1), acute pancreatitis (Rec 16.4.1), gallstone/ gallbladder disease (16.5.1), inflammatory bowel disease (Rec 16.6.1);

• Acute hepatitis (Rec 16.7.2);

• Severe hyperparathyroidism (Rec 18.2).

1.2: Use a multidisciplinary team, which includes at a minimum a transplant physician, transplant surgeon and a health care professional experienced in the psychosocial aspects of transplantation, to evaluate and decide about suitability for kidney transplantation (Not Graded).

Commentaar:

Een transplantatie immunoloog behoort tot het multidisciplinair team. De immunoloog zal niet daadwerkelijk bij de klinische beoordeling betrokken zijn, maar kan het immunologisch risico en daarmee de kans op transplantatie inschatten wat bijdraagt om het gesprek met patiënt aan te gaan.

1.3: Approve patients for kidney transplantation that have an estimated survival which is acceptable according to national standards (Not Graded).

Commentaar:

Patiënten worden in Nederland geschikt geacht voor niertransplantatie wanneer wordt verondersteld dat niertransplantatie leidt tot een langere levensverwachting en/of toename van kwaliteit van leven.

Bij postmortale transplantatie dienen tevens de maatschappelijke belangen zoals schaarste van organen meegewogen te worden. Een transplantatie van een levende donor dient in samenspraak met donor en ontvanger te gebeuren, wat ertoe kan leiden dat een relatief beperkte levensverwachting acceptabel kan zijn, mits het risico van de transplantatie en donatie opweegt tegen de gewonnen kwaliteit van leven.

1.3.1: Inform patients of their option to seek a second opinion from another transplant center if they are declined (Not Graded).

Commentaar:

Het beoordelen van transplantatie kandidaten is tot zekere hoogte een subjectieve beoordeling; Aan afgewezen patiënten moet de mogelijkheid van een second opinion in een ander transplantatiecentrum aangeboden worden.

1.4: We recommend pre-emptive transplantation with a living kidney donor as the preferred treatment for transplant-eligible CKD patients (1A).

1.4.1: We recommend pre-emptive transplantation (living or deceased donor) in adults when the estimated glomerular filtration rate (eGFR) is < 10ml/min/1.73 m2 or earlier with symptoms (1D).

1.4.2: We recommend pre-emptive transplantation (living or deceased donor) in children when the eGFR is < 15ml/min/1.73 m2 or earlier with symptoms (1D).

Screening voor Nier-pancreastransplantatie:

Eerste screening ter beoordeling geschiktheid:
Inclusiecriteria

- Diabetes mellitus op basis van ernstig beta-cel falen.
- De glomerulaire filtratiesnelheid (gemeten aan creatinineklaring) is minder dan 30 ml/min

Exclusiecriteria

- Cardiaal:
  - Zeer slechte LV functie (LVEF <30%), ernstige hartklepafwijkingen of ernstige pulmonale hypertensie.
  - Belangrijke cardiale ischemie (>2 segmenten op myoview)

  (NB als bepaalde zaken reversibel zouden kunnen zijn (bijv. ischemie, klepafwijkingen, is patiënt wellicht transplantabel na evt. correctie/behandeling hiervan).
- Ernstig longlijden.
- Levercirrose.
- Leeftijd > 55 jaar (relatieve contra-indicatie).
- Overgewicht (BMI > 30) of ondergewicht (BMI < 18).
- Ernstige psychiatrische stoornissen/psychosociale instabiliteit.

- Non-compliance.
- Alcohol/ drugs misbruik.
- Relevante maligniteiten/ infecties.

Belangrijk om op te merken is dat de wachttijd voor een nier-pancreastransplantatie ingaat vanaf het moment van plaatsen op de wachtlijst (en dus niet vanaf het moment van starten van dialyse). Dit is ook de reden om patienten vroeg te verwijzen (bij eGFR < 30 ml/min), zodat de patiënten pre-emptief getransplanteerd kunnen worden.

Er bestaat in Nederland een voorlichtingsprogramma voor patienten en hun sociale netwerk, die (mogelijk) in aanmerking komen voor niertransplantatie.: Protocol Nier Team Aan Huis (NTAH)

https://www.nefro.nl/richtlijnen/protocol-nier-team-aan-huis-ntah-2022

SECTION 2: AGE

2.1: Consider age in the context of other comorbidities, including frailty, that may impact outcome when deciding about suitability for kidney transplantation (Not Graded).

2.1.1: We recommend not excluding patients from kidney transplantation because of age alone (1A).

Commentaar:

Patiënten worden niet alleen vanwege hun leeftijd uitgesloten van niertransplantatie, echter > 70 jaar wordt de meerwaarde van transplantatie onduidelijker.

Frailty wordt in deze richtlijn in hoofdstuk 7 besproken.

7.2: We suggest that candidates be assessed for frailty at the time of evaluation and while on the waitlist to inform post-transplant risk and enable optimization strategies, such as pre-operative rehabilitation (2C).

Commentaar:

Er is een duidelijke associatie tussen kwetsbaarheid en mortaliteit, ziekenhuisopnames na niertransplantatie en een delayed graft function, maar er is geen consensus/gouden standaard (en dus geen perfecte screeningstool) voor potentiele transplantatie kandidaten. Zowel landelijk als internationaal zijn er verschillende werkwijzen voor het screenen op frailty. We adviseren de Clinical Frailty Score te gebruiken, indien de score >4 is het advies om een korte multidomein screening uit te (laten) voeren en indien die afwijkend is te verwijzen naar de ouderengeneeskundige/geriater.

SECTION 3: PEDIATRIC ISSUES

3.1: We suggest performing a neurocognitive assessment in pediatric candidates who experienced end-stage kidney disease before the age of 5 years (2D).

3.2: We suggest performing an academic assessment in pediatric candidates of school age who are experiencing academic difficulties (2D).

Commentaar:

In Nederland bestaat er een kind specifieke checklist, die in de kindernier- transplantatie centra gebruikt wordt ter voorbereiding op een niertransplantatie.

SECTION 4: PSYCHOSOCIAL ASSESSMENT

4.1: We suggest performing a psychosocial assessment in all candidates (2D).

4.1.1: Refer candidates to a health care professional experienced in the psychosocial aspects of kidney transplantation (eg, social worker, psychologist, psychiatrist, psychiatric nurse/nurse practitioner) to perform this assessment (Not Graded).

4.1.2: Use measurement tools completed by the patient and/or evaluating clinician to supplement the assessment (Not Graded).

Commentaar:

Gebruik meetinstrumenten zoals PST (psychosociale screening transplantatie) om potentiële problemen in kaart te brengen, deze is niet bedoeld als eindoordeel. Zie bijlage voorstel voor landelijke PST.

4.1.2.1: We suggest not using measurement tools in isolation to determine transplant candidacy (2D).

4.1.3: Refer candidates with a diagnosable psychiatric or psychological condition, substance use disorder or nonadherence for pre-transplant counseling and services to enhance the likelihood of a favorable post-transplant outcome (Not Graded).

4.2: We recommend not transplanting patients with an unstable psychiatric disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk (1C).

4.3: We recommend not transplanting patients with ongoing substance use disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk (1C).

Rationale: Er is weinig bekend over de associatie tussen drugs gebruik, drugs misbruik en afhankelijkheid en de medische en psychosociale posttransplantatie uitkomsten. Patienten met actief of recent middelen gebruik zouden geëvalueerd en zo nodig behandeld moeten worden door een verslavingsarts/psychiater vanwege een hoog risico op een recidief binnen deze patiëntenpopulatie.

4.4: We suggest that patients without current social support be considered for kidney transplantation if they are able to care for themselves and have an identified support plan in place prior to transplantation (2D).

SECTION 5: ADHERENCE

5.1: Assess adherence and adherence barriers pre-transplantation to allow for appropriate education, counseling and post-transplant surveillance (Not Graded).

5.2: Refer candidates with a history of health-compromising nonadherent behavior or identified adherence barriers for adherence-based education and counseling pre-transplant (Not Graded).

5.3: We suggest that candidates with a history of graft loss due to nonadherence undergo adherence-based counseling prior to re-transplantation (2D).

5.4: We recommend that candidates with a history of nonadherence be considered for transplantation unless there is ongoing, health-compromising nonadherent behavior (1D).

Commentaar:

Adherence gaat niet alleen over medicatie inname, maar wordt breder gezien. Het gaat ook over leefregels. Wanneer er twijfel is over de adherence van een patient wordt overleg met de verwijzer (eigen nefroloog, nurse practitioner) aanbevolen.

Er is overigens geen bewijs dat nonadherence tijdens dialyse behandeling voorspellend is voor therapietrouw post transplantatie.

SECTION 6: TOBACCO

6.1: Assess past and present use of tobacco products by candidates at transplant evaluation and while on the waiting list (Not Graded).

6.2: We recommend counseling all candidates to avoid tobacco products before and indefinitely after transplantation (1B).

6.3: We recommend offering a tobacco cessation program to candidates who are using tobacco products (1B).

6.4: We recommend that candidates abstain from tobacco use, at a minimum 1 month prior to waitlisting or living donor transplantation (1B).

6.5: We suggest chest computed tomography (CT) for current or former heavy tobacco users (≥ 30 packyears) as per local guidelines to screen for occult lung cancer (2C).

Commentaar:

In de KDIGO richtlijn wordt geadviseerd een CT-thorax te verrichten als screening bij zware rokers, deze diagnostiek is niet van toepassing op de Nederlandse praktijk. In Nederland wordt met uitzondering van een conventionele thorax foto niet gescreend op longkanker. Een CT-thorax wordt daarom niet geadviseerd. Voor de Nederlandse praktijk geldt de afspraak dat alle screening wordt verricht zoals geadviseerd bij het bevolkingsonderzoek, dit om de vele irrelevante nevenbevindingen te voorkomen. Er wordt wel gedacht over het vervangen van de X-thorax door een CT-thorax in het kader van bevolkingsonderzoek, maar dit is tot op heden nog niet landelijk ingevoerd.

SECTION 7: SURGICAL ISSUES INCLUDING OBESITY

7.1: We recommend candidates to have their body habitus examined by a transplant surgeon at the time of evaluation and while on the waiting list (1B).

Commentaar:

De transplantatiechirurgen zijn betrokken bij de gehele beoordeling van transplantatie kandidaten, niet alleen bij onderzoek van de lichaamsbouw. Ze zijn betrokken bij zowel bij initiële screening en tijdens herevaluatie, echter het moment waarop de patienten beoordeeld worden is afhankelijk van lokale afspraken.

7.1.1: We suggest that candidates not be excluded from transplantation because of obesity (as defined by body mass index or waist-to-hip ratio) (2B).

7.1.2: We suggest weight loss interventions be offered to candidates with obesity prior to transplantation (2D).

Commentaar:

Een BMI onder de 30 is geen bezwaar voor transplantatie. Bij een BMI tussen de 30 en 35 zijn er wisselende acceptatiecriteria tussen de verschillende academische centra in Nederland, mede op basis van chirurgische expertise. Bij een BMI tussen de 35 en 40 is er een sterk advies voor gewichtsreductie met diëtist, indien niet succesvol (of bij een BMI >40) kan patiënt worden aangeboden voor bariatrie, waarbij een gastric sleeve de voorkeur heeft boven een Roux-Y procedure ivm kans op secundaire oxalose.

7.2: We suggest that candidates be assessed for frailty at the time of evaluation and while on the waitlist to inform post-transplant risk and enable optimization strategies, such as pre-operative rehabilitation (2C).

Commentaar:

Zie ook hoofdstuk 2. Er is een duidelijke associatie tussen kwetsbaarheid en mortaliteit, ziekenhuisopnames na niertransplantatie en een delayed graft function, maar er is geen consensus/gouden standaard (en dus geen perfecte screeningstool) voor potentiele transplantatie kandidaten. Zowel landelijk als internationaal zijn er verschillende werkwijzen voor het screenen op frailty. We adviseren de Clinical Frailty Score te gebruiken, indien de score >4 is het advies om een korte multidomein screening uit te (laten) voeren en indien die afwijkend is te verwijzen naar de ouderengeneeskundige/geriater.

7.3: We suggest that candidates be assessed for medical conditions that inhibit wound healing, including obesity, undernutrition, tobacco use, and prior abdominal surgeries, to inform risks of delayed wound healing and hernia formation (2B).

7.4: Candidates should not be excluded from consideration for kidney transplantation because of their need for anticoagulation, antiplatelet therapy or a history of heparin-induced thrombocytopenia (HIT) (Not Graded).

7.4.1: Single antiplatelet agents (eg, aspirin, clopidogrel, ticagrelor) can be continued while waiting for deceased donor transplant (Not Graded).

Commentaar:

Ticagrelor heeft een interactie met tacrolimus, indien mogelijk wordt ticagrelor omgezet naar een andere trombocyten aggregatie remmer.

7.4.2: Delay transplantation for the mandated period of treatment with dual antiplatelet therapy (eg, aspirin plus clopidogrel) when the risk of stopping medication (eg, stent thrombosis) or operating while on treatment (eg, surgical bleeding) exceeds the anticipated benefit of transplantation (Not Graded).

7.4.2.1: Antiplatelet agents (except aspirin) should be stopped 5 days prior to living donor transplantation (unless cessation is contraindicated) and during the perioperative period for deceased donor transplantation (Not Graded).

Commentaar:

Duale aggregatie remming is gecontra-indiceerd (DAPT). Monotherapie (TAR) kan worden gecontinueerd of wordt of in geval van clopidogrel/ticagrelor vervangen worden door acetylsalicylzuur afhankelijk van lokale richtlijnen.

7.4.3: Do not transplant patients on direct-acting oral anticoagulants (DOACs; eg, apixaban, rivaroxaban) except when there is specific expertise using DOACs perioperatively and access to DOAC reversal agents (Not Graded).

7.4.3.1: Switch to an alternative anticoagulant (eg, warfarin) prior to waitlisting or living donor transplantation if recommended by a thrombosis expert/hematologist or if there is no expertise using DOACs perioperatively or access to DOAC reversal agents (Not Graded).

Commentaar:

Voor plaatsing op de wachtlijst wordt DOAC vervangen door een vitamine K-antagonist zonder consultatie van een stollingsspecialist.

7.4.4: Use non-heparin based agents for perioperative anticoagulation in candidates with a history of HIT (Not Graded).

7.5: Assess vascular anatomy and patency for patients with significant peripheral arterial disease (Section 14), prior transplant procedures, venous dialysis catheters, pelvic surgery, or deep venous thrombosis (Not Graded).

7.6: Evaluate native kidney size in patients with polycystic kidney disease (Not Graded).

Commentaar:

Het is ter beoordeling van de transplantatiechirurg met welke frequentie patienten met een ADPKD op de wachtlijst herbeoordeeld moeten worden.

7.6.1: We suggest staged or simultaneous native nephrectomy and transplantation for candidates with polycystic kidney disease that is symptomatic (eg, recurrent pain, recurrent infection), a suspicion of malignancy, or if the patient has insufficient room for a transplant (2D).

7.7: Refer to a urologist experienced in transplant issues for patients at increased risk for or those with a history of urologic malignancy, recurrent urinary tract infections, dysfunctional voiding, prior bladder augmentation/division, an ileal conduit, significant structural anomalies of the kidneys or urinary tract, or nephrolithiasis (Not Graded).

Commentaar:

In de meeste gevallen is het niet noodzakelijk patienten door een uroloog met ervaring in transplantatie te laten beoordelen, met uitzondering van de blaasaugmentatie en pouch, urostoma en andere urinwegderivaties.

7.7.1: We suggest cystoscopy to screen for bladder carcinoma in candidates at increased risk, such as those with high-level exposure to cyclophosphamide or heavy smoking (≥ 30 pack-years) (2D).

Commentaar:

Bij patienten met een verhoogd risico op blaascarcinoom wordt niet standaard een cystoscopie geadviseerd, echter bij patiënten met hoge blootstelling aan cyclofosfamide, valt een cystoscopie te overwegen.

7.7.2: We suggest that pre-transplant unilateral or bilateral nephrectomy be considered for pediatric candidates with high urine volumes (> 2.5ml/kg/hour) or heavy proteinuria associated with hypoalbuminemia (2D).

SECTION 8: DIABETES

8.1: We recommend that candidates with type 1 or type 2 diabetes mellitus (DM) be considered for kidney transplantation (1B).

8.1.1: We suggest candidates with ESKD and type 1 DM be considered for simultaneous pancreas-kidney transplantation in regions where this procedure is available (2A).

Commentaar:

Patienten kunnen naar een pancreastransplantatie centrum worden verwezen wanneer de klaring onder 30 ml/min is, zie ook hoofdstuk 1.

Indien er de mogelijkheid is voor levende niertransplantatie, deze in de linker fossa plaatsen, zodat postmortale pancreastransplantatie nadien in rechter fossa mogelijk is (in verband met een verhoogde kans op trombose bij plaatsing in de linker fossa).

8.2: We suggest testing for abnormal glucose metabolism by oral glucose tolerance test in candidates who are not known to have diabetes (2A).

Commentaar:

In de Nederlandse situatie wordt niet standaard op gestoorde glucosemetabolisme gescreend middels een orale glucosetolerantie test. Wij stellen voor om kandidaten voorafgaand aan niertransplantatie die niet bekend zijn met diabetes te screenen op een abnormaal glucosemetabolisme, bijvoorbeeld middels het bepalen van HbA1c en/of glucose. Hierbij moet rekening worden gehouden met verkorte erytrocytenoverleving bij dialyse patiënten waardoor het Hba1c vals verlaagd kan zijn.

SECTION 9: CAUSE OF END-STAGE KIDNEY DISEASE (ESKD)

9.1 Cause of ESKD and kidney transplantation

9.1.1: We recommend that the cause of ESKD in candidates be determined, where possible, to inform risks and management after kidney transplantation (1A).

Rationale

- Veel oorzaken van ESKD kunnen na transplantatie terugkeren en transplantaat en patient overleving beïnvloeden. Primaire ziektes keren tot 20% van de transplantaties terug en zijn verantwoordelijk voor 8,4% van het transplantaatverlies na 10 jaar, dit vertegenwoordigt de 3e oorzaak van transplantaatverlies.
- Ondanks de kans op recurrence is transplantatie de voorkeursbehandeling bij potentiële kandidaten. Patiënten dienen voorgelicht te worden over het risico op recurrence van de primaire nierziekte en de gevolgen hiervan op de graft-survival. (Bij een aanzienlijk deel van de patiënten is de oorzaak van ESKD niet bekend. Een recente registeranalyse suggereert dat het risico op recurrence bij dergelijke patiënten laag is.

Commentaar:

Bij onbekend basislijden bij renale patiënten onder de 45 jaar of bij iets oudere patienten met een living related donor wordt genetische analyse geadviseerd.

9.1.2: Advise candidates about the disease-specific risk of recurrence and resultant risk of graft loss (Not Graded).

9.2 Focal segmental glomerulosclerosis (FSGS)

9.2.1: We recommend not excluding candidates with primary FSGS from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

9.2.1.1: Loss of a prior graft due to recurrent FSGS indicates a high risk of recurrence upon subsequent transplantation and this factor should be a major consideration in determining candidacy (Not Graded).

9.2.2: We suggest genetic testing (eg, for podocin and nephrin gene mutations, among others) be performed in children and young adults with a clinical course consistent with genetic FSGS to inform the risk of recurrence (2C).

9.2.3: We suggest avoiding routine use of pre-transplant plasma exchange or rituximab to reduce the risk of recurrent FSGS (2D).

Rationale

- Er is een significant risico op recurrence van de primaire FSGS na transplantatie, dit wordt bij 10-56% van de transplantaties gerapporteerd (gemiddeld 30%). Bij recurrence van de ziekte wordt 30-50% van het transplantaatverlies toegeschreven aan het recidief. Bij ontvangers met primaire FSGS gaat ongeveer 10-20% van de grafts verloren aan recurrence.

- Factoren geassocieerd met een recurrence FSGS zijn: jonge leeftijd, niet-blanke etniciteit, levende donornier transplantatie, mesangiale hypercellulariteit, snelle progressie naar ESKD, hoeveelheid proteïnurie pre-transplantatie en recurrence FSGS in een eerder transplantaat.

- Ondanks dat levende donornier transplantatie een onafhankelijke risicofactor is voor recurrence van de ziekte, is de overleving over het algemeen gelijk of beter dan die van postmortale donoren. Levende donatie is daarom niet gecontra-indiceerd. Registry data suggereren dat de uitkomst beter is bij 0 mismatches.

- Meeste studies suggereren dat genetische vormen van de ziekte een lager recidiefpercentage hebben, hoewel recidief is gerapporteerd.

- Het recurrence risico bij potentiële ontvanger die eerder een transplantaat hebben verloren als gevolg van recurrence disease is hoog, ongeveer 80%.

- Patienten met recurrence FSGS wordt vaak behandeld met plasmaferese. Casus en casus series hebben rituximab gesuggereerd om FSGS recurrence te voorkomen, maar werking is onzeker door de afwezigheid van RCT's en de aanwezigheid van negatieve casusrapporten. Geen van beide behandelingen wordt aanbevolen.

9.3 Membranous nephropathy (MN)

9.3.1: We recommend not excluding candidates with MN from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

9.3.1.1: We suggest not excluding candidates with prior graft loss due to MN; however, the risk of recurrence should be considered and discussed with the candidate (2D).

9.3.2: We suggest that autoantibodies to phospholipase A2 receptor (PLA2R) be measured pretransplant to inform the risk of recurrence in patients with MN (2C).

Rationale

- Er is een significant risico op recurrence MN na transplantatie, dit wordt bij 10-50% van de transplantaties gerapporteerd. Dit grote verschil van gerapporteerde recidiefpercentages is te wijten aan verschillende follow-up tijden en rapportage van klinisch recidief versus histologisch recidief, (indicatie biopt of protocollair biopt).

- Het effect van recurrent primaire MN op de uitkomst is onduidelijk, er zijn meldingen met slechtere of gelijkwaardige uitkomsten bij patiënten met recidiverende primaire MN. Dit verschil kan een gevolg zijn van de vraag of de ziekte wordt gedetecteerd op basis van een protocollair biopt of op basis van een indicatiebiopt en door het gebruik van nieuwere behandelingsstrategieën. Het is duidelijk dat recurrence primaire MN kan leiden tot graft falen. Bij patienten met recurrence primaire MN wordt 50% van het graft falen (death censored) toegeschreven aan het recidief MN.

- Onze kennis van de pathogenese van primair MN is aanzienlijk verbeterd sinds de identificatie van auto-antilichamen tegen de fosfolipase A2-receptor (PLA2R). Ongeveer 70% van de patiënten met primaire MN heeft anti-PLA2R-antilichamen. Patiënten die anti-PLA2R-antilichaampositief zijn, hebben een hoger risico op recidief (60-83%) in vergelijking met patiënten die antilichaamnegatief zijn (28-53%). Veel proteïnurie voorafgaand aan een transplantatie is ook een risicofactor voor recurrence.

- Het bewijs voor het gebruik van anti-CD20-therapie voor de behandeling van recurrence primaire MN groeit. Volledige of gedeeltelijke klinische remissie is gemeld in 80% van de gevallen die werden behandeld met rituximab. Er zijn momenteel onvoldoende gegevens om te bepalen of de aanwezigheid van anti-PLA2R-antilichamen een voorspellende waarde heeft voor de respons op een anti-CD20-behandeling. Alkylerende middelen zijn ook gebruikt om recurrence primaire MN te behandelen, vergelijkbaar met de behandeling van de natieve nierziekte. Er is momenteel echter geen bewijs voor preventieve behandeling met rituximab of alkylerende middelen om recurrence primaire MN te voorkomen.

Commentaar:

Wanneer eerder geen aPLA2R antistoffen in bloed is verricht, kan het natieve biopt worden gereviseerd middels een PLA2R kleuring.

9.3.3: We suggest not routinely using rituximab or alkylating agents to reduce the risk of recurrent MN (2D).

Commentaar:

We adviseren überhaupt geen Rituximab of alkylerende middelen te gebruiken voor deze indicatie.

9.4 IgA nephropathy (IgAN)

9.4.1: We recommend not excluding candidates with IgAN from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

Rationale

- Er is een significante variabiliteit in het gerapporteerde recurrence percentages van IgAN na transplantatie. Dit komt door de verschillende criteria voor een biopt (protocollair of indicatie) en de duur va de follow-up. Klinisch recidief komt in ongeveer 30% voor. Histologisch recidief komt met 50% van de gevallen vaker voor, waarbij dit percentage toeneemt in de tijd.

- Over het algemeen is het resultaat van een transplantatie voor patienten met IgAN gelijk aan of beter dan bij andere primaire diagnoses. Ondanks een over het algemeen goede uitkomst bij patiënten met IgAN, is recurrence echter geassocieerd met een hoger risico op graft falen. Vroegtijdig recidief van IgAN is ongebruikelijk, maar komt mogelijk vaker voor bij jongere patienten met een snel progressieve, crescentische ziekte in hun natieve nieren.

9.5 IgA vasculitis

9.5.1: We recommend not excluding candidates with IgA vasculitis from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

Rationale

- Een primaire diagnose van IgA-vasculitis, voorheen aangeduid als Henoch-Schönlein-purpura, is geassocieerd met een vergelijkbare (death censored) graft survival dan andere diagnoses. Het risico op recurrence is lager dan bij IgAN met een recidiefpercentage van 11,5% na 10 jaar. Het gedeelte van graft loss ten gevolge van recurrence was in deze groep 7,5 -13,6 % in Europese series en in UNOS-database.

9.6 Immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) and C3 glomerulopathy (C3G)

9.6.1 IC-MPGN

9.6.1.1: We recommend not excluding candidates with IC-MPGN from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

9.6.1.2: We recommend investigation for an infective, autoimmune, or paraprotein-mediated cause of IC-MPGN prior to transplantation to guide treatment and inform risk of recurrence (1C).

9.6.1.3: We suggest that, when possible, the cause of the IC-MPGN be treated prior to transplantation (2C).

9.6.2 C3G, including dense deposit disease (DDD) and C3 glomerulonephritis (C3GN)

9.6.2.1: We recommend not excluding candidates with C3G from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

9.6.2.2: We suggest that candidates with C3G be screened for genetic or acquired causes for the dysregulation of the complement alternative pathway to guide treatment and inform risk of recurrence (2C).

9.6.2.3: Loss of a prior graft due to recurrent C3G indicates a high risk of recurrence upon subsequent transplantation and this factor should be a major consideration in determining candidacy (Not Graded).

Rationale

- Recente vooruitgang van de pathogenese van MPGN heeft tot herziening van de classificatie geleid, afhankelijk van de aanwezigheid van immuunglobuline bevattende immuuncomplexen (IC-MPGN) of dominant C3 (C3G). De beoordeling van potentiële ontvangers en het risico van recurrence ziekte is afhankelijk van het type MPGN, daarom moeten studies die daar geen onderscheid in maken met de nodige voorzichtigheid worden geïnterpreteerd. Over het algemeen is het percentage recurrence hoog en wordt dit geassocieerd met inferieure transplantaatuitkomsten.
- Risico op recurrence IC-MPGN is 41% bij protocollaire biopten, met een hoger risico bij patienten met monoklonale IgG deposities. Recurrence MPGN met monoklonale deposities wordt geassocieerd met een slechte transplantaat uitkomst. Slechts een minderheid van de patienten heeft detecteerbaar paraproteïne (30%) en er is een laag risico van progressie naar multipel myeloom. Het risico op recurrence bij patienten met polyklonale IgG afzetting, inclusief secondaire cryoglobulinemie is laag, mits de onderliggende oorzaak adequaat wordt behandeld.
- C3G wordt onderverdeeld in 2 ziekten afhankelijk van beeld onder elektronenmicroscopie: dense deposit disease (DDD) en C3 glomerulonefritis (C3GN). Recurrence percentage van beide types is hoog, 70% in C3GN en 50-100% in DDD.

- Recurrence van C3G heeft een negatieve invloed op transplant overleving. Cijfers van de North American Pediatric Renal Transplant Cooperative Study liet een 5-jaars transplant-overleving zien van slecht 50 % bij ontvangers met DDD als diagnose, vergeleken met 74% van gehele populatie. Bij recurrence DDD is aandeel transplantaat verlies door recidief 50%. Een vergelijkbaar 5-jaars transplant-overleving wordt gerapporteerd voor patienten met C3GN. Niettemin voor patiënten met C3GN of DDD wordt een 5 jaars overleving van > 50% gezien, waardoor transplantatie een realistische optie voor dit patiënten cohort is.
- De verschillende factoren gerapporteerd bij C3G die een hoger kans op recidief en een slechte uitkomst voorspellen zijn jonge leeftijd, ernstige proteïnurie en crescentische primaire ziekte.

9.7 Lupus nephritis (LN)

9.7.1: We recommend not excluding candidates with LN from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

9.7.2: We recommend that lupus activity should be clinically quiescent on no or minimal immunosuppression prior to transplantation (1D).

9.7.3: We recommend evaluation for secondary antiphospholipid antibodies prior to transplantation to inform perioperative management (1C).

Rationale

- De incidentie van recurrence lupus erythematosus varieert sterk (2,5 – 54%), afhankelijk of de diagnose klinisch of bij protocollaire biopten wordt gesteld. Klinische relevant recidief is om de nabij 5%.
- Uit de UNOS-data blijkt dat het risico op graft failure na recidief 4x zo groot is dan zonder recidief. Echter slechts bij 7% van graft loss werd dit toegeschreven aan recurrence LN. Graft loss ten gevolge van recurrence disease is even groot dan bij andere primaire nierziekten.
- Uit UNOS-data en andere Registry wordt gesuggereerd dat het zwarte ras, vrouwelijk geslacht en jonge leeftijd het risico op recurrence verhogen.
- Er zijn casus van succesvolle transplantaties bij patienten met serologisch actieve lupus, maar het risico op recurrence is hoger bij patienten met klinisch of serologische ziekteactiviteit op moment van transplantatie. Daarom wordt het in het algemeen aangenomen dat de lupusactiviteit klinisch rustig moet zijn zonder of met minimale immunosuppressie.
- Er is geen relatie tussen tijd op dialyse en risico op recurrence, er wordt echter een periode van dialyse voorafgaand aan transplantatie geadviseerd om het risico te verminderen, hier is onvoldoende bewijs voor.
- Een deel van de patiënten met LN vertoont kenmerken van antifosfolipidensyndroom (APS). Vanwege de implicaties van APS bij niertransplantatie (zie paragraaf 9.8) wordt screening op de aanwezigheid van antifosfolipiden antilichamen (APLA's) bij recipients met LN geadviseerd.

9.8 Antiphospholipid syndrome (APS)

9.8.1: We recommend not excluding candidates with APS from kidney transplantation; however, the risks of post-transplant thrombosis and perioperative anticoagulant therapies should be considered and discussed with the candidate (1B).

9.8.2: We suggest that APS should be clinically quiescent prior to transplantation (2D).

9.8.3: Continue anticoagulation (eg aspirin, warfarin) at the time of activation on the transplant waitlist (Not Graded).

Rationale

- Primaire of secundaire APS kan (meestal in associatie met LN) intrarenal vascular disease en trombotische microangiopathie veroorzaken, leidend tot ESKD. APS is geassocieerd met arteriële en veneuze trombose en bloeding tijdens transplantatie, recurrence nefropathie of catastrofisch APS. Hierdoor is de aanwezigheid van APS geassocieerd met een slechtere transplantaat overleving en overleving van patient, vooral bij patienten met hoge pre-transplantatie antilichamen.
- De relevantie van geïsoleerde positieve antilichamen met name anti-cardiolipine bij afwezigheid van klinische kenmerken van APS is minder duidelijk. Anti cardiolipine antilichamen kunnen bij 1/3 van de dialyse patienten worden gevonden. Er zijn enkele rapporten die melden dat de aanwezigheid van antifosfolipiden antilichamen het risico op vroegtijdig graft verlies verhogen, andere studies hebben geen verhoogd trombotisch risisco aangetoond.

9.9 Anti-neutrophil cytoplasmic antibody (ANCA)- associated vasculitis

9.9.1: We recommend not excluding candidates with ANCA-associated vasculitis from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

9.9.2: We suggest that ANCA-vasculitis should be clinically quiescent prior to transplantation (2D).

Rationale

- De gerapporteerde recurrence percentage voor ANCA-geassocieerde vasculitis varieert van 9 – 36,8%. Meta-analyse van deze rapporten liet een recurrence rate van 17% zien. Deze variatie kan worden verklaard door de verschillende behandelingsregimes om de primaire ziekte te behandelen en de verschillende criteria die gebruikt worden om de diagnose te stellen. Een recente studie meldde een lager recurrence rate van 8,6%. De enige gevallen van recurrence waren extrarenaal en hadden geen nadelig effect of graft overleving.
- Zowel transplant als patient overleving is goed bij ontvangers met een primaire diagnose van ANCA-geassocieerde vasculitis, met 10 jaar patiënten overleving van 87% en 10 jaars death censored transplant overleving van 70-84%.
- Risico op recurrence wordt niet beïnvloed door het patroon van oorspronkelijke ziekte (granulomatose met polyangiitis of microscopische polyarteritis) of ANCA-type.
- ANCA positiviteit ten tijde van transplantatie geeft geen verhoogd risico op graft verlies, maar een hoger titer antilichamen (met name PR3-ANCA) op moment van transplantatie is geassocieerd met vroegtijdige recurrence. Er zijn aanwijzingen dat risico op recurrence groter is wanneer een transplantatie binnen een jaar van klinische remissie wordt verricht, daarom wordt een periode van 1 jaar na remissie aanbevolen voorafgaand aan transplantatie.

Commentaar:

ANCA positiviteit ten tijde van transplantatie geeft geen verhoogd risico op transplantaat verlies, maar een hoger titer antilichamen op moment van transplantatie is geassocieerd met vroegtijdige recurrence. Er wordt een periode van 6 maanden na remissie aanbevolen voorafgaand aan transplantatie. Bij voorkeur is de PR3-ANCA negatief (MPO-ANCA blijft vaker positief).

9.10 Anti-glomerular basement membrane (anti-GBM) disease

9.10.1: We recommend not excluding candidates with anti-GBM disease from kidney transplantation (1B).

9.10.2: We recommend that anti-GBM antibody titers be measured in candidates and that transplantation is only performed when antibodies are undetectable (1D).

Rationale

- Recurrence percentage na transplantatie is niet bekend, maar wordt geschat op < 10% en is waarschijnlijker wanneer er anti-GBM-antilichamen detecteerbaar zijn op moment van transplantatie. Om deze reden wordt geadviseerd om serologische remissie te bevestigen voor transplantatie. Hoewel 9-12 maanden serologisch remissie wordt gesuggereerd is er onvoldoende bewijs om dit aan te bevelen.

9.11 Hemolytic uremic syndrome (HUS)

9.11.1: We recommend not excluding candidates with HUS due to infection with a Shiga-toxin producing organism, usually E. coli (STECHUS), from kidney transplantation (1A).

9.11.2: We recommend assessment of candidates with suspected atypical HUS (aHUS) for a genetic or acquired defect in complement regulation or other genetic causes of aHUS to inform risk of recurrence (1B).

9.11.3: We recommend not excluding candidates with aHUS from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

9.11.3.1: We recommend that if the candidate has an abnormality in complement regulation placing them at high risk of recurrence, kidney transplantation should not proceed unless a complement inhibitor can be administered or combined liver-kidney transplant can be performed (1B).

Rationale

- Hemolytisch uremisch syndroom (HUS) komt het meest voor door infectie met een Shigatoxine-producerende E. coli (STEC-HUS), 90% van de gevallen. STEC-HUS is een zelflimiterende ziekte die slechts zelden in ESKD resulteert. STEC-HUS komt zelden terug na niertransplantatie (0-1%), waardoor deze diagnose geen contra-indicatie voor transplantatie is.
- De lage frequentie van ESKD bij STEC-HUS verhoogt de mogelijkheid van alternatieve diagnose wanneer ESKD optreedt, vooral een atypisch, complement gemedieerde vorm van de ziekte. In deze situatie moet er gezocht worden naar een genetisch of verworven defect in complement regulatie.
- Wanneer er een recurrence is van STEC-HUS na transplantatie moet een alternatieve diagnose zoals aHUS worden overwogen.

- De renale prognose van aHUS is slecht waarbij 50% van de patienten ESKD ontwikkelt. De recurrence rate is hoog. Patienten met een pathologische variant van complementfactor H (CFH), complementfactor I (CFI), C3, complementfactor B (CFB) of hoge titer anti-CFH-autoantilichamen hebben 80-90% kans op recurrence en zonder behandeling met een complement remmer gaan de meeste grafts verloren na recurrence.
- Bij patienten met een variant Membrane Cofactor Protein of lage titer anti-CFH-antilichamen kan transplantatie worden overwogen want risico op recurrence is laag.
- Bij potentiele ontvangers waarbij geen oorzaak van aHUS is vastgesteld lopen een gemiddeld risico op recurrence.
- Potentiele ontvangers met risico op recurrence aHUS, moet worden geadviseerd over het preventief gebruik van complementremmer of noodzaak de behandeling te starten als aHUS optreedt na transplantatie.

Commentaar:

Wij adviseren om potentiële ontvangers met aHUS, te behandelen volgens de “Richtlijn voor behandeling van patiënten met trombotische microangiopathie 2021”

Richtlijn 2021-TMA_def-300321.pdf (hematologienederland.nl)

Indien mogelijk is er de voorkeur voor een levende donor (cave genetische familiebanden).

9.12 Systemic sclerosis

9.12.1: We recommend not excluding candidates with systemic sclerosis from kidney transplantation in the absence of severe pulmonary, gastrointestinal, or other life-threatening extra-renal disease (1C).

Rationale

- Transplantatie moet worden overwogen bij potentiële ontvangers met systemisch sclerose als oorzaak van ESKD, op voorwaarde dat de ernst van de extrarenale manifestaties van de zieke transplantatie niet uitsluit
- Hoewel transplantatie de uitkomst verbetert van patienten met systemisch sclerose, de overleving is minder gunstig dan voor patienten met andere ziekten. (graft- overleving van 68% in een jaar.

9.13 Plasma cell dyscrasias (PCDs) Please consult Section 17.6 Hematologic Disorders for recommendations related to monoclonal gammopathy of undetermined significance (MGUS)

9.13.1 Multiple myeloma

~~9.13.1.1: We suggest that candidates with multiple myeloma be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).~~

Commentaar:

Voor multiple myeloom verwijzen wij naar hoofdstuk 11, waarin deze richtlijn gebaseerd wordt op Preexisting melanoma and hematological malignancies, prognosis, and timing to solid organ transplantation: A consensus expert opinion statement. A. J. Transplant. 2021;21(2): 475 - 483)

9.13.2 Monoclonal immunoglobulin deposition disease (MIDD)

9.13.2.1: We suggest that candidates with light chain deposition disease (LCDD) be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).

9.13.2.2: We suggest that candidates with heavy chain deposition disease (HCDD) be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).

9.13.2.3: We suggest that candidates with light and heavy chain deposition disease (LHCDD) be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).

9.13.3 AL amyloidosis

~~9.13.3.1: We suggest that candidates with AL amyloidosis be excluded from kidney transplantation unless they have minimal extra renal disease (e.g., cardiac amyloid), have received a potentially curative treatment regimen and are in stable remission (2D).~~

Commentaar:

Voor AL amyloïdose wordt ook verwezen naar hoofdstuk 11, waarin deze richtlijn gebaseerd wordt op Preexisting melanoma and hematological malignancies, prognosis, and timing to solid organ transplantation: A consensus expert opinion statement. A. J. Transplant. 2021;21(2): 475 - 483)

9.14 AA amyloidosis

9.14.1:We recommend not excluding candidates with AA amyloidosis from kidney transplantation after adequate treatment of the underlying cause and in the absence of severe extra renal organ involvement (1D).

Rationale:

- Er zijn tegenstrijdige gegevens over de uitkomst van niertransplantatie bij ontvangers met een AA-amyloïdose, waarbij zowel gelijkwaardige als inferieure transplantaat en patient overleving werden gerapporteerd.

9.15 Fibrillary/immunotactoid glomerulonephritis

9.15.1: We recommend not excluding candidates with fibrillary or immunotactoid glomerulonephritis from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1D).

Rationale:

- Fibrillaire en immunotactoïde glomerulonefritis kan terugkeren na niertransplantatie. In een case serie werd recurrence in 43% van de gevallen gemeld, en recurrence was nog vaker bij patienten met een monoklonale gammopathie. Fibrillaire glomerulitis met monoclonale gammopathie is geassocieerd met een hoog risico op graft verlies, dit suggereert dat behandeling van de onderliggende PCD nodig is voorafgaand aan transplantatie.
- Uit recente Registry analyse bleek dat patienten met een fibrillaire glomerulonefritis een vergelijkbare transplantaatoverleving hadden dan andere oorzaken van ESKD.

9.16 Hyperoxaluria (oxalosis), primary and secondary

9.16.1: We suggest that candidates with primary hyperoxaluria type 1 be considered for combined or sequential liver-kidney transplantation (2C).

9.16.2: We suggest genetic testing to identify the cause of primary hyperoxaluria to inform treatment decisions (2C).

9.16.3: We suggest not excluding candidates with correctable hyperoxaluria—pyridoxineresponsive or secondary—from kidney transplantation alone; however, the risk of recurrence should be considered and discussed with the candidate (2D).

9.16.4: We recommend the use of strategies to lower total body oxalate burden prior to transplantation in patients with hyperoxaluria, including intensive dialysis, diet modification, and pyridoxine treatment as appropriate on a case-by-case basis (1D).

Rationale:

- Primaire hyperoxalurie veroorzaakt nierschade ten gevolge van kristaldeposities in de nieren wat kan leiden tot ESKD. Naarmate de ziekte voortschrijdt, overschrijdt de oxalaatproductie de uitscheiding en treedt weefselophoping op. Tijdens dialyse wordt niet voldoende oxalaat verwijderd om accumulatie te voorkomen. Na niertransplantatie wordt de nier blootgesteld aan zowel nieuwe oxalaat dat in de lever wordt geproduceerd als aan weefseloxalaat dat wordt gemobiliseerd bij het herstel van de nierfunctie, dit kan lijden tot vroegtijdig falen van het transplantaat.
- Een recent studie naar de uitkomst van niertransplantatie bij primaire hyperoxalurie van de International Hyperoxaluria Registry rapporteerde een 5-jaars overleving van 45%.
- Een levertransplantatie zal de metabole afwijkingen bij hyperoxalurie type 1 omkeren, bij andere typen hyperoxalurie is minder bekend over het voordeel. Gecombineerde lever - nier transplantatie geeft superieure death censored graft survival vergeleken met niertransplantatie alleen.

Commentaar:

We adviseren om potentiële transplantatie kandidaten met (primaire) hyperoxalurie altijd te overleggen met een expertisecentrum.

9.17 Cystinosis

9.17.1: We recommend not excluding candidates with cystinosis from kidney transplantation in the absence of severe extra renal manifestations (1C).

Rationale:

- Cystinose keert niet terug in het niertransplantaat, waardoor transplantatie de beste behandeling is voor patienten met cystinose en ESKD wanneer extrarenale betrokkenheid geen onaanvaardbaar risico vormt.

9.18 Fabry disease

9.18.1: We recommend not excluding candidates with Fabry disease from kidney transplantation in the absence of severe cardiac or other systemic extra renal organ involvement (1C).

Rationale:

- De ziekte van Fabry keert niet terug in het niertransplantaat. Reports suggereren dat graft en patient overleving goed is na transplantatie bij patienten met Fabry.

9.19 Sickle cell disease

9.19.1: We recommend not excluding candidates with sickle cell disease from kidney transplantation in the absence of active, severe extra renal sickle cell disease (1C).

Rationale:

- Sikkelcelziekte kan terugkeren in de allograft, maar er zijn onvoldoende gegevens om de recurrence rate vast te stellen.

9.20 Sarcoidosis

9.20.1: We recommend not excluding candidates with renal sarcoidosis from kidney transplantation in the absence of severe extra renal disease (1C).

Rationale:

- Sarcoïdose kan terugkeren in het transplantaat. Bij een serie van 18 ontvangers van niertransplantatie met sarcoïdose, waarvan 10 ook renale sarcoïdose, bleek bij 3 van de 10

recurrence sarcoïdose. Transplantaatverlies werd niet gezien bij recurrence maar wel inferieure nierfunctie.

9.21 Alport syndrome

9.21.1: We recommend not excluding candidates with Alport syndrome from kidney transplantation (1C).

Rationale:

- De ontwikkeling van post transplantatie anti-GBM ziekte komt bij 3- 5% van de ontvangers voor en potentiële ontvangers moeten hiervan op de hoogte zijn. Dit komt vaker voor bij patienten met grote gendeleties. In het recent rapport van 51 patienten werd dit niet gezien, wat suggereert dat moderne immunosuppressiva mogelijk hiervoor beschermen.

SECTION 10: INFECTIONS

10.1 Active infections

10.1.1: We recommend that kidney transplantation be delayed until active infections (bacterial, fungal, viral [except hepatitis C], parasitic) are treated (1C).

10.2 Colonization

10.2.1: Follow local protocols for detection and management of colonization with drugresistant organisms (Not Graded).

10.2.2: We recommend not excluding patients from kidney transplantation with asymptomatic bacterial, parasitic or fungal colonization (1C).

10.3 Specific Infections

10.3.1 Urinary tract infections (UTIs)

10.3.1.1: We recommend treating symptomatic UTIs prior to kidney transplantation (1B).

10.3.1.2: We suggest not routinely performing prophylactic nephrectomy for recurrent pyelonephritis or cyst infections (2D).

10.3.2 Tuberculosis (TB)

10.3.2.1: We suggest complete treatment of active TB prior to kidney transplantation, as per World Health Organization or local guidelines (2C).

Commentaar:

Voor screening en behandeling van latente tuberculose (TBC) verwijzen we graag naar de Nederlandse richtlijn. De onderstaande aanbevelingen komen hiermee te vervallen.

https://richtlijnendatabase.nl/richtlijn/tbc-screening_immuunsuppressiva

~~10.3.2.2: We recommend screening for latent TB at the time of candidate evaluation in low TB prevalence areas with a chest radiograph along with a purified protein derivative (PPD) skin test or interferon-gamma release assay (1C).~~

~~10.3.2.3: We suggest starting treatment of latent TB prior to or immediately following kidney transplantation in low TB prevalence areas (2C).~~

~~10.3.2.4: We suggest screening for latent TB at the time of candidate evaluation as per local guidelines in intermediate and high TB prevalence areas with post-transplantation vigilance for active TB (2C).~~

10.4 Screening for periodontal disease

10.4.1: We suggest dental evaluation, as per local general population guidelines, to screen for dental/periodontal disease prior to kidney transplantation (2C).

10.5 Screening for viral infections (see Table 11)

10.5.1 Human immunodeficiency virus (HIV)

10.5.1.1: We recommend screening all patients for HIV infection, using HIV serology (1A).

10.5.1.2: We recommend not excluding patients with controlled HIV infection from kidney transplantation (1C).

10.5.1.3: Kidney transplant candidates with HIV should be managed in a center with experience in this area (Not Graded).

10.5.2 Hepatitis C virus (HCV) [This section is adapted from 2022 KDIGO HCV Guideline]

10.5.2.1: We recommend screening all patients for HCV infection at the time of evaluation for kidney transplantation (1A). (KDIGO HCV Guideline Recommendation 1.1.4)

10.5.2.2: We recommend using an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A). (KDIGO HCV Guideline Recommendation 1.1.1.1)

10.5.2.3: We recommend kidney transplantation as the best therapeutic option for patients with CKD G5 irrespective of presence of HCV infection (1A). (KDIGO HCV Guideline Recommendation 4.1.1)

10.5.2.4: We suggest that all candidates with HCV infection be evaluated for severity of liver disease and presence of portal hypertension (if indicated) prior to acceptance for kidney transplantation (Figure 3) (2D). (KDIGO HCV Guideline Recommendation 4.1.2)

10.5.2.4.1: We recommend that patients with HCV, compensated cirrhosis, and no portal hypertension undergo isolated kidney transplantation and that ~~patients with decompensated cirrhosis or clinically significant portal hypertension (i.e., hepatic venous pressure gradient ǂ10 mm Hg or evidence of portal hypertension on imaging or exam) undergo a simultaneous liver–kidney transplantation~~ (1B). Treatment of those with mild-to-moderate portal hypertension should be determined on a case-by-case basis(KDIGO HCV Guideline Recommendation 4.1.2.1)

10.5.2.4.2: ~~We recommend referring patients with HCV and decompensated cirrhosis for combined liver-kidney transplantation~~ (1B). (KDIGO HCV Guideline Recommendation 4.1.2.2)

Aanpassing (10.5.2.4.1 en 10.5.2.4.2) voor de Nederlandse situatie:

- Bij patiënten met gedecompenseerde cirrose danwel belangrijke portale hypertensie moet een verwijzing naar een lever-niertransplantatiecentrum worden overwogen om te beoordelen of er een indicatie is voor gecombineerde lever-niertransplantatie ongeacht HCV status.

10.5.2.5: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), wait-list times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, and severity of liver fibrosis (Not Graded). (KDIGO HCV Guideline Recommendation 4.1.3)

10.5.2.5.1: We recommend that all kidney transplant candidates with HCV be considered for DAA therapy, either before or after transplantation (1A). (KDIGO HCV Guideline Recommendation 4.1.3.1)

10.5.2.5.2: We suggest that candidates with HCV with a living kidney donor can be considered for treatment before or shortly after transplantation depending on the anticipated timing of transplantation (2B). (KDIGO HCV Guideline Recommendation 4.1.3.2)

10.5.2.5.3: We recommend that kidneys from HCV-infected donors be considered regardless of HCV status of potential kidney transplant recipients (1C). (KDIGO HCV Guideline Recommendation 4.2.3)

10.5.3 Hepatitis B virus (HBV) [See Section 10.7 for related recommendations on HBV vaccinations]

10.5.3.1: We recommend screening for HBV infection with HBsAg, antiHBs, and anti-HBc (1A).

10.5.3.2: We recommend screening with HBV DNA for patients with a positive HBsAg or anti-HBc (1A).

10.5.3.3: We recommend that patients from hepatitis D virus (HDV) endemic areas be screened with HDV serology if they are positive for HBsAg or anti-HBc (1A).

10.5.3.4: We recommend that HBsAg positive and/or HBV DNA positive candidates be referred to a specialist with expertise in the management of liver disease and HBV infection to determine appropriate antiviral treatment (1D).

10.5.3.4.1: We recommend that HBsAg positive and/or HBV DNA positive candidates undergo isolated kidney transplantation if they do not have decompensated cirrhosis and are stable on antiviral therapy after specialist evaluation (1B).

10.5.3.5: We recommend not excluding anti-HBc antibody positive (HBsAg negative) patients from kidney transplantation (1C).

10.5.3.5.1: We recommend that antiHBc antibody positive (HBsAg negative) patients not receive antiviral prophylaxis given that the risk of reactivation is low (1D).

10.5.3.5.2: We suggest that anti-HBc antibody positive (HBsAg negative) patients have a plan in place for posttransplant monitoring of HBsAg and HBV DNA for a minimum of 1-year posttransplantation (2C).

10.5.4 Cytomegalovirus (CMV)

10.5.4.1: We recommend screening for CMV with CMV IgG (1C).

10.5.5 Epstein-Barr virus (EBV)

10.5.5.1: We recommend screening for EBV with EBV viral capsid antigen (VCA) IgG and/or EBV nuclear antigen (EBNA) IgG (1C).

10.5.6 Herpes simplex virus (HSV)

10.5.6.1: We suggest screening for HSV with HSV IgG (2C).

10.5.7 Varicella-zoster virus (VZV)

10.5.7.1: We recommend screening for VZV with VZV IgG (1C).

10.5.7.1.1: We recommend varicella immunization for VZV seronegative candidates at least 4 weeks prior to transplantation (1C).

10.5.8 Measles, mumps, and rubella (MMR)

10.5.8.1: We suggest screening for MMR using IgG serology (2C).

10.5.8.1.1: We suggest MMR immunization for MMR seronegative candidates at least 4 weeks prior to transplantation (2C).

10.5.9 BK virus

10.5.9.1: We recommend not screening for BK virus infection in candidates (1C).

10.5.9.1.1: We recommend not excluding patients for repeat transplantation if a previous graft was lost due to BK nephropathy (1C).

10.5.10 Human T-cell lymphotropic virus (HTLV)

10.5.10.1: We recommend screening for HTLV 1/2 with IgG serology in candidates from endemic areas as per World Health Organization (1C).

10.6 Screening for non-viral infections

10.6.1 Syphilis

10.6.1.1: We recommend screening for syphilis (Treponema pallidum) with serology at the time of candidate evaluation and treatment prior to transplantation if infection is identified (1C).

10.6.2 Strongyloides

10.6.2.1: We suggest screening for strongyloidiasis with serology at the time of evaluation in candidates from endemic areas, and treatment prior to transplantation if infection is identified (2C).

10.6.3 Chagas disease

10.6.3.1: We recommend screening for Chagas disease with serology at the time of evaluation in candidates from endemic areas, and treatment prior to transplantation if infection is identified (1C).

10.6.4 Malaria

10.6.4.1: We recommend screening for malaria with a malaria blood smear at the time of evaluation in candidates who have recently travelled to endemic areas, and treatment prior to transplantation if infection is identified (1C).

10.7 Vaccinations

Commentaar:

Voor adviezen met betrekking tot vaccinatie pre-niertransplantatie verwijzen we graag naar de Nederlandse richtlijn. De onderstaande aanbevelingen komen hiermee te vervallen.

https://www.nefro.nl/richtlijnen/lont-vaccinatie-pre-niertransplantatie-voor-volwassenen-ntv-2022

~~10.7.1: We recommend that the vaccination series be commenced using an accelerated schedule, if necessary, prior to kidney transplantation for any inactivated vaccines (Table 12) (1B).~~

~~10.7.1.1: We suggest not excluding candidates who do not complete an inactivated vaccine series prior to kidney transplantation (2D).~~

~~10.7.2: We recommend that the vaccination series be completed prior to kidney transplantation for any live attenuated vaccines (Table 12) (1B).~~

~~10.7.2.1: We recommend a 4-week delay in kidney transplantation if a live vaccine is administered (eg, MMR, VZV, shingles, yellow fever, oral typhoid, oral polio vaccine) (1B).~~

~~10.7.3: We recommend that splenectomized candidates or those at increased risk for post-transplant splenectomy receive pretransplant pneumococcal, hemophilus, and meningococcal vaccination (1B).~~

~~10.7.4: We recommend that candidates requiring complement inhibitors perioperatively or post-transplant undergo meningococcal vaccination (1B).~~

~~10.7.5: We suggest administering the following vaccines to candidates who, due to age, direct exposure, residence or travel to endemic areas, or other epidemiological risk factors, are at increased risk for the specific diseases:~~

~~• Rabies (2D)~~

~~• Tick-borne meningoencephalitis (2D)~~

~~• Japanese encephalitis (inactivated) (2D)~~

~~• Meningococcus (2D)~~

~~• Salmonella typhi (inactivated) (2D)~~

~~• Yellow fever (2D)~~

SECTION 11: MALIGNANCY

11.1 Cancer screening

11.1.1: We recommend candidates undergo routine cancer screening, as per local guidelines for the general population (Table 13) (1D).

11.1.1.1: We suggest chest imaging prior to transplantation in all candidates (2C). (Same as Rec 12.2)

11.1.1.2: We suggest chest CT for current or former heavy tobacco users (≥ 30 pack-years) as per local guidelines, and chest radiograph for other candidates (2C). (Same as Rec 12.2.1)

11.1.2: Screen candidates at increased risk for renal cell carcinoma (eg ≥ 3 years dialysis, family history of renal cancer, acquired cystic disease or analgesic nephropathy) with ultrasonography (Not Graded).

11.1.3: We suggest cystoscopy to screen for bladder carcinoma in candidates at increased risk, such as those with high-level exposure to cyclophosphamide or heavy smoking (≥ 30 pack-years) (2D).

11.1.4: We recommend screening for hepatocellular carcinoma in candidates with cirrhosis prior to transplantation using techniques (eg, ultrasound, α-fetoprotein) and frequency as per local guidelines (1C).

11.1.5: We recommend screening for bowel cancer in candidates with inflammatory bowel disease as per local guidelines (1C).

Commentaar:

We adviseren dat alle transplantatie kandidaten deelnemen aan de verschillende bevolkingsonderzoeken, zoals het bevolkingsonderzoek naar mammacarcinoom, cervixcarcinoom en colorectale carcinomen. In Nederland is het niet gebruikelijk om naast deze bevolkingsonderzoeken uitgebreide andere screening te doen, met uitzondering van een conventionele thoraxfoto. Ook het routinematig bepalen van een PSA wordt niet aangeraden, tenzij:

- 3 of meer familieleden prostaatkanker hebben.
- er in de familie 2 of meer mannen zijn die prostaatkanker kregen voor hun 55e. Het gaat alleen om eerstegraads of tweedegraads familieleden. Dat zijn vader, zoon of broer en opa of kleinzoon.
- er borstkanker of eierstokkanker voorkomt bij familieleden onder de 50 jaar.
- Patient zelf of een familielid een mutatie in het BRCA2-gen hebt.

Voor de adviezen betreffende transplantatie kandidaten met een doorgemaakte maligniteit verwijzen we in plaats van de KDIGO guideline naar de onderstaande 2 reviews:

Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement. A. J. Transplant. 2021;21:460-474 (zie bijlage 1)

Preexisting melanoma and hematological malignancies, prognosis, and timing to solid organ transplantation: A consensus expert opinion statement. A. J. Transplant. 2021;21(2): 475 – 483 (zie bijlage 2)

Commentaar:

Als algemene regel kan gesteld worden, dat iemand met een (doorgemaakte) maligniteit getransplanteerd kan worden als zijn prognose en levensverwachting meer beïnvloed wordt door de dialyse afhankelijkheid dan door de prognose van maligniteit. Bovendien is het soms bij een recidief maligniteit gunstig dat er een betere nierfunctie is om meer oncologische behandelopties te hebben.

SECTION 12: PULMONARY DISEASE

12.1: Assess candidates with lung disease in collaboration with a pulmonary specialist to determine suitability for transplantation (Not Graded).

12.2: We suggest chest imaging prior to transplantation in all candidates (2C). (Same as Rec 11.1.1.1)

12.2.1 We suggest chest CT for current or former heavy tobacco users (≥ 30 pack-years) as per local guidelines, and chest radiograph for other candidates (2C). (Same as Rec 11.1.1.2)

12.3: We recommend pulmonary function testing in candidates with impaired functional capacity, respiratory symptoms, or known pulmonary disease (1C).

12.4: We recommend counseling all candidates to avoid tobacco products before and indefinitely after transplantation (1B). (Same as Rec 6.2)

12.5: We recommend excluding patients with severe irreversible obstructive or restrictive lung disease from kidney transplantation (1C).

Commentaar:

Zoals reeds eerder vermeld in hoofdstuk 6 wordt in Nederland als voorbereiding op transplantatie (nog) niet gescreend op longkanker middels een CT thorax.

SECTION 13: CARDIAC DISEASE

13.1: Evaluate all candidates for the presence and severity of cardiac disease with history, physical examination, and electrocardiogram (ECG) (Not Graded).

Commentaar:

Als primaire inschatting kan het helpen om patienten b.v. 2 trappen te laten lopen. Wanneer dit lukt zijn patienten meestal in staat om transplantatie te ondergaan (bij het ontbreken van andere risicofactoren zoals angina pectoris, eerder myocardinfarct, hartfalen).

13.2: Patients with signs or symptoms of active cardiac disease (eg, angina, arrhythmia, heart failure, symptomatic valvular heart disease) should undergo assessment by a cardiologist and be managed according to current local cardiac guidelines prior to further consideration for a kidney transplant (Not Graded).

Commentaar:

In vrijwel alle gevallen betekent dit ook een echo cor.

13.3: We suggest that asymptomatic candidates at high risk for coronary artery disease (CAD) (eg, diabetes, previous CAD) or with poor functional capacity undergo non-invasive CAD screening (2C).

13.3.1: We recommend that asymptomatic candidates with known CAD not be revascularized exclusively to reduce perioperative cardiac events (1B).

13.3.2: We suggest that patients with asymptomatic, advanced triple vessel coronary disease be excluded from kidney transplantation unless they have an estimated survival which is acceptable according to national standards (2D).

13.4: We suggest that asymptomatic candidates who have been on dialysis for at least two years or have risk factors for pulmonary hypertension (eg, portal hypertension, connective tissue disease, congenital heart disease, chronic obstructive pulmonary disease) undergo echocardiography (2D).

13.5: Patients with an estimated pulmonary systolic pressure greater than 45mm Hg by echocardiographic criteria should be assessed by a cardiologist (Not Graded).

13.5.1: We recommend not excluding candidates with uncorrectable pulmonary artery systolic pressure greater than 60mm Hg (obtained from right heart catherization) from kidney transplantation; however, the risks of sudden deterioration or progression after transplantation should be a key consideration and the patient should have an estimated survival which is acceptable according to national standards (1C).

Commentaar:

Bij irreversibele primaire pulmonale hypertensie is de overleving dusdanig beperkt dat we in de Nederlandse situatie deze patienten afwijzen voor transplantatie.

13.6: Patients with severe valvular heart disease should be evaluated and managed by a cardiologist according to local cardiac guidelines (Not Graded).

13.7: We suggest that patients with uncorrectable, symptomatic New York Heart Association (NYHA) Functional Class III/IV heart disease [severe CAD; left ventricular dysfunction (ejection fraction < 30%); severe valvular disease] be excluded from kidney transplantation unless there are mitigating factors that give the patient an estimated survival which is acceptable according to national standards (2D).

13.7.1: Patients with severe heart failure (NYHA III/IV) who are otherwise suitable for kidney transplantation should be assessed by a cardiologist and considered for combined/ simultaneous heart and kidney transplantation (Not Graded).

Commentaar: In Nederland zijn er afgelopen jaren geen gecombineerde hart/nier transplantaties verricht. Voor een harttransplantatie geldt een minimale klaring >30 ml/min. Overleg in voorkomende gevallen met een transplantatiecardioloog.

13.8: Perform cardiac imaging in patients with systemic amyloidosis. Exclude such patients from kidney transplantation if significant cardiac amyloid is confirmed (Not Graded). (see Rec 9.13.3.1)

13.9: We suggest that candidates who have a myocardial infarction be assessed by a cardiologist to determine whether further testing is warranted and when they can safely proceed with kidney transplantation (2B).

13.10: We suggest that transplantation be delayed an appropriate amount of time after placement of a coronary stent as recommended by the patient's cardiologist (2B).

Commentaar:

Ook duale plaatjes remming is een contra-indicatie.

13.11: We suggest that maintenance aspirin, β-blockers, and statins be continued while on the waiting list and perioperatively, according to local cardiac guidelines (2A).

Aanvulling:

Bij cardiale interventies wordt geadviseerd om de arterie femoralis te sparen om aansluitmogelijkheden voor NTx zoveel mogelijk te behouden.

Revisie wordt in de volgende gevallen geadviseerd:

- Jaarlijks bij patienten > 70 jaar
- Instabiele patienten
- Iedere 2 jaar bij patienten > 65 jaar
- Vaker op indicatie

SECTION 14: PERIPHERAL ARTERIAL DISEASE (PAD)

14.1: Evaluate all candidates for presence and severity of peripheral arterial disease (PAD) with history and physical examination (Not Graded).

14.2: We suggest that candidates without clinically apparent PAD, but who are at high risk for PAD, undergo non-invasive vascular testing (2D).

Rationale: lower extremity segmental flow and pressure studies and non-invasive duplex evaluation. These tests have been demonstrated to be reliable and correlate with post-transplant outcomes

14.3: Candidates with clinically apparent PAD should undergo imaging and management of their PAD in consultation with a vascular surgeon prior to transplantation (Not Graded).

14.4: We suggest that candidates with clinically apparent PAD, abnormal non-invasive testing, or prior vascular procedures, undergo non-contrast CT imaging of the abdomen/pelvis to evaluate arterial calcification and improve operative planning (2D).

Commentaar:

In Nederland zijn er verschillende strategieën in de Academische centra. Bij kandidaten met vaatlijden is er consensus deze patienten voor te bereiden middels duplex en blanco CT abdomen om te beoordelen of er voldoende mogelijkheid is voor het plaatsen van het niertransplantaat. Bij afwezigheid van restdiurese wordt de voorkeur gegeven aan een CT met contrast. In een aantal centra wordt er bij voorkeur ook bij patienten zonder evident vaatlijden beeldvorming in de vorm van duplex en blanco CT abdomen verricht. Volg hiervoor het lokale protocol.

14.5: Exclude candidates with non-healing extremity wounds with active infection from transplantation until the infection is resolved (Not Graded).

14.6: We suggest not excluding patients with prior aorto-iliac procedures including iliac artery stent placement from kidney transplantation if there is sufficient native artery available for vascular anastomosis (2D).

Commentaar:

Het plaatsen van het niertransplantaat hoeft niet per definitie op een natief vat, ook een anastomose op een prothese behoort tot de mogelijkheden en is ter beoordeling van de transplantatiechirurg.

14.7: We suggest not excluding patients with severe aorto-iliac disease or distal vascular disease from kidney transplantation; however, the risk of progression after transplantation should be a key consideration and the patient should have an estimated survival which is acceptable according to national standards (2D).

Commentaar:

Ernstig vaatlijden is alleen contra-indicatie als er chirurgisch geen opties zijn tot het maken van een anastomose of de overleving van de kandidaat dusdanig beperkt is op basis van het vaatlijden (en meest waarschijnlijk de daarmee samenhangende comorbiditeit).

SECTION 15: NEUROLOGIC DISEASE

15.1: We suggest waiting at least 6 months after a stroke or 3 months after a transient ischemic attack (TIA) before kidney transplantation (2D).

15.2: We recommend not screening asymptomatic candidates for carotid artery disease (1D).

15.3: We suggest screening candidates with autosomal dominant polycystic kidney (ADPKD) disease for intracranial aneurysms only if they are at high risk due to prior history of or a family history of subarachnoid hemorrhage (2D).

Commentaar:

Screening van aneurysmata bij ADPKD valt onder de reguliere nefrologische zorg en is niet specifiek voor de transplantatierichtlijn van toepassing. We adviseren te screenen volgens de landelijke richtlijn: Screening op intracraniële aneurysma bij patiënten met Autosomaal Dominante Polycysteuze Nierziekte (ADPKD), 2022

https://www.nefro.nl/richtlijnen/screening-op-intracrani%C3%ABle-aneurysma-bij-pati%C3%ABnten-met-autosomaal-dominante-0

15.4: Patients with progressive central neurodegenerative disease should not undergo kidney transplantation if survival and quality of life are not expected to be substantially improved by transplantation (Not Graded).

15.5: Assess mental status in candidates with known or suspected cognitive impairment (Not Graded).

15.5.1: We recommend not excluding candidates from kidney transplantation because of non-progressive intellectual, developmental, or cognitive disability (1D).

Commentaar:

Bij deze patiëntencategorie kan (intensievere) psychosociale begeleiding nodig zijn.

15.6: Patients with symptomatic peripheral neuropathy should be assessed by a neurologist (Not Graded).

15.6.1: We suggest people with progressive peripheral neuropathy attributed to uremia be considered for urgent kidney transplantation, if available (2D).

15.6.2: We recommend not excluding candidates from kidney transplantation because of peripheral neuropathy (1D).

Commentaar:

Binnen Eurotransplant is neuropathie geen high urgency indicatie meer. Het is dan ook niet zinvol om patienten om deze reden door de neuroloog te laten beoordelen.

SECTION 16: GASTROINTESTINAL AND LIVER DISEASE

16.1: Evaluate all candidates for the presence of gastrointestinal disease, including liver disease, with a targeted history and physical examination (Not Graded).

16.2 Peptic ulcer disease

16.2.1: We recommend that candidates with symptoms suggestive of active peptic ulcer disease undergo esophagogastroscopy and H. pylori testing prior to kidney transplantation (1C).

16.2.2: Delay kidney transplantation in candidates with endoscopically-proven peptic ulcer disease until symptoms have resolved (Not Graded).

16.2.3: We recommend not screening candidates with a history of peptic ulcer disease with esophagogastroscopy (1C).

16.2.4: We recommend not excluding candidates with a history of peptic ulcer disease from kidney transplantation (1D).

16.3 Diverticulitis

16.3.1: Delay kidney transplantation in candidates with active diverticulitis until symptoms have resolved (Not Graded).

16.3.2: We recommend not screening asymptomatic candidates for diverticulosis (1C).

16.3.3: We recommend not performing prophylactic colectomy in patients with a history of diverticulitis or asymptomatic diverticulosis (1C).

16.3.4: We recommend not excluding candidates with a history of diverticulitis from kidney transplantation (1C).

16.4 Pancreatitis

16.4.1: Delay kidney transplantation in candidates with acute pancreatitis a minimum of three months after symptoms have resolved (Not Graded).

16.4.2: We suggest not excluding candidates with a history of acute or chronic pancreatitis from kidney transplantation (2C).

Commentaar:

Overweeg bij chronische pancreatitis/malabsorptie te screenen op secundaire oxalose, middels oxalaat in 24-uurs urine bij predialyse patiënten of serum oxalaat in dialyse patiënten. Denk ook aan screening op exocriene pancreasdysfunctie bij DM type 1.

16.5 Cholelithiasis

16.5.1: Delay kidney transplantation in candidates with symptomatic gallstone or gallbladder disease until symptoms have resolved (Not Graded).

16.5.2: We recommend that candidates with a history of cholecystitis undergo cholecystectomy before kidney transplantation (1C).

16.5.3: We recommend not screening asymptomatic candidates for cholelithiasis (1C).

16.5.4: We recommend not performing prophylactic cholecystectomy in candidates with asymptomatic cholelithiasis (1C).

16.5.5: We recommend not excluding candidates with asymptomatic cholelithiasis from kidney transplantation (1A).

16.6 Inflammatory bowel disease

16.6.1: Delay kidney transplantation in candidates with active symptomatic inflammatory bowel disease (Not Graded).

16.6.1.1: Determine timing of transplantation for such patients in consultation with a gastroenterologist (Not Graded).

16.6.2: We recommend screening for bowel cancer in candidates with inflammatory bowel disease as per local guidelines (1C). (Same as Rec 11.1.5).

16.6.3: We recommend not excluding candidates with a history of inflammatory bowel disease from kidney transplantation (1D).

Commentaar:

Overweeg bij IBD ook te screenen op secundaire oxalose, met name bij betrokkenheid van terminale ileum of resectie van terminale ileum. Bij totale colectomie of ileostoma is screening niet zinvol omdat bij secundaire hyperoxalurie door binding van calcium aan vrije vetzuren in colon het oxalaat niet gebonden kan worden en daardoor overmatig geresorbeerd kan worden.

16.7 Liver disease

16.7.1: Screen kidney transplant candidates for liver disease with a total bilirubin, alanine aminotransferase, international normalized ratio, and albumin (Not Graded).

16.7.2: Delay kidney transplantation until acute hepatitis, of any cause, has resolved and a long-term strategy for managing liver disease has been implemented (Not Graded).

16.7.3: We recommend that candidates with cirrhosis or suspected cirrhosis be referred to a specialist with expertise in combined liver-kidney transplantation for evaluation (1B).

16.7.3.1: We recommend that patients undergo isolated kidney transplantation if deemed to have compensated cirrhosis after specialist evaluation (1B).

For liver disease associated with HBV or HCV infection, see Sections 10.5.2 and 10.5.3

16.7.4: We recommend screening for hepatocellular carcinoma in candidates with cirrhosis prior to transplantation using techniques (eg, ultrasound, alpha-fetoprotein) and frequency as per local guidelines (1C). (Same as Rec 11.1.4).

SECTION 17: HEMATOLOGIC DISORDERS

17.1: We recommend not routinely screening for thrombophilia in candidates (1C).

17.1.1: We suggest screening for thrombophilia only in candidates who have experienced a venous thromboembolic event, recurrent arteriovenous access thromboses, non-atherosclerotic arterial thrombosis, or family history of venous thromboembolism to identify candidates at higher risk of graft thrombosis (2C).

Commentaar:

In de Nederlandse praktijk wordt gescreend bij recidiverende events. Denk hierbij ook aan miskramen.

17.2: We suggest testing for antiphospholipid antibodies (APLAs) in patients with systemic lupus erythematosus or features of antiphospholipid syndrome (APS) (2C).

17.3: Candidates should not be excluded from consideration for kidney transplantation because of their need for anticoagulation, antiplatelet therapy or a history of HIT (Not Graded). [same as Rec 7.4]

17.3.1: Single antiplatelet agents (eg, aspirin, clopidogrel, ticagrelor) can be continued while waiting for deceased donor transplant (Not Graded). [same as Rec 7.4.1]

Commentaar:

Ticagrelor heeft een interactie met tacrolimus, indien mogelijk wordt ticagrelor omgezet naar een andere trombocyten aggregatie remmer.

17.3.2: Delay transplantation for the mandated period of treatment with dual antiplatelet therapy (eg, aspirin plus clopidogrel) when the risk of stopping medication (eg, stent thrombosis) or operating while on treatment (eg, surgical bleeding) exceeds the anticipated benefit of transplantation (Not Graded). [same as Rec 7.4.2]

17.3.2.1: Antiplatelet agents (except aspirin) should be stopped 5 days prior to living donor transplantation (unless cessation is contraindicated) and during the perioperative period for deceased donor transplantation (Not Graded). [same as Rec. 7.4.2.1]

Commentaar:

Duale aggregatie remming is gecontra-indiceerd (DAPT). Monotherapie (TAR)kan worden gecontinueerd of wordt of in geval van clopidogrel/ticagrelor vervangen worden door acetylsalicylzuur afhankelijk van lokale richtlijnen.

17.3.3: Do not transplant patients on direct-acting oral anticoagulants (DOACs; eg, apixaban, rivaroxaban) except when there is specific expertise using DOACs perioperatively and access to DOAC reversal agents (Not Graded). [same as Rec 7.4.3]

17.3.3.1: Switch to an alternative anticoagulant (eg warfarin) prior to waitlisting or living donor transplantation if recommended by a thrombosis expert/hematologist or if there is no expertise using DOACs perioperatively or access to DOAC reversal agents (Not Graded). [same as Rec. 7.4.3.1]

Commentaar:

Voor plaatsing op de wachtlijst wordt DOAC vervangen door vitamine K-antagonist zonder consultatie van een stollingsspecialist.

17.3.4: Use non-heparin based agents for perioperative anticoagulation in candidates with a history of HIT (Not Graded). [same as Rec. 7.4.4]

17.4: Evaluate transplant suitability of patients with significant cytopenias based on cause and severity (Not Graded).

17.5: We recommend that candidates with sickle cell disease or thalassemia not be excluded from kidney transplantation [see sections on recurrent disease: Section 9.19: sickle cell disease]. (1C)

17.6 Monoclonal gammopathy of undetermined significance (MGUS)

17.6.1: We suggest not excluding candidates with MGUS from kidney transplantation; however, a higher risk of post-transplant lymphoproliferative disease and other hematological malignancies should be considered and discussed with candidates (2D).

17.6.2: We suggest not excluding candidates with smouldering multiple myeloma from kidney transplantation; however, a significant risk of transformation into multiple myeloma should be considered and discussed with candidates (2D).

17.6.3: We recommend careful evaluation of candidates with MGUS for other types of plasma cell disorders prior to kidney transplantation (1D).

Voor overige hematologische maligniteiten wordt verwezen naar hoofdstuk 11.

~~17.7 Acute leukemia and high-grade lymphoma, including post-transplant lymphoproliferative disease (Same as Section 11.3.1)~~

~~17.7.1: Avoid transplanting patients with leukemia or lymphoma until they have received curative therapy, achieved remission and remained cancer free for a period to be determined in consultation with the patient, a hematologist/oncologist and the transplant program (Not Graded).~~

~~17.8 Myelodysplasias, chronic leukemia and chronic/ low-grade lymphoma (Same as Section 11.3.2)~~

~~17.8.1: Decisions about kidney transplantation in patients with myelodysplasia should be made in collaboration with a hematologist (Not Graded).~~

~~17.8.2: Advise consultation with a hematologist with transplant experience in determining transplant candidacy since many lesions may be deemed to be at high risk of accelerated progression or transformation posttransplant (Not Graded).~~

~~17.9: Decisions about kidney transplantation in patients with a prior history of hematological malignancy who are now in remission should be made in collaboration with a hematologist (Not Graded) (Same as Rec 11.3.3).~~

SECTION 18: BONE AND MINERAL METABOLISM

18.1: Measure serum parathyroid hormone (PTH) at the time of transplant evaluation (Not Graded).

18.2: We suggest not transplanting patients with severe hyperparathyroidism until they are adequately treated (medically or surgically) as per KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) guideline (2D).

Commentaar:

Er is volgens de Nederlandse richtlijn sprake van ernstige hyperparathyreoidie als het PTH meer dan 9x de bovenwaarde van normaal is. Voor de behandeling van hyperparathyreoidie bij chronische nierschade verwijzen we naar hoofdstuk 4.2 van de NFN richtlijn Mineraal- en botstoornis bij chronische nierschade.

https://www.nefro.nl/sites/www.nefro.nl/files/richlijnen/Richtlijn%20Mineraal-%20en%20botstoornis%2C%202020_0.pdf

18.3: Bone mineral density (BMD) should not be measured as part of the transplant evaluation (Not Graded).

Commentaar:

Maar er is geen bezwaar tegen het meten van BMD als dit consequenties heeft voor het immunosuppressieve schema.

SECTION 19: IMMUNOLOGICAL ASSESSMENT

19.1: Communicate all sensitizing events (eg, blood product transfusion, including platelets, pregnancy or miscarriage) or clinical events that can impact panel reactive antibody (PRA) (eg, vaccination, withdrawal of immunosuppression, transplant nephrectomy, significant infection) to the human leukocyte antigen (HLA) laboratory (Not Graded).

19.2: Perform HLA antibody testing at transplant evaluation, at regular intervals prior to transplantation and after a sensitizing event or a clinical event that can impact PRA (Not Graded).

19.3: We recommend that HLA antibody testing be performed using solid phase assays (1B).

19.4: We recommend HLA typing of candidates at evaluation using molecular methods, optimally at all loci (1D).

Commentaar:

In de Nederlandse situatie geldt dat patienten moeten voldoen aan de ETRL (Eurotransplant Reference Laboratory) voorwaarden.

19.5: We suggest not routinely testing candidates for non-HLA antibodies (2C).

19.6: We suggest not routinely testing candidates for complement-binding HLA antibodies (2C).

19.7: We suggest informing candidates about their access to transplantation based on blood type and histocompatibility testing results (2C).

19.7.1: We recommend offering candidates with immunologically-reduced access to transplant access to a larger deceased donor pool, kidney exchange programs, and/or desensitization (1C).

19.7.2: We suggest that antibody avoidance (eg, kidney exchange programs or deceased donor acceptable mismatch allocation) be considered before desensitization (2C).

Commentaar:

Het bespreken van de kans op transplantatie zal in de praktijk alleen gedaan worden bij hoog geïmmuniseerde kandidaten (bijv. HLA antistoffen, uitsluitingen op basis van eerdere transplantaties) of wanneer een aanbod uitblijft.

Voor de mogelijkheden ten aanzien van HLA desensibilisatie, verwijzen we naar de Nederlandse richtlijn.

Protocol ‘Desensibilisatie voor HLA-incompatibele niertransplantatie met een nierdonor bij leven’. https://www.transplantatievereniging.nl/wp-content/uploads/2022/03/ExternalLink_Protocol20HLAi20niertransplantatie20versie204.20April202021.pdf

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COMPREHENSIVE REVIEW

AJT

Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement

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Abbreviations: AJCC, American Joint Committee on Cancer; AST, American Society of Transplantation; CRC, colorectal cancer; CRLM, colorectal liver metastases; ctDNA, circulating tumor DNA; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HPV, human papilloma virus; HR, hazard ratio; MIBC, muscle invasive bladder cancer; NMIBC, nonmuscle invasive bladder cancer; NSCLC, nonsmall cell lung cancer; PARP, Poly (ADP) ribose phosphorylase; POLE, DNA-polymerase-ε; PR, progesterone receptor; PTM, pretransplant malignancy; RCC, renal cell carcinoma; SBRT, stereotactic body radiation therapy; SOT, solid organ transplantation; SRM, small renal mass.

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Patients undergoing evaluation for solid organ transplantation (SOT) often have a history of malignancy. Although the cancer has been treated in these patients, the benefits of transplantation need to be balanced against the risk of tumor recurrence, especially in the setting of immunosuppression. Prior guidelines of when to transplant patients with a prior treated malignancy do not take in to account current staging, disease biology, or advances in cancer treatments. To develop contemporary recommendations, the American Society of Transplantation held a consensus workshop to perform a comprehensive review of current literature regarding cancer therapies, cancer stage-specific prognosis, the kinetics of cancer recurrence, and the limited data on the effects of immunosuppression on cancer-specific outcomes. This document contains prognosis based on contemporary treatment and transplant recommendations for breast, colorectal, anal, urological, gynecological, and nonsmall cell lung cancers. This conference and consensus documents aim to provide recommendations to assist in the evaluation of patients for SOT given a history of a pretransplant malignancy.

KEYWORDS
cancer / malignancy / neoplasia, clinical research / practice, editorial / personal viewpoint, organ transplantation in general, patient safety, recipient selection

1 | INTRODUCTION

The primary barrier for consideration of solid organ transplantation (SOT) in patients with pretransplant malignancy (PTM) is the concern that immunosuppression amplifies the risk of cancer recurrence, potentially impacting posttransplant mortality. While it is clear that immunosuppression administered to SOT recipients is associated with an increased likelihood of de novo cancer,[1] clinical evidence on the safety of immunosuppression in the circumstance of PTM is limited.

The most utilized guidelines for the selection of patients with PTM for SOT were extrapolated from recommendations made for potential renal transplant recipients.[2] In most cases, a minimum of 2 years between cancer treatment and SOT was advised. Two-year waiting times were recommended even for cancers with extremely low or zero risk of recurrence, such as ductal carcinoma in situ of the breast. For cancers at increased risk of recurrence, even longer wait times of 2 to 5 or greater than 5 years were recommended, with little or no supporting data. Historical data on transplant recipients with PTM obtained from the Israel Penn International Transplant Tumor Registry reported a 21% overall risk of cancer recurrence following SOT, and higher rates in certain, high-risk malignancies.[3] This information formed the basis for previous recommendations.

Contemporary, population-based studies have reported lower cancer recurrence rates than the original registry provided,[4] although poorer outcomes persist in those with PTM.[5,6] Recent studies also indicate a higher incidence of all-cause mortality in SOT recipients with PTM than those without, but the cause of mortality is not entirely linked to recurrence of the cancer.[5,7] However, despite these increased risks, overall patient survival may still be superior to what would be anticipated without transplantation and may approach acceptable transplant-specific outcomes. In addition, newer therapies may improve outcomes for recurrences.

As improvements in cancer therapies result in better prognosis and survival, more individuals with a history of cancer are likely to present with a need for SOT. In fact, SOT in patients with PTM has increased substantially in recent decades (<1% in 1994 to 8.3% in 2016 for kidney transplant recipients).[7] The risk of cancer recurrence and the possibility for worse outcome following SOT must be weighed against the benefit the patient will receive from the transplant (life-saving vs. life-prolonging), while also considering the potential alternatives (eg, dialysis and ventricular assist devices) (Figure 1).

The risk of cancer recurrence may also vary depending on the organ transplanted and the immunosuppression regimen used. For example, lung recipients historically carry the greatest risk as they are often under the influence of the highest immunosuppression. Transplantation of a patient who later dies of cancer recurrence, rather than a patient without cancer, may result in loss of an organ. Therefore, it is imperative to establish reasonable and updated recommendations to assist practitioners in selecting the appropriate transplant candidates with PTM in a safe and consistent manner.

1.1 | Purpose and scope of consensus

Our goal is to assist transplant practitioners in determining suitability and timing of transplantation after a successfully treated malignancy. The recommendations presented here are limited to commonly encountered solid organ cancers, including breast, colorectal, anal,

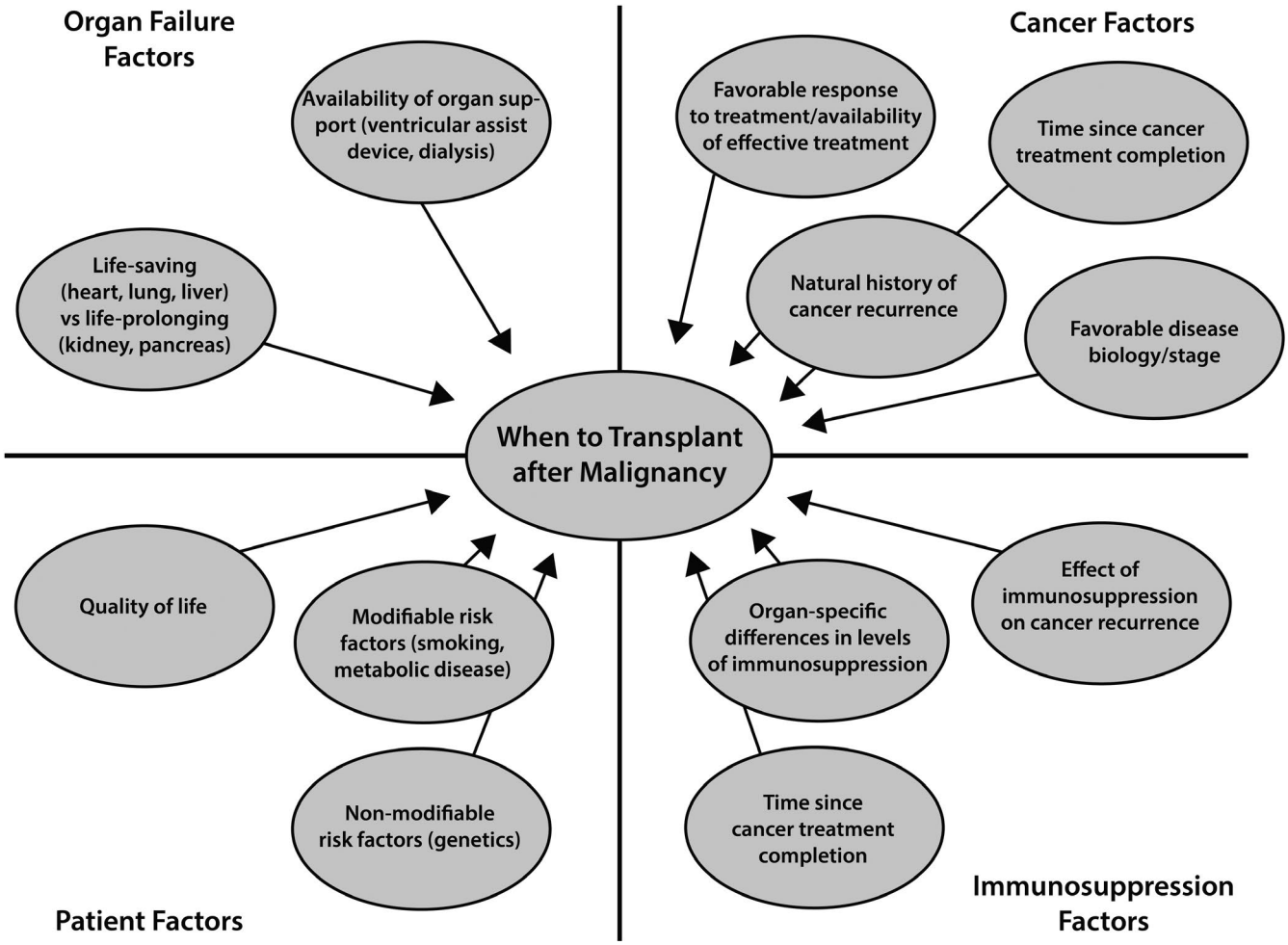

FIGURE 1 Potential factors to consider when evaluating a patient with a PTM for transplantation

urological, gynecological, nonsmall cell lung cancers. Hematological cancers and melanoma are discussed in a separate manuscript. The type of solid organ transplant needed may significantly affect recipient candidacy, due to both variability in waitlist mortality and degree of immunosuppression expected posttransplant. Furthermore, it is important to consider the limitations of this document; while comprehensive, the recommendations cannot account for every clinical situation or the needs of each individual patient.

2 | METHODS

To address the unmet needs in our field, the AST held a consensus workshop on September 29-30, 2019 in Dallas-Fort Worth, Texas. The Malignancy and Transplantation Meeting convened transplant physicians (including surgeons, medical specialists, and anesthesiologists) along with experts in surgical and medical oncology, and cancer epidemiology to review the timing of SOT after successful treatment of a PTM. The resulting recommendations are based on current literature regarding contemporary cancer therapies, cancer stage-specific prognosis, the kinetics of cancer recurrence in the general population, and the limited data on the effects of immunosuppression on cancer-specific outcomes. There are significant gaps in knowledge and most of the data are extrapolated from the general population, therefore, the authors have made the best recommendations with these limited data.

There were over 30 participants in attendance at the meeting, where three experts in each of the fields of breast, colorectal, urological, gynecological, and lung cancer presented summaries of these diseases and their relation to transplantation. After the presentations, the opinion of the oncology experts within each field was discussed as a panel and consensus agreements were then made (modified Delphi method), with the general consideration that a 5-year cancer survival rate of near 80% to be an acceptable benchmark before proceeding with transplantation. The stage-based survival rate, disease biology, and recurrence kinetics were considered when making waiting time recommendations. Writing groups for each cancer consisted of the three cancer-specific experts and two or more transplant physicians.

This is a consensus document rather than a guideline; thus, levels of evidence were not graded. Instead, a comprehensive literature review and consensus expert opinion are presented. This manuscript is a work product of the American Society of Transplantation's Liver and Intestinal Community of Practice. The recommendations

are not to omit the valuable input oncologists play in appropriately selecting those to be transplant candidates, and we encourage ongoing discussions with our oncology colleagues.

2.1 | Breast cancer

2.1.1 | Background and staging

Breast cancer encompasses a group of genetically distinct diseases, each with significantly variable approaches to management, treatment, and prognosis. Over 50,000 new cases of ductal carcinoma in situ (DCIS) and 250,000 new cases of invasive disease are diagnosed annually in the United States.[8] Given the excellent prognosis for many women with early-stage breast cancer, it is reasonable to assume that the treatment for breast cancer will often result in "cure".[9–11] Currently, one in 38 women will die from breast cancer in the United States, but this number is decreasing.[9] The latest American Joint Committee on Cancer (AJCC) staging manual recently refined prognostic staging groups by including the traditional tumor, node, and metastasis, as well as tumor biomarkers (ER=estrogen receptor, PR=progesterone receptor, and HER2=human epidermal growth factor receptor 2), tumor grade, and tumor genomic testing (eg, Oncotype DX). These changes have led to more women being diagnosed with stage I disease.[12]

2.1.2 | Ductal carcinoma in situ

DCIS should be considered a precursor to breast cancer. The traditional measures for assessing risk of recurrence for DCIS are similar to those used in invasive breast cancer: age, residual tumor/margin width, grade, histology, tumor size, and menopausal status. None of these characteristics, however, provides a quantitative assessment of recurrence risk, leading to a significant gap in our understanding of the clinical significance of a diagnosis of DCIS and optimal approaches to treatment.

2.2 | Therapy

Changes in treatment paradigms have made the algorithm for prognostication much more diverse.[12,13] Most women with nonmetastatic breast cancer will undergo breast surgery and surgical evaluation of the axillary nodes. For women who undergo a partial mastectomy, most will also receive radiation therapy, while postmastectomy radiation is often reserved for those with large tumors and positive nodes. If the tumor is hormone receptor positive, endocrine therapy (such as tamoxifen or aromatase inhibitors) is typically recommended for 5-10 years. Chemotherapy is the most variable component of treatment, and numerous factors are considered, including tumor size, nodal status, receptor status, and genomic testing.

2.3 | Transplant recommendations

2.3.1 | Low-risk breast cancer

Several tools can help predict which women are most likely to develop recurrences and potentially die from their disease.[14–16] For example, Oncotype DX stratifies women with early-stage, ER+/HER2- breast cancer into subgroups that are associated with risk of recurrence. For women in the low-risk subgroup, their 5-year risk of recurrence (distant or local regional) is <2%.[14,17,18] In contrast, women with ER disease have a significant spike in breast cancer deaths within the first 2-3 years (peak annual mortality rate of 7.5% at 1-2 years), but that peak annual mortality rate sharply declines to 4% or less by 4 years after diagnosis.[19] In general, better prognoses are associated with negative nodes, small tumor size (<1 cm), and stage I disease.[19]

The consensus recommendation is that women with low-risk disease such as DCIS and stage I breast cancer, should be considered transplant candidates after the completion of all standard treatments (such as surgery, radiation, and/or nonendocrine systemic therapy), with no additional waiting time (**Table 1**). Endocrine therapy is often continued for 5-10 years after the completion of other therapies and should not affect the decision on when to transplant, as these medications are well tolerated with few significant side effects. For women with stage II disease, the 5-year overall survival is 78%-83%.[18] Therefore, these patients could be considered for transplantation after a disease-free interval of 1-2 years after all treatments have been completed. Prior to transplant, obtaining a mammogram is recommended.

2.3.2 | High-risk breast cancer

Patients with advanced stage breast cancer (stage III) have 5-year survival rates ranging from 50 to 70%.[18] However, most recurrences will occur within the first 3 years. As such, after a disease-free interval of 3-5 years after all treatments have been completed, these patients could be considered as transplant candidates.

Inflammatory breast cancer represents one of the most aggressive presentations of breast cancer.[20] Median survival for women with inflammatory breast cancer is approximately 2.9 years, and the overall 5-year survival is <55%.[21,22] Similarly, all women with metastatic disease have a poor prognosis, with a median overall survival of 2 to 3 years.[23–25] Therefore, these patients generally should not be considered as transplant candidates.

2.4 | Colorectal cancer

2.4.1 | Background and staging

Colorectal cancer (CRC) is the third most common cancer worldwide, and several factors determine its treatment and prognosis.[26]

These factors are largely contained in the AJCC staging criteria.[27] Recently, the AJCC staging classification has been refined to account for new prognostic factors and subcategorization of the stage groups, with an emphasis on histopathologic and molecular features. For example, molecular classification of CRC has identified defects in DNA mismatch repair, and epigenetic DNA hypomethylation and CpG Island hypermethylation. These distinctions are important, as mismatch repair defect tumors have been associated with markedly improved prognosis, whereas CpG Island hypermethylation tumors associated with BRAF mutations have markedly worse survival.[28,29] However, additional prognostic factors that are not currently included in the overall staging classification include the presence of tumor deposits, perineural invasion, lymphatic or vascular invasion, high-grade, or signet ring and mucinous histology. The most recent addition to the list of prognostic classifiers is circulating tumor DNA (ctDNA). In the setting of advanced disease, ctDNA is emerging as a highly sensitive marker of treatment response and holds great promise for the detection of minimal residual disease.[30,31] Such information may have great utility for postsurgical treatment decision-making, including transplantation.

2.5 | Therapy

Most newly diagnosed CRC patients present with locoregional disease stage. For these patients, surgical resection remains central to their treatment. Multimodal treatment with less invasive approaches results in better outcomes. Following surgery for colon cancer, survival is excellent for early-stage tumors (91% 5-year survival), and adjuvant chemotherapy is recommended for those patients with stage III disease as well as patients with high-risk stage II disease. However, following curative-intent surgical treatments, between 5 and 40% of patients in this intermediate group will develop cancer recurrence, with approximately 80% identified within the first 3 years, and nearly all recurrences identified by 5 years upon completion of treatment.[32]

Historically, rectal cancer was treated with abdominoperineal resection until sphincter sparing procedures became refined and treatment included neoadjuvant therapies.[33] At this time, there is increasing interest in total neoadjuvant therapy to improve systemic disease management and potential for organ preservation, that is, treatment without surgery at all. With the introduction of nonoperative treatment of rectal cancer, transplant considerations have become more challenging in these patients, as there is increasing confusion about when the patient with rectal cancer is considered "cancer free." Today, patients treated nonoperatively for rectal cancer undergo surveillance for at least 5 years.[34]

2.6 | Transplant recommendations

There is a paucity of data on transplantation of patients with a known history of treated CRC. In 1993 and 1997, Israel Penn reported on 38 and 53 patients with CRC who underwent transplantation, respectively. The recurrence rate in these studies was 21%, with 63% resulting in death. In addition, late recurrences (>5 years postcancer treatment) were common (27%).[35,36] Of patients with recurrence, only 13% had been treated for their CRC within 2 years prior to transplantation, while the remaining 87% of recurrences occurred in patients who were transplanted 3-6 years postmalignancy.[35] This delay in recurrence is concerning, considering that most recurrences in the general population occur within 3 years, with very few (<1%) occurring >5 years postcancer treatment.[37] However, these data derive from a different cancer treatment and transplant era and are limited by unknown complete staging.

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.

Given modern treatment options and improved prognosis in the current era, expert consensus suggests that a patient with a history of fully treated colon cancer may be considered for transplantation within 1-2 years for low-risk disease and 3-5 years for higher risk disease (Table 2). A patient with a history of surgically treated rectal cancer may be considered for transplantation with similar timeframes (Table 3). Patients who have not undergone surgical resection will require multidisciplinary discussion of the individual scenario.

2.6.1 | Special consideration for colorectal liver metastasis and transplantation

Recent advances in medical and surgical treatments of colorectal liver metastases (CRLM) have allowed for an important expansion in resectability and life expectancy in this population.[38] For patients with insufficient liver remnant (precluding liver resection) and absence of extra-hepatic involvement, liver transplantation may be an option since the total hepatectomy will remove all viable disease.[39,40] Recently published data show that with strict selection criteria, overall survival after liver transplantation at 1 and 5 years are 100% and 83%, respectively.[41] Therefore, in selected patients, there appears to be a possible benefit of liver transplantation for unresectable CRLM in select cases. This data and experience is limited and clinical trials are ongoing.

2.6.2 | Anal cancer

Squamous cell anal carcinoma accounts for a small (<3%) proportion of digestive system cancers. Anal cancer risk in transplant patients is of particular interest, due to the relationship between immunosuppression and the inability to clear human papilloma virus (HPV) infections.[42] No data exist on patients with preexisting anal cancer at the time of transplantation, but data from the general population suggest a 5-year survival below 70% with invasive anal squamous cell cancer.[43] Considering the risk of aggressive anal lesions after immunosuppression, the consensus expert panel recommends transplantation can proceed in patients with a history of *invasive*, HPV-related anal cancer after a 5-year disease-free interval. Patients with *noninvasive* anal

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.

lesions require careful consideration before transplanting due to the increased risk for progression of these lesions. Aggressive surveillance practice would be warranted after transplant.

2.7 | Urological malignancies

2.7.1 | Prostate cancer

Autopsy studies have identified prostate cancer in 20%-30% of men in their 30s, 30%-50% in their 50s and 50%-70% in their 70s, with 50% being "high-grade" (Gleason≥7).[44] Despite the high prevalence, only 3% of US men die from prostate cancer and the overwhelming majority of these cancers are never destined to become clinically evident. Surveillance of newly diagnosed low- or intermediate-risk cases without immediate treatment is common and associated with a 10-year cancer-specific survival of >95%.[45]

In many large studies of men with solid organ transplants, there is no worrisome signal that immunosuppression increases the risk of a clinically meaningful prostate cancer,[46–48] recurrence following previous treatment,[49] or 5-year cancer-specific mortality (<1%) after a posttransplant diagnosis of prostate cancer.[49,50] Accordingly, approximately two thirds of kidney transplant programs allow surveillance of prostate cancer prior to transplantation.[51] Population-based data suggest that surveillance in men with prostatae cancer who are being considered for transplant has become more common, without any apparent long-term adverse cancer-specific consequences.[47]

For men diagnosed with prostate cancer during a transplant evaluation and electing treatment, multinomial predictive tools (eg, cancer of the prostate [CAPRA], nomograms) are available to predict the likelihood of cancer-specific death over the next 15 years. Even for the highest possible risk profile within 'intermediate-risk' prostate cancer (PSA=19 ng/ml, Gleason 4 + 3=7, T3a, margin-positive, node-negative), likelihood of a cancer-specific death within 15 years of treatment is

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.

<5%. Our recommended waiting time and management guidelines after a diagnosis of prostate cancer are listed in Table 4.

2.8 | Renal cell carcinoma (RCC)

The majority of renal masses detected in patients being considered for transplantation are incidental and ≤4 cm, considered a small renal mass (SRM).[52] Most SRMs are RCC (75%-80%), the majority are low grade (85%), and risk of metastasis at presentation is <2%.[53] Following treatment of a SRM, the 3-year probability of metastases is ≤2%.[53] Nephrectomy remains the standard approach for SRM treatment for patients on a transplant waiting list. However, active surveillance of SRMs (solid and cystic) is a safe, standard-of-care option in the general population.[54,55] The majority demonstrate slow (<0.3 cm/year) or no growth, low risk of future metastases (1%-2%), and low rates of stage progression (<10%).[55] Long-term safety data of surveillance in patients being considered for transplant is lacking and nephrectomy (radical/partial) remains the most popular treatment prior to transplantation.[56] Biopsy is often helpful to guide management decisions since a significant minority of SRMs are benign or cancers with negligible metastatic potential. Tumor size predicts probability of cancer and aggressive histology.[57]

Nephrectomy in patients with organ failure has significant risk of postoperative complications that may outweigh the benefit of surgery, in light of the low risk of disease progression.[58] Therefore, in the context of a life-saving transplant (eg, heart, lung, liver) surveillance should be considered in SRM (<3 cm). Following a successful transplant and outcome, the posttransplant nephrectomy can be performed 3-6 months posttransplant with superior outcomes.[58] In nonimmunosuppressed patients on surveillance, the American Society of Clinical Oncology guidelines consider tumor growth >0.5 cm/ year or tumor size >4 cm to be an indicator for intervention.[52] In patients on surveillance awaiting heart/lung/liver transplant, and in patients with ablated renal tumors, no data exist on whether increased immunosuppression has detrimental effects. Consequently, recommendation is for definitive management posttransplantation, and nephrectomy of ablated renal masses with enhancement or growth. Table 5 outlines the disease-free survival by stage as well as our recommendations on wait time following treatment.[57,59,60]

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	FG 1-2: no wait time
	80%-82% for FG 3/4	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).

2.9 | Bladder cancer

Five-year survival with bladder cancer is 77%, with 10-year survival at 70%.[61] Although the recurrence rate is extremely high for patients with localized bladder cancer, the progression is extremely low. Therefore, the proposed wait times for patients with nonmuscle invasive bladder cancer (NMIBC) are based on the understanding that most recurrences can be salvaged with local resection, but since progression is rare, the bladder can remain intact. Patients with low-risk NMIBC should undergo surveillance for at least 6 months to determine recurrence kinetics (Table 6). If there is no recurrence within 6 months, transplant can be considered, as the risk of progression is extremely low (ranging from 1%-2% over 5 years) despite a recurrence rate of up to 28% at 5 years.[62] For patients with intermediate-risk NMIBC, the risk of progression remains low, although the risk of recurrence is slightly higher. Again, recurrences can be managed, and a wait time of 6 months is recommended. For patients with high-risk NMIBC, the risk of progression is significantly higher upon diagnosis (approximately 18% at 5 years),[63,64] and the timing of transplant remains controversial. However, a waiting time of at least 2 years is generally advised after local control and intravesical therapy.[49] Based on conditional recurrence/progression models, the risk of recurrence is only 7%-18% and the risk of progression is only 4%-6% if there is no evidence of disease for 2 years after diagnosis.[62]

For patients with muscle invasive bladder cancer (MIBC) treated with radical cystectomy, most recurrences occur within 2 years of surgery and can either occur locally, within the remaining urinary tract, or be metastatic. Beyond 2 years, the recurrence rate is low[65] and, therefore, consideration may be given to transplantation in patients with at least no evidence of disease 2 years after radical cystectomy. In fact, a 2-year disease-free survival rate is an adequate surrogate for 5-year overall survival.[66] However, in patients with MIBC treated with a bladder sparing approach utilizing chemoradiation, there remains a substantial lifetime risk of local recurrence with NMIBC (30%) or MIBC (25%). Therefore, these patients should be considered for solid organ transplantation on a case-by-case basis.

2.10 | Gynecologic cancers

2.10.1 | Background and staging

Gynecologic cancers have impacted over 100,000 women in the United States in 2019, and will be the cause of death in over 33,000.[61] Among these cancers, those emanating from the uterus are the most common, but cancers of the ovary remain the most fatal. The incidence of lower genital track cancers in women is lower but still was the cause of death in almost 7000 women in 2019. Unlike most solid tumors, these cancers are staged using the International Federation of Gynecologic Oncology classification, which relies on surgical findings and has been consistently demonstrated to be prognostic.

2.11 | Therapy

For women with newly diagnosed high-risk stage IA disease to IIIC ovarian cancer, curative treatment requires surgical therapy and adjuvant chemotherapy. The goal of surgery is complete resection of disease; when that is not possible, neoadjuvant chemotherapy is indicated.[67] For women with a mutation in BRCA1 or BRCA2 and those whose tumor shows evidence of homologous recombination deficiency, data support the use of further treatment beyond chemotherapy, using a poly(ADP) ribose phosphorylase (PARP) inhibitor.[68,69]

For women with endometrial disease, the vast majority will be diagnosed with low stage, grade 1 endometrioid cancer.[70] These cancers are most often cured with surgical treatment alone, with radiation therapy reserved for certain high-risk features, such as lymphovascular invasion or deep myometrial invasion.[71] Women with grade 2 or 3 endometrioid or serous carcinomas may present with later stages of disease. These patients will often require multi-modality therapy for curative-intent treatment, which may consist of surgery, radiation therapy, and/or adjuvant chemotherapy.[72] The Cancer Genome Atlas has led to the recognition

TABLE 6 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 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.

of at least four clinically distinct phenotypes of endometrial cancer: DNA-polymerase-ε (POLE) ultramutated; microsatellite instability hypermutated; copy-number low; and copy-number high. Among these phenotypes, POLE-mutant tumors (comprising approximately 10% of endometrioid tumors) appear to be associated with significantly better progression-free survival, while those with copy-number high tumors have the least favorable prognosis.[73]

For women with cervical cancer, surgery is reserved for those without evidence of bulky cervical disease (primary cervical lesion 4 cm or larger) or other advanced features (eg, local invasion beyond the uterus). For these women, surgery can be curative, although adjuvant therapy may be indicated if high-risk features are present.[74,75] For those with locally advanced disease, chemoradiation is the standard of care.[76]

2.12 | Transplant recommendations

There is minimal literature on survival and risk of cancer recurrence after transplant in patients with pretransplant gynecological malignancy.[6] Recommendations for the most common types of endometrial, ovarian, and cervical cancer were stratified by the risk of recurrence: low, intermediate, and high (Table 7).

Patients at low risk of recurrence can be considered at any time after completion of primary treatment. Patients at intermediate risk of recurrence have a 5-year disease-specific survival that exceeds 90%, with the greatest risk of disease recurrence in the first 2 years.[77] As a result, one should consider transplant if no evidence of disease at least 2-3 years after the completion of therapy. Patients at high risk of recurrence include patients with advanced uterine ovarian or cervical cancer. Although some patients with ovarian

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.

cancer are cured, more than half will relapse in the first 2 years of follow-up.[78] However, women who are candidates for a Poly (ADP) ribose phosphorylase (PARP) inhibitor can extend progression-free survival by 3 years or longer with maintenance therapy.[68,69] For women with high-risk endometrial cancers, approximately 40% will relapse within the first 3 years.[79] For women with stage III cervical cancer, the rate of progression-free survival is 80% at 4 years.[74] Taken together, transplant should only be considered if the patient is without disease recurrence for at least 3-5 years after primary treatment.

2.13 | Nonsmall cell lung cancer

2.13.1 | Background and staging

Nonsmall cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality in the United States, with more annual deaths than breast, prostate, and colorectal cancers combined.[80] While curative therapy remains elusive in advanced disease, early-stage disease can be cured by surgical resection and/or radiation therapy. In a large study of over 23,000 patients diagnosed with NSCLC between 1996 and 2007, 16.4% were alive 5 years following diagnosis.[81] This increases the prospect of a NSCLC survivor seeking a solid organ transplant. NSCLC staging is based on tumor size and location, extent and location of lymph node involvement, and the presence of distant metastases. Molecular information is not currently factored into the AJCC 8th edition staging manual, but may impact precision-based risk stratification in the future.[82]

2.14 | Therapy

For early-stage NSCLC, surgical resection is the preferred strategy.[83] Adjuvant chemotherapy is recommended to treat micro-metastatic disease for some stage IB tumors (≥4 cm) and for all stage II and III NSCLC. While adjuvant therapy has traditionally consisted of chemotherapy and/or radiation therapy, immunotherapy in the form of checkpoint blockade is rapidly evolving, but remains in clinical trials currently.[84]

Stage III NSCLC encompasses a heterogeneous group of patients. Patients with limited nodal (N1) involvement may be candidates for upfront surgical resection followed by adjuvant chemotherapy and/or radiation. Those with more advanced nodal (N2) involvement are treated with neoadjuvant therapy (chemotherapy or chemoradiotherapy) prior to surgery, given improved survival with this approach.[85] Patients with more advanced nodal (N3) involvement are generally not considered surgical candidates, but are treated with chemoradiotherapy followed by consolidation immunotherapy. Other modalities, such as stereotactic body radiation therapy (SBRT) or hypo-fractionated radiation therapy, can be utilized for patients unable to tolerate resection.

Most recurrences in NSCLC occur in the first 2 years following definitive treatment, however, recurrence can occur as far out as 5 years in as many as one third of patients.[86,87] Additionally, a second primary lung cancer occurs at a rate of about two per 100 patient years.[88] Local recurrence after SBRT is rare and will generally occur in the first 2 years after treatment. The most common pattern of failure is development of distant disease. Most patients treated with SBRT (60%-100%) will have radiographic changes that range from diffuse consolidation to patchy ground glass opacities.[89] Thus, assessing for local recurrence on imaging can be difficult. PET can differentiate benign radiographic changes from possible tumor recurrence but inflammatory changes from SBRT can be FDG avid for more than 12 months after therapy.[90] Tissue should be obtained prior to transplant consideration if a lesion remains suspicious.

Preexisting lung cancer may not be diagnosed before lung transplant due to the overlapping radiographic findings of cancer and end-stage lung disease. The overall incidence of lung cancer in explanted lungs has increased to 2.5% in recent years.[91] A retrospective institution review of explanted lungs found the median survival time for those with node-negative disease (stage I NSCLC) was 27 months, and those with node positive disease (advanced NSCLC) had a median survival of 7 months.[92]

2.15 | Transplant recommendations

Deciding whether a patient can be listed for transplant following NSCLC diagnosis depends on the stage of disease, history of curative therapy, and, for thoracic transplant recipients, the extent of complexity in the thorax due to prior radiation and/or surgery. Although lung transplant guidelines seem to suggest a 5-year observation window,[93] there are some specific considerations for NSCLC that inform the selection process for solid organ transplant candidacy (Table 8). The main message from this table is that early-stage disease that has responded to treatment *may be* considered for transplantation after 3 years with *significant* caution. It is also worth noting that the effects of checkpoint inhibition pretransplant may have unintended immunological consequences posttransplant.[94] Furthermore, the cancer control/remission through the use of checkpoint inhibitors may dissipate and lead to relapse when immunosuppression is introduced after transplantation. There are limited data regarding the timing of or the use of checkpoint inhibitors prior to transplantation, however, it is an area of interest and currently under investigation. In addition, checkpoint inhibitors use in the posttransplant patient population is being considered in selected patients. Recently, two systematic reviews have summarized the use of checkpoint inhibitor therapies for treatment of skin, liver and lung cancers after kidney, heart, or liver transplantation.[95,96] Although beyond the scope of this consensus review, these studies highlight the consideration that the immunological checkpoint inhibition for cancer therapy must be weighed against the risk of organ rejection and potential graft loss.

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.

3 | CONCLUSIONS

Pretransplant malignancy is increasingly common in patients with end-stage organ disease undergoing evaluation for SOT and can affect posttransplant outcomes. Given the advances in the contemporary treatment of cancer with improved patient survival, an updated consensus document on when to transplant patients with PTM was deemed a high priority by the AST. Recognizing the paucity of data surrounding the recurrence of solid organ malignancies after transplantation, this conference and consensus document aimed to update the recommendations for proceeding with SOT given a history of a PTM. In order to improve the strength of these recommendations, future goals are to create a multi-institutional database to collect cancer- and transplant-specific outcomes on patients transplanted using these recommendations. In addition, future areas of research should focus on appropriate cancer surveillance and decreasing modifiable risk factors for cancer recurrence after transplant in a patient with a PTM.

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AUTHOR CONTRIBUTIONS

David P. Al-Adra, Laura Hammel, David P. Foley, and Kymberly D. Watt contributed equally to the literature search, figures, study design, data interpretation, and writing of the manuscript. John Roberts, E. Steve Woodle, Deborah Levine, Didier Mandelbrot, Elizabeth Verna, Jayme Locke, Jonathan D'Cunha, Maryjane Farr, Deirdre Sawinski, Piyush K. Agarwal, Jennifer Plichta, Sandhya Pruthi, Deborah Farr, Richard Carvajal, John Walker, Fiona Zwald, Thomas Habermann, Morie Gertz, Philip Bierman, Don S. Dizon, Carrie Langstraat, Talal Al-Qaoud, Scott Eggener, John P. Richgels, George J. Chang, Cristina Geltzeiler, Gonzalo Sapisochin, Rocco Ricciardi, Alexander Sasha Krupnick, Cassie Kennedy, and Nisha Mohindra contributed equally to the literature search, study design, data analysis, data interpretation, and writing of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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COMPREHENSIVE REVIEW

Preexisting melanoma and hematological malignancies, prognosis, and timing to solid organ transplantation: A consensus expert opinion statement

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Abbreviations: AJCC, American Joint Committee on Cancer; AL, amyloid light-chain; AST, American Society of Transplantation; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; EFS24, event-free survival at 24nonbreakingspacemonths; FISH, fluorescence in situ hybridization; FL, follicular lymphoma; MBL, monoclonal B cell lymphocytosis; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PFS24, progression-free survival at 24nonbreakingspacemonths; PTM, pretransplant malignancy; SOT, solid organ transplantation.

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Patients undergoing evaluation for solid organ transplantation (SOT) frequently have a history of malignancy. Only patients with treated cancer are considered for SOT but the benefits of transplantation need to be balanced against the risk of tumor recurrence, taking into consideration the potential effects of immunosuppression. Prior guidelines on timing to transplant in patients with a prior treated malignancy do not account for current staging, disease biology, or advances in cancer treatments. To update these recommendations, the American Society of Transplantation (AST) facilitated a consensus workshop to comprehensively review contemporary literature regarding cancer therapies, cancer stage specific prognosis, the kinetics of cancer recurrence, as well as the limited data on the effects of immunosuppression on cancer-specific outcomes. This document contains prognosis, treatment, and transplant recommendations for melanoma and hematological malignancies. Given the limited data regarding the risk of cancer recurrence in transplant recipients, the goal of the AST-sponsored conference and the consensus documents produced are to provide expert opinion recommendations that help in the evaluation of patients with a history of a pretransplant malignancy for transplant candidacy.

KEYWORDS
cancer/malignancy/neoplasia, clinical research/practice, editorial/personal viewpoint, organ transplantation in general, patient safety, recipient selection

1 | INTRODUCTION

The timing of when to perform a solid organ transplant (SOT) in patients with a history of prior malignancy depends on several variables. Some of these variables include the stage of cancer at diagnosis, the time from treatment, treatment response, as well as the organ needed and the degree of immunosuppression. The most cited guidelines for the selection of patients with pretransplant malignancy (PTM) for SOT were extrapolated from recommendations made for potential renal transplant recipients, are outdated and in need of revision.[1] Previously, a minimum of 2 years, and frequently longer between cancer treatment and SOT was advised, regardless of staging and prognosis.

Although poorer outcomes are noted in recipients with PTM,[2,3] it may or may not relate to recurrence of the cancer.[2,4] More patients now emerge from contemporary cancer treatments with a good prognosis that will generally improve over time. In many cases, individual patient survival will be superior with transplant than without transplantation and be within acceptable transplant-specific outcomes. Recurrence does not necessarily mean death from the cancer, as modern therapies may effectively treat recurrent cancer. However, challenges will exist with optimizing graft function during these therapies. The effects of treating cancer recurrence with immunotherapy after SOT are beyond the scope of this review.

The risk of cancer recurrence after SOT and possible death of the patient and the loss of the organ also requires consideration of the ethical principle of justice. Balancing the fair distribution of a scarce resource with benefits of transplant for an individual patient with a PTM behooves us to provide updated recommendations for the transplant community to apply consistent, safe, and collaborative input in selecting the appropriate transplant candidates.

1.1 | Waiting time before transplantation for patients with PTM

The number of patients that would develop recurrent cancer during the waiting period prior to transplantation listing, and therefore, the effectiveness of the waiting period, is very dependent upon the shape of the recurrence curve versus time. Ideally, the curve would have a steep initial portion where most of the recurrence risk occurred, followed by a curve that is flat, suggesting a low risk after the initial waiting period. This would mean that the initial waiting time would capture much of the recurrence risk, with few recurrences

1.2 | The need for a consensus

In 2019, the American Society of Transplantation (AST) conducted a survey of its members to assess practice patterns and institutional variations for selection of patients with PTM for SOT. Of the 80 respondents, most were medical (79%) and surgical (19%) transplant specialists from academic institutions (93%). There were deviations in the existence of institutional policies for listing those with PTM, utilization of an oncologist to assist with decision-making, and acceptable cancer-specific survival prior to consideration for transplant (Figure 1). Seventy-seven percent of respondents were aware of prior published guidelines; however, more than 90% of respondents indicated a need for updated consensus for the management of patients with a PTM. Of note, most respondents considered a 5-year cancer survival rate of 80% to be an acceptable benchmark before proceeding with transplantation.

1.3 | Purpose and scope of consensus

The goal is of this consensus is to aid the transplant community in assessing the suitability and timing of transplantation after a successfully treated malignancy. The recommendations presented are limited to hematological cancers and melanoma. Other commonly encountered solid organ cancers, including breast, colorectal, anal, urological, gynecological, nonsmall cell lung cancers are discussed in a separate document. Recipient candidacy may be affected by the type of solid organ transplant needed, and immunosuppression required after transplant. It is important to consider the limitations of this document; while comprehensive, the recommendations cannot account for every clinical situation and consultation with oncology practitioners is encouraged.

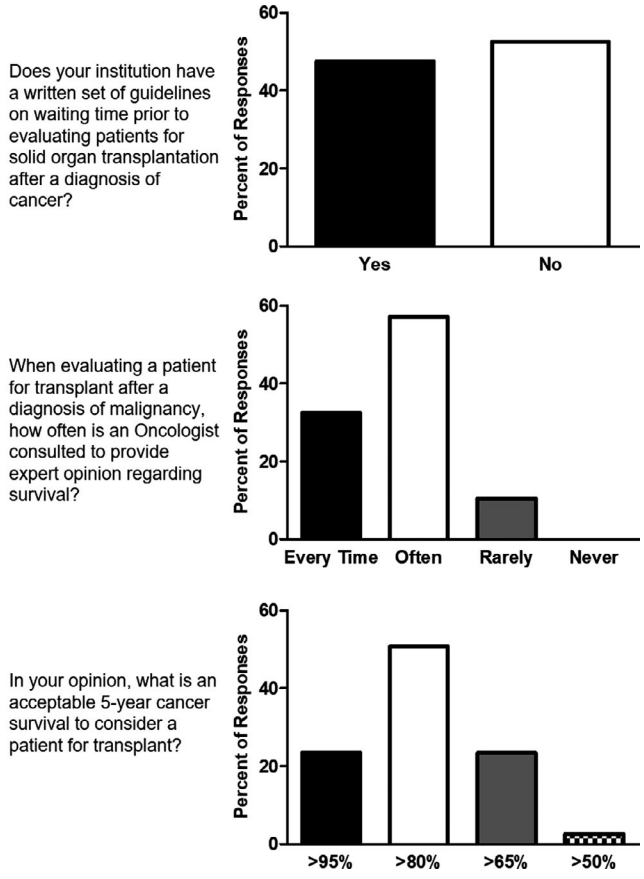

FIGURE 1 American Society of Transplantation survey results

1.4 | Methods

The AST held The Malignancy and Transplantation Meeting on September 29-30, 2019, in Dallas-Fort Worth, TX, with the goal of producing recommendations of when a patient with a PTM should be considered a SOT candidate. The challenge faced at this meeting was navigating the timing and uncertainty of whether offering a transplant to a patient with a PTM will lead to loss of immune control of their cancer and initiate a cancer recurrence. Therefore, this meeting convened transplant physicians (including surgeons, medical specialists, and anesthesiologists) along with experts in surgical and medical oncology, and cancer epidemiology to review the current literature regarding contemporary cancer therapies, cancer stage-specific prognosis, the kinetics of cancer recurrence, and the limited data on the effects of immunosuppression on cancer-specific outcomes. There were over 30 participants in attendance at the meeting, where three experts in each of the fields of melanoma and hematological malignancies presented summaries of these diseases and their relation to transplantation. Discussion and consensus agreements were then made. Writing groups for each cancer consisted of the three cancer experts and two or more transplant physicians.

In light of progress made in medical and surgical oncology, past recommendations on timing to transplantation may be too restrictive in many circumstances. Unfortunately, compelling data from rigorous studies do not exist for the determination of waiting time before SOT after successful treatment of a PTM. Unfortunately, clinical studies to answer this question would be challenging to design while also considering all relevant variables (eg, life-saving vs. life prolonging organ transplant, organ-specific levels of immunosuppression, type of cancer, and the availability of living donation). Although the authors have made the best recommendations possible, it is important to emphasize that there are significant gaps in knowledge, because much of the data is extrapolated from the general population. In addition, the recommendations are not meant to omit the valuable input oncologists play in appropriately selecting those to be transplant candidates, and we encourage ongoing discussions with our oncology colleagues. This document represents a consensus expert opinion; therefore, the levels of evidence were not graded.

1.5 | Mechanisms of cancer recurrence after transplantation

For most SOT recipients, immunosuppression is given to prevent acute and chronic rejection of the organ. While the exact

mechanisms are unclear, the effects of an inefficient immune system likely create a variety of pathways for cancer recurrence. One potential mechanism is through decreased immune surveillance, where there is an accumulation of oncogenic mutations or cells that would otherwise be identified and repaired by the immune system. This mechanism may be predominant in skin cancers, where immunosuppression impairs the cells ability to repair ultraviolet radiation-induced DNA damage through defective nucleotide excision repair.[6] Although logical, it is uncertain if a decrease in immune surveillance is the main contributor to the worse survival seen in patients with a PTM who develop a cancer recurrence after transplantation.[2–4]

Induction therapy with T cell depleting agents, increases the risks of cancers, such as melanoma.[7,8] In addition, T cell depleting agents used in the treatment of acute rejection of the kidney allograft also increase the risk of cancer development.[8] The mechanisms behind the short-term use of these therapies and the development or recurrence of cancer years later are incomplete. However, after T cell depletion, there is often an incomplete T cell recovery,[9] which can have a long-term effect on immune homeostasis leading to an impaired immune system[10,11] which can then predispose to the development or recurrence of cancer.

2 | MALIGNANT MELANOMA

2.1 | Background and staging

Dramatic improvements in treatment outcomes for patients with melanoma over the past decade mandate a new review of transplant candidacy and cancer-free interval guidelines. Estimated melanoma-specific survival outcomes are commonly determined by staging according to the American Joint Committee on Cancer (AJCC) 8th Edition Melanoma Staging System, which takes into account the thickness of the primary tumor, presence of ulceration, number of tumor-involved regional lymph nodes and the presence of in-transit, satellite, and/or microsatellite metastases, as well as distant organ metastasis.[12] However, melanoma-specific survival estimates within the AJCC manual do not reflect the dramatic advances in both adjuvant therapy for resected high-risk melanoma and systemic therapy for metastatic disease, with associated improvements in overall survival. With current therapeutic options, including immunological checkpoint blockade as well as the approved MAPK inhibitor regimens for BRAF mutant melanoma,[13–16] the 5-year overall survival rate for patients with metastatic melanoma is now greater than 50%. Given their efficacy in the metastatic setting, immunological checkpoint inhibition as well as targeted therapy have migrated to the postresection setting, with a decrease in the risk of melanoma relapse of over 40%.[17–20] Despite these favorable responses, it is unclear if cancer recurrence will increase posttransplant if the immune response toward the cancer that was facilitated by checkpoint inhibition is diminished by immunosuppression. This has been suggested by rare examples of donor derived malignancy from reportedly disease-free organ donors.[21] Additionally, the use of checkpoint inhibitors in the transplant patient population is also evolving. A recent systematic review and meta-analysis summarized the available literature investigating the use of these therapies for treatment of a variety of cancers after a variety of solid organ transplants.[22] Although beyond the scope of this consensus review, these studies highlight the consideration that the immunological checkpoint inhibition for cancer therapy must be weighed against the risk of organ rejection and potential graft loss.

Data supporting concerns for poor post-transplantation outcomes/recurrence in patients with a pretransplant history of melanoma is limited, with existing studies characterized by incomplete staging and treatment information.[23–26] Melanoma-specific mortality is elevated threefold in transplant recipients compared with nontransplant recipients, and was strongest for localized stage melanoma, suggesting that *de novo* melanoma behaves aggressively in the setting of immunosuppression.[27] This Scientific Registry of Transplant Recipients study is subject to the limitations of clinically relevant information, such as Breslow thickness, sentinel lymph node biopsy, and details on surgical treatment. The Transplant Cancer Match study determined recipients with pretransplant melanoma had an absolute risk difference of 3% for posttransplant melanoma and a 30% increase in overall mortality (but not clearly or solely due to melanoma).[26]

2.2 | Expert opinion transplant recommendations

To determine transplant eligibility, prior consensus guidelines considered the AJCC survival curves for each melanoma stage in combination with the post-transplantation survival rate goal.[28] If one accepts an 80% 5-year melanoma-specific survival as a threshold for transplantation, then all patients with a pretransplant melanoma diagnosis except for stage IIIC, IIID, and stage IV disease would be eligible following resection of disease. If the bar were raised to a 10-year melanoma-specific survival of 80%, then those with stage IA, IB, IIA, IIB, and IIIA would be eligible immediately following resection of disease. Thus, all patients with a pretransplant diagnosis of locoregional melanoma (stages I, II, and possibly some patients with stage IIIa) may be transplant candidates. Imaging of the brain, chest, abdomen, and pelvis (and neck for those with a primary melanoma affecting the head or neck) are recommended for patients with a history of at least stage IIA melanoma prior to consideration for transplantation.

Recommendations for wait times prior to transplantation must take into consideration not only the absolute risk of disease recurrence but also the kinetics of response (Table 1). The 5-year melanoma-specific survival for those with stage IA, IB, IIA, and IIIA is greater than 90%,[12] thus, we recommend a maximum of a 1-year wait time prior to transplantation for this group of patients, with 1- to 2-year wait time for stage IIIA patients. The 5-year melanoma-specific survival for those with stage IIB, IIC, and IIIB is greater than 80%, with a plateau observed on the survival curve beyond

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.

5 years.[12] Therefore, we recommend a wait time of 2–4 years prior to transplantation for this group of patients. Consideration for the effect of immunosuppression effects on patients with node positive disease controlled by checkpoint inhibition, needs to be included in the decision. In addition, the effects of checkpoint inhibition for treatment of melanoma may have unintended immunological consequences posttransplant, which should be a part of the informed consent process.

The 5-year melanoma-specific survival for those with stage IIIC and IIID is between 30% and 70%, with a plateau observed on the survival curve at 4–5 years.[12] Furthermore, the 5-year overall survival rates for patients with metastatic melanoma is now over 35%, with long-lasting treatment responses even after discontinuation of active checkpoint inhibitor therapy.[16,29] Institution of a wait time of at least 5 years prior to transplantation would be expected to prevent transplantation of most of this group of patients who will develop fatal melanoma recurrence. Concern for the effect of immunosuppression on the immune control incited by the checkpoint inhibitors is high in this population. In addition, given the potential for organ rejection with checkpoint inhibitor therapy in recurrent melanoma after transplantation,[22] no consensus recommendation could be reached regarding transplantation of this group of patients, including patients with stage IV disease; therefore, we recommend that such cases be discussed on an individual basis.

3 | HEMATOLOGICAL MALIGNANCIES

3.1 | Lymphoma

There are more than 100 subtypes of lymphoma. Diffuse large B cell lymphoma (DLBCL) has the highest prevalence, followed by follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma.[30] DLBCL, high-grade B-cell lymphoma with MYC and/or BCL2 and BCL6 rearrangements, Burkitt lymphoma, and other aggressive lymphomas are potentially curable. In contrast, follicular lymphoma (FL), marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), and other low-grade lymphomas have a long survival time but are not curable and respond to different therapies over time.[30]

Approximately 65%–75% of patients with DLBCL are cured with standard of care chemotherapy. However, variable outcomes can be predicted based on clinical factors.[31] Patients who have not relapsed

or have their cancer progress 2 years after treatment of their DLBCL (achieved progression-free survival; PFS24) have excellent outcomes. After PFS24 is obtained, overall survival is defined as time from achieving PFS24 to death from any cause, and these patients have a 5-year survival of 87.6%, which is similar to an age- and sex-matched cohort from the general population.[32]

For patients with follicular lymphoma, Rituximab combined with immunochemotherapy has improved their overall survival. For example, if a patient achieves an event-free survival of 24 months (EFS24) after treatment with immunochemotherapy, they have no greater mortality when compared to the general population.[33] Furthermore, in a pooled analysis of FL grade 1-3a in the immunochemotherapy era, the 10-year overall survival approximates 80%.[34]

The outcomes of Hodgkin lymphoma are very good, even in patients with advanced disease. At a median follow-up of 6.4 years, the complete remission rates are 73% and the failure-free survival was 74% for all patients treated with standard of care chemotherapy.[35] Most relapses occur within 2 years of treatment.

The T cell lymphoproliferative disorders are a complex group of diseases. If the EFS24 is achieved, it associates with improved survival with 78% of patients surviving 5 years.[36] Burkitt lymphoma is a malignancy characterized by rapid tumor growth, with a 2-year event-free survival rate of 80%. For patients in complete remission, the 2-year relapse risk was 6%, and further decreased to 0.6% for patients reaching 12 months of postremission event-free survival.[37]

Monoclonal B cell lymphocytosis (MBL), a premalignant condition, precedes all cases of chronic lymphocytic leukemia (CLL).[38] MBL is typically an incidental finding, with an estimated prevalence of ~5%–12% in patients over the age of 60 years. It has a very favorable prognosis. CLL is a complex low-grade lymphoproliferative disorder. New therapeutic interventions have significantly changed outcomes for these patients.[39] The CLL international prognostic index (IPI) includes five factors that are independently associated with survival, including age ≥65 (1 point), clinical Rai stage greater than 0 (1 point), unmutated immunoglobulin heavy chain gene (2 points), beta 2 microglobulin greater equal 3.5 mg/L (2 points), and a deletion(17p13) or *TP53* mutation (4 points).[40] Among patients with untreated CLL, the CLL-IPI score can predict the 5-year treatment-free survival: 78% in the low-risk group (score 0–1), 54% in intermediate-risk group (score 2–3), 32% in high-risk group (score 4–6), and 0% in the very high-risk group (score 7–10). Of note, these survival predictions do not consider the potential for cancer recurrence in the setting of immunosuppression. However, there is limited experience with eight patients with MBL or CLL who received a renal transplant found no posttransplant lymphoproliferative disorder. In addition, after a median follow-up of 52 months, no patient had progression of the underlying CLL.[41] The recommended waiting times before transplant are listed in Table 2.

3.2 | Multiple myeloma

Renal failure can complicate the treatment of multiple myeloma, necessitating discussions of renal transplant candidacy. Currently, myeloma remains incurable. Overall and progression-free survival is determined by response depth,[42,43] but relapse inevitably occurs. However, the patients who have the longest progression-free survival have achieved minimal residual disease negativity in the bone marrow and a stringent complete response by measurement of the monoclonal proteins and bone marrow plasma cells (Table 3). Median progression-free survival is 63 months with modern therapy, and overall survival at 10 years is over 60%.[42,43] Achievement of a state of minimal residual disease negativity should be a strong consideration before agreeing to proceed with renal transplantation.

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.

Prognosis is also driven by fluorescence in situ hybridization (FISH) genetics. Patients who have high-risk genetics have a much shorter progression-free and overall survival compared to patients with standard-risk genetics.[42] For example, patients with deletion(17p), t(4;14), or t(14;16) have a 3.6 times higher mortality and 2.3 times lower progression-free survival. Event-free survival for deletion(17p) varies from 14 to 28 months and overall survival is 49% at 4 years, based on therapeutic options available. t(4;14) has an event-free survival of 21–28 months with an overall survival of 44%–66% at 4 years.

Today, the standard of care for maintenance therapy in multiple myeloma patients in deep response is low dose lenalidomide therapy. Unfortunately, there are multiple reports of renal allograft rejection, resulting from lenalidomide therapy.[44] Five new active agents have been approved for the treatment of multiple myeloma, therefore, only trials after 2012 truly represent renal graft survival. A number of recent reports indicate that patients who are in remission for 6–12 months become safe candidates for renal transplantation if stem cell transplantation is part of the regimen to deepen response.[45,46] No data are available for nonkidney SOT, but other organ transplantation may be a consideration.

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.

3.3 | Amyloid

To consider a patient with amyloid light-chain (AL) amyloidosis for heart transplant, the patient must be willing to potentially have a stem cell transplant as part of posttransplant management, although many patients may be managed with chemotherapy after heart transplant and avoid bone marrow transplant. In one series of cardiac transplantation recipients with AL amyloidosis, 14 received a heart only, and 2 received a heart and a kidney; the Kaplan-Meier curve at 5 years showed a 76.6% survival.[47] Amyloidosis is a common cause of end-stage renal disease, with nearly one third of patients ultimately requiring renal replacement therapy. A deep response to treatment is required to prevent recurrent amyloidosis,[48] where survival at 10 years is 80%. Renal transplantation has been performed a median of 2.4 years after hematologic response occurred, and a minimum duration of hematologic response of 6–12 months prior to renal transplantation (Table 3). Graft survival at 10 years exceeded 60% and the median survival from renal transplantation was 10.5 years. No data exist for other SOT recipients.

3.4 | Myelodysplastic syndrome

Renal failure has occurred after bone marrow transplant for myelodysplastic syndrome. Consideration for renal or any transplant is dependent on pretransplant karyotype.[49] Patients that have low-risk genetics have less than a 20% chance of relapse at 12 years. Patients with high-risk genetics have a 50% chance of relapse at 4 years. Discussions between the transplant team and hematology, to determine the overall risk of transplantation, are needed.

3.5 | Expert opinion transplant recommendations

Transplant can generally be considered after 2 years in remission for many lymphoproliferative diseases (Table 2). In select circumstances, myeloma, amyloidosis, and myelodysplastic disease may not preclude transplant options (Table 3).

4 | CONCLUSIONS

Pretransplant malignancy is common in patients with end-stage organ disease undergoing evaluation for SOT, and the presence of a PTM can affect posttransplant outcomes. With advances in the contemporary therapy of cancer with improved overall survival, an updated consensus document on when to transplant patients with PTM was deemed a high priority by the AST. The importance of standardized surveillance of patients with a PTM after transplantation was also recognized and guidance is being created by this group. Recognizing the paucity of data surrounding the recurrence of melanoma and hematological malignancies, this conference and consensus documents can only aim to update *expert opinion recommendations* for proceeding with SOT given a history of a PTM. In order to improve the strength of these recommendations, prospective data from patients transplanted within these guidelines must be collected and shared, and is currently an initiative within the AST's Liver and Intestinal Community of Practice.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHOR CONTRIBUTIONS

David P. Al-Adra, Laura Hammel, David P. Foley, and Kymberly D. Watt contributed equally to the literature search, figures, study design, data interpretation, and writing of the manuscript. John Roberts, E. Steve Woodle, Deborah Levine, Didier Mandelbrot, Elizabeth Verna, Jayme Locke, Jonathan D'Cunha, Maryjane Farr, Deirdre Sawinski, Piyush K. Agarwal, Jennifer Plichta, Sandhya Pruthi, Deborah Farr, Richard Carvajal, John Walker, Fiona Zwald, Thomas Habermann, Morie Gertz, Philip Bierman, Don S. Dizon, Carrie Langstraat, Talal Al-Qaoud, Scott Eggener, John P. Richgels, George J. Chang, Cristina Geltzeiler, Gonzalo Sapisochin, Rocco Ricciardi, Alexander Sasha Krupnick, Cassie Kennedy, and Nisha Mohindra contributed equally to the literature search, study design, data analysis, data interpretation, and writing of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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