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Pre-Transplant Solid Organ Malignancy and Organ Transplant Candidacy: A Consensus Expert Opinion Statement

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Abstract

Patients undergoing evaluation for solid organ transplantation often have a history of malignancy. Although the cancer has been treated in these patients, the benefits of transplantation needs 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, non-small cell lung cancers. This conference and consensus documents aim to provide recommendations to assist in the evaluation of patients for solid organ transplantation given a history of a pre transplant malignancy.

Introduction

The primary barrier for consideration of solid-organ transplantation (SOT) in patients with pre-transplant malignancy (PTM) is the concern that immunosuppression amplifies the risk of cancer recurrence, potentially impacting post-transplant 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 two 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 two to five or greater than five 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 (e.g. dialysis and ventricular assist devices) (Fig. 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.

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, urological, gynecological, non-small 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 wait list mortality and degree of immunosuppression expected post-transplant. Further, 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.

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 were discussed as a panel and consensus agreements were then made (modified Delphi method), with the general consideration that a five-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.

Breast Cancer

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 US.[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 (e.g., Oncotype DX). These changes have led to more women being diagnosed with stage I disease.[12]

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.

Therapy

Changes in treatment paradigms have made the algorithm for prognostication much more diverse.[12,13] Most women with non-metastatic 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 post-mastectomy 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.

Transplant Recommendations

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 five-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 completion of all standard treatments (such as surgery, radiation, and/or non-endocrine systemic therapy), with no additional waiting time (Table 1). Endocrine therapy is often continued for 5–10 years after 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 five-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.

High Risk Breast Cancer—Patients with advanced stage breast cancer (stage III) have five-year survival rates ranging from 50–70%[18]. However, most recurrences will occur within the first three 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 five-year survival is <55%.[21,22] Similarly, all women with metastatic disease have a poor prognosis, with a median overall survival of two to three years.[23–25] Therefore, these patients generally should not be considered as transplant candidates.

Colorectal Cancer

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 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 post-surgical treatment decision-making, including transplantation.

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 5–40% 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, i.e., treatment without surgery at all. With the introduction of non-operative 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 non-operatively for rectal cancer undergo surveillance for at least five years.[34]

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 post-cancer treatment) were common (27%).[35,36] Of patients with recurrence, only 13% had been treated for their CRC within two years prior to transplantation, while the remaining 87% of recurrences occurred in patients that were transplanted 3–6 years post-malignancy.[35] This delay in recurrence is concerning, considering that most recurrences in the general population occur within three years, with very few (<1%) occurring >5 years post-cancer treatment.[37] However, these data derive from a different cancer treatment and transplant era and are limited by unknown complete staging.

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.

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 one and five 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.

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 time of transplantation, but data from the general population suggests 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 *non-invasive* anal lesions require careful consideration before transplanting due to the increased risk for progression of these lesions. Aggressive surveillance practice would be warranted after transplant.

Urological Malignancies

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 five-year cancer-specific mortality (<1%) after a post-transplant 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 (e.g., 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 <5%. Our recommended waiting time and management guidelines after a diagnosis of prostate cancer are listed in Table 4.

Renal Cell Carcinoma (RCC)

The majority of renal masses detected in patients being considered for transplantation are incidental and ≤4cm, 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 three-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 (<0.3cm/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 post-operative 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, (e.g., heart, lung, liver) surveillance should be considered in SRM (<3cm). Following a successful transplant and

outcome, the post-transplant nephrectomy can be performed 3–6 months post-transplant with superior outcomes.[58] In non-immunosuppressed 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 post-transplantation, 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]

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 non-muscle 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 six months to determine recurrence kinetics (Table 6). If there is no recurrence within six months, transplant can be considered, as the risk of progression is extremely low (ranging from 1–2% over five years) despite a recurrence rate of up to 28% at five 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 six months is recommended. For patients with high risk NMIBC, the risk of progression is significantly higher upon diagnosis (approximately 18% at five years),[63,64] and the timing of transplant remains controversial. However, a waiting time of at least two 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 two years after diagnosis.[62]

For patients with muscle-invasive bladder cancer (MIBC) treated with radical cystectomy, most recurrences occur within two years of surgery and can either occur locally, within the remaining urinary tract, or be metastatic. Beyond two years, the recurrence rate is low[65] and, therefore, consideration may be given to transplantation in patients with at least no evidence of disease two years after radical cystectomy. In fact, a two-year disease-free survival rate is an adequate surrogate for five-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.

Gynecologic cancers

Background and Staging

Gynecologic cancers have impacted over 100,000 women in the US 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.

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 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 4cm or larger) or other advanced features (e.g., local invasion beyond the uterus). For these women, surgery can be curative, though 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]

Transplant Recommendations

There is minimal literature on survival and risk of cancer recurrence after transplant in patients with pre-transplant 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 five-year disease-specific survival that exceeds 90%, with the greatest risk of disease recurrence in the first two years.[77] As a result, one should consider transplant if no evidence of disease at least 2–3 years after completion of therapy. Patients at high risk of recurrence include patients with advanced uterine ovarian or cervical cancer. Although some patients with ovarian cancer are

cured, more than half will relapse in the first two years of follow-up.[78] However, women who are candidates for a Poly (ADP) ribose phosphorylase (PARP) inhibitor can extend progression-free survival by three years or longer with maintenance therapy.[68,69] For women with high-risk endometrial cancers, approximately 40% will relapse within the first three years.[79] For women with stage III cervical cancer, the rate of progression free survival is 80% at four 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.

Non-small Cell Lung Cancer

Background and Staging

Non-small 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 1996–2007, 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 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]

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 (≥4cm) 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 two years following definitive treatment, however, recurrence can occur as far out as five 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 two 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.

Pre-existing 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 seven months.[92]

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 five-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 three years with *significant* caution. It is also worth noting that the effects of checkpoint inhibition pre-transplant may have unintended immunological consequences post-transplant.[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 post-transplant 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.

Conclusions

Pre-transplant malignancy is increasingly common in patients with end-stage organ disease undergoing evaluation for SOT and can affect post-transplant 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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Abbreviations:

(AJCC)	American Joint Committee on Cancer
(AST)	American Society of Transplantation
(ctDNA)	Circulating tumor DNA
(CRC)	Colorectal cancer
(CRLM)	Colorectal liver metastases
(POLE)	DNA-polymerase-ε
(DCIS)	Ductal Carcinoma in situ
(ER)	Estrogen receptor
(HR)	Hazzard Ratio
(HER2)	Human epidermal growth factor receptor 2
(HPV)	Human papilloma virus
(MIBC)	Muscle-invasive bladder cancer
(NMIBC)	Non-muscle invasive bladder cancer
(NSCLC)	Non-small cell lung cancer
(PARP)	Poly (ADP) ribose phosphorylase
(PTM)	Pre-transplant malignancy
(PR)	Progesterone receptor
(RCC)	Renal cell carcinoma
(SRM)	Small renal mass
(SOT)	Solid-organ transplantation

(SBRT) Stereotactic body radiation therapy

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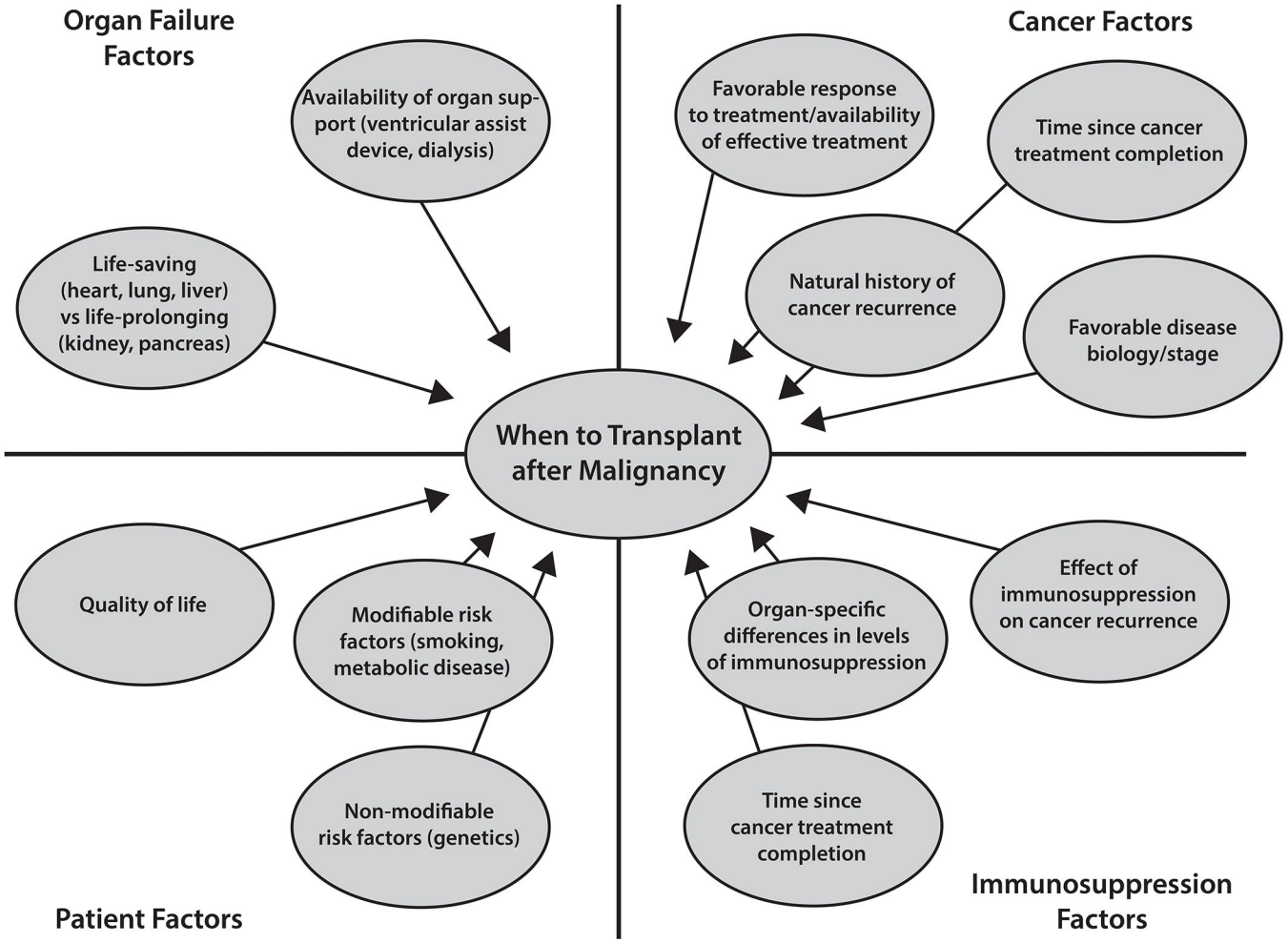

Figure 1.
Potential factors to Consider When Evaluating a Patient with a PTM for Transplantation.

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 *	-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 *	-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 *	-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	

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

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

Table 2.

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

Risk/Stage	Recurrence Free Survival 5-year[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

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

Table 3.

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

Risk/Stage	Recurrence Free Survival 5-year[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 & 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

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

Table 4:

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

Risk/Stage	Survival[60, 62, 64]	Time Interval to Transplant	Additional Considerations
VERY LOW RISK - PSA< 10 ng/ml - 3 or fewer cores of Gleason 6 (grade group 1); no greater than 50% of individual core - T1c-T2a	<1% risk of mets/death over 15 years	None	Surveillance is strongly recommended Extenuating circumstances may require treatment
LOW RISK - PSA< 10 ng/ml - Gleason 6 (not meeting very low-risk criteria) - T1c-T2a	~2–3% risk of mets/death over 15 years	None	Surveillance is strongly recommended Extenuating circumstances may require treatment
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

PSA: Prostate specific antigen

Table 5:

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

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

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

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 *	19%	6 months
Intermediate risk **	39%	6 months
high risk ***	38% ***	2 years
MIBC, post radical cystectomy	25–37%	2 years
MIBC, post chemoradiation	25–30% (10 year)	Not a SOT candidate

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

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

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

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

Table 7:

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

5-year Recurrence Risk[92,93,94]	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 * 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

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

Table 8:

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

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

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