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CANCER REHABILITATION (MD STUBBLEFIELD, SECTION EDITOR)

The Role of Rehabilitation Medicine in Managing Cardiopulmonary Complications of Cancer

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Abstract

Purpose of Review Cancer survivors represent the largest cohort of patients seeking specialty rehabilitative care. They carry a heavy burden of cardiopulmonary complications, but in the past have been excluded from many exercise studies, owing to perceived increased risk.

Recent Findings Cardiopulmonary dysfunction in cancer survivors is a complex phenomenon that goes beyond lung volume loss, dilated cardiomyopathy, or accelerated coronary artery disease. All training modalities have been explored in cancer survivors before, during, and after active treatment, proving effective against aerobic capacity decline due to cancer.

Summary We summarize common adverse treatment effects, particularly due to newer chemotherapeutic agents, and provide examples of exercise interventions, designed to mitigate cardiopulmonary decline in a cancer survivor. Carefully designed routines can be safely applied in most situations, where aerobic reconditioning is needed. Lastly, physiatrists may be the most effective advocates in overcoming systemic barriers, such as insurance regulations, that limit access to cardiopulmonary rehabilitation.

Keywords Oxygen consumption (VO_{2peak}) · Prehabilitation · High-intensity interval training (HIIT) · Survivorship · Ventricular assist device (VAD) · Orthotopic heart transplant (OHT)

Introduction

The most common cause of death in the USA is cardiovascular disease (CVD) [1]. Cancer and CVD share risk factors, such as age and smoking exposure; thus, even without additional treatment-related morbidity, a cancer survivor is likely to have some form of underlying cardiopulmonary dysfunction (CPD). Owing to treatment advances, the overall 5-year survival for cancer survivors has improved from 49% in 1975–1977 to 69% in 2006–2012 and death rate decreased by 25% since 1991 [2]. Thus, the cancer survivor population, which already outnumbers other recipients of specialty rehabilitation services such as patients with stroke or traumatic brain injury, will continue to grow [1, 3]. The likelihood that a given cancer survivor has a CPD depends on several factors, including the treatment era, age at diagnosis, treatment modality, and the presence of pre-morbid conditions, such as hypertension (HTN), dyslipidemia (DL), abnormal glucose metabolism (AGM), or obesity. Classic cardiotoxic agents, such as anthracyclines, remain widely used due to their effectiveness, thus making it very likely that a cancer rehabilitation physiatrist will treat a patient with anthracycline cardiomyopathy. Typical course begins with the asymptomatic decline in ejection fraction, eventually manifesting as overt heart failure with fatal cardiac event hazard ratio of 3.46 and 50% mortality rate at 2 years [4]. The survivors of childhood cancers likely represent the cohort with the largest CPD burden. These patients suffer from cardiac mortality equivalent to that of the population 20 to 30 years older [5]. Childhood Hodgkin lymphoma (HL) survivors are twice as likely to have CPD as population controls (89% prevalence) and have at least one severe condition by 50 years of age, despite having the same prevalence of HTN and DL [6]. Childhood recipients of hematopoetic stem cell transplants (HSCT) carry higher burden of CPD than other cancer survivors, with up to 19.6% having a severe cardiovascular and 16.1% having a severe pulmonary disorder, along with higher prevalence of HTN, DL, AGM, and

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obesity [7]. Similarly, all children treated with high-dose carmustine in the 1980s and early 1990s developed upper zone pulmonary fibrosis with over 50% mortality [8]. In contrast, recently developed chemotherapeutics, e.g., small molecule tyrosine kinase inhibitors (TKIs, or "-inibs"), appear to have a much lower incidence of pulmonary fibrosis (around 1–4%), though also carry a 50–60% mortality rate, similar to the classic agents such as busulfan and nitrosureas [9]. It is important to remember that the global CPD in a cancer patient is more than the sum of individual treatment morbidities and that appropriate rehabilitative strategies along with lifestyle changes, such as weight control and smoking cessation, can mitigate some of the decline.

Overview of the Cardiopulmonary Function Decline Along the Survivorship Continuum

Direct echocardiographic measure of the left ventricular ejection fraction (LVEF) has long been accepted as a proxy of cardiac function and a marker of morbidity; however, it does not adequately describe one's work reserve. Aerobic capacity, or the ability to make adenosine triphosphate (ATP) and use it for muscular work, is the underpinning of any sustained human activity. It can be directly measured via a cardiopulmonary exercise test (CPET), a tool that has been successfully employed in cancer survivors. Peak oxygen consumption (VO_{2peak}) has been shown to decline with more treatment cycles [10, 11], which is not surprising, given that commonly used agents, such as cyclophosphamide, have been shown to decrease the amount of ATP generated [12]. However, at least one investigation suggests that the decline in VO_{2peak} could be seen even before exposure to chemotherapy, and that despite having normal LVEF, up to one third of breast cancer patients have VO_{2peak} below the independent living threshold [13]. One possible explanation for that observation could be the Warburg effect, the discovery that yielded the 1924 Nobel Prize in Medicine. Even when oxygen is available, cancer drives a shift toward a less efficient glycolytic pathway that increases the availability of lactate to the tumor cells and decreases a body's ability to utilize oxygen [14]. One exciting therapeutic application of this phenomenon is the potential that aerobic conditioning which improves a person's ability to clear lactate can have direct effect on cancer growth and spread.

Detailed discussion of every possible reason behind CPD in a cancer survivor is beyond the scope of this text. In the broadest sense, cardiopulmonary capacity is the ability to effectively use oxygen for muscular contractions expressed as observable work. We believe that any decline in a survivor's ability to move or take part in the activities of daily living is a manifestation of impaired oxygen utilization, unless the loss of function can be fully explained by other issues, such as uncontrolled pain, loss of limb, or psychologic factors. There are several events that have to take place so that an inhaled molecule of oxygen contributes to an externally apparent muscular effort. Figure 1 summarizes those steps, factors contributing to decreased aerobic capacity across the entire cancer care continuum, and lists corresponding corrective strategies. It is important to remember that there is an opportunity for effective rehabilitative intervention at every stage and that often there are systemic barriers, such as lack of insurance instruments that will demand creative solutions for a specific care scenario.

Prehabilitation

It is well accepted that oxidative stress plays a large role in morbidity related to cancer treatment. Free radical formation happens as the result of exposure to radiotherapy and medications, most notably anthracyclines, such as doxorubicin, a classic cardiotoxic agent. While there has been increased interest in using the anti-oxidant effects of aerobic exercise to prevent treatment-related toxicity [16], the first studies on this subject are almost four decades old [17]. Murine data demonstrate beneficial effects on micro- and macroscopic levels, showing improved survival after the anthracycline administration. Unfortunately, at this time, there are no insurance regulations that would make it possible for patients to undergo supervised structured aerobic conditioning in preparation to cardiotoxic cancer treatment. One possible solution to this problem is utilizing existing principles of generalized aerobic conditioning, such as progressive aerobic loads with patient-specific training heart rate zones and providing patients with easily adopted self-directed exercise routine.

High-intensity training (HIIT) has been successfully employed in a variety of CPD scenarios. Owing to the short duration of intervention, HIIT is an appealing solution for situations when there is only a limited time window for rehabilitative intervention. As little as 7 days of intense training prior to planned pulmonary resection have been shown to reduce the incidence of immediate complications and the length of stay [18, 19] while longer programs helped mitigate the decline in VO_{2peak} [20].

Exercise During Active Treatment and Hospitalization

Prevention of Hospital-Acquired Immobility

Risks of low mobility during hospital admission have been recognized in peer-reviewed literature since the 1940s [21] and have been associated with readmission, regardless of the presenting diagnosis [22–24]. Early mobilization has been

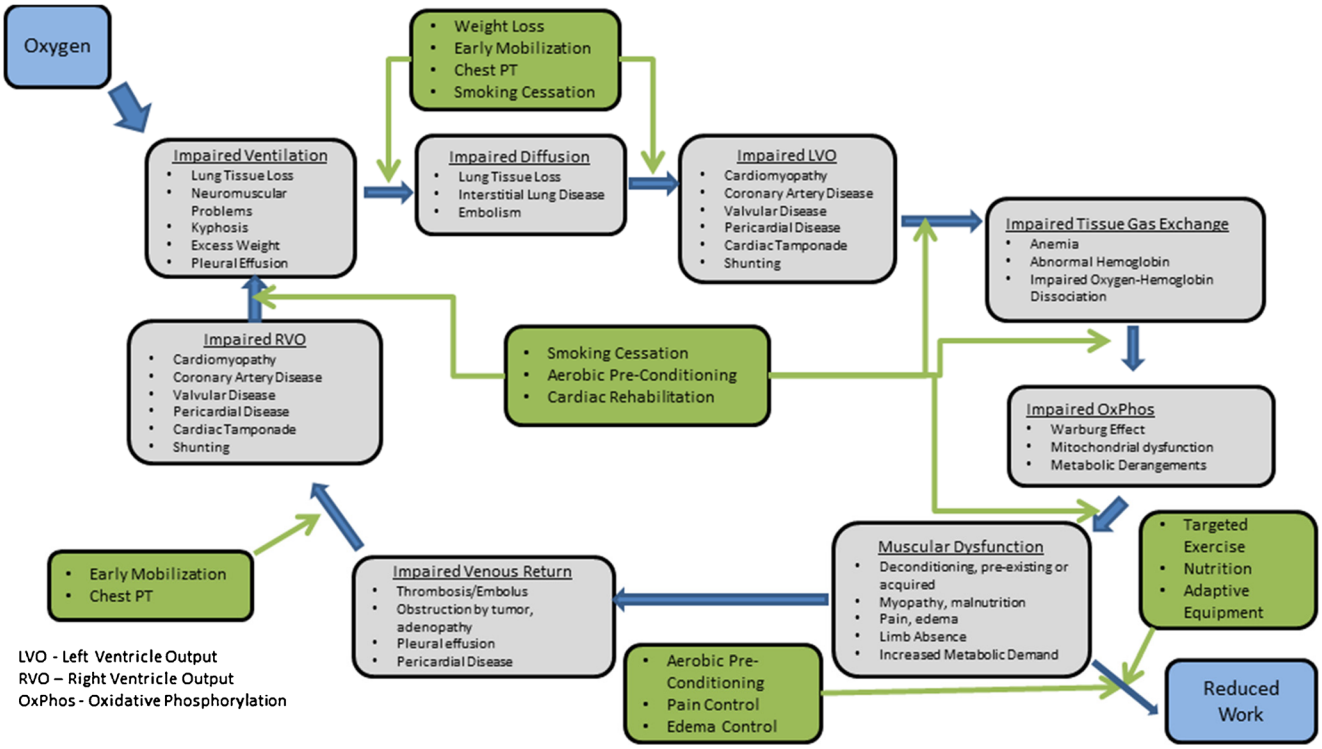

Fig. 1 Cycle of abnormal oxygen utilization in a cancer patient. It is a multi-step process that converts atmospheric oxygen into externally apparent work (mobility and activities of daily living). Gray boxes represent discrete stages with possible morbidities. Green boxes list corrective interventions that are within the scope of physiatric practice. Adapted from Bartels MN, Syrkin G: Cardiovascular Complications of Cancer and Their Treatment. In: Stubblefield, MD, editor. *Cancer Rehabilitation, Principles and Practice*, Second Edition. Demos Medical, 2018 (in print) [15]

shown to benefit even the critically ill [25]. This has particular relevance for cancer patients, especially those undergoing surgical procedures. Measures that promote early mobility, such as regional anesthesia, early enteral feeding, and careful fluid balance, have shown benefit in such high morbidity procedures as esophagectomies and lung lobectomies [26, 27]. Mobilizing patients out of bed to chair on postoperative day 1 in the thoracic unit at Memorial Sloan Kettering Cancer Center reduced the incidence of pulmonary complications from 14.4 to 2.9%, rate of ICU admission from 5.1 to 4.2%, and length of hospital stay from 9.3 to 8.2 days [28]. A cancer rehabilitation physiatrist serving as an acute care consultant can help prevent unnecessary immobilization by prescribing safe and effective exercise interventions in the immediate postoperative period.

Exercise During Active Treatment

Exercise has also been shown to be safe and beneficial even in such taxing circumstances as high-dose chemotherapy and HSCT in the management hematologic malignancies, where acute and 1-year mortality reaches 2.8–5.7% and 21% respectively [29, 30]. Approaches ranging from supine in-bed bicycling to multimodal resistance and endurance routines have been shown to positively affect cardiopulmonary fitness and reduce adverse effects of treatment [29, 31–38]. All studies utilized a baseline CPET to determine target heart rate and continuous pulse monitoring to ensure exercise efficacy. One of the more elegant investigations demonstrated that a 30-min daily intervention consisting of in-bed cycling intervals (1 min cycling at 50% cardiac reserve, followed by 1 min rest) can decrease length of stay, duration of neutropenia, thrombocytopenia, reduce diarrhea, pain, and limit the decline of physical function [31]. Newer studies employ psychologic counseling and relaxation for a more comprehensive approach [37, 38]. Similarly, exercise interventions have shown benefit in other diagnoses including lung, breast, prostate, and gastrointestinal cancers [39–46]. As with inpatients undergoing myeloablation, even simple exercise interventions, such as walking three times per week for 30 min at 50% of predicted cardiac reserve, significantly improved oxygen uptake and functional performance [43].

As in the prehabilitation period, properly designed and carefully administered high-intensity interval training (HIIT) is a promising training modality for cancer patients in active treatment, who often have low exercise tolerance. Due to the short session duration, work can be completed prior to the onset of debilitating fatigue. HIIT has been shown to be safe and effective in a variety of patient populations, including those with heart failure and recent cardiac surgery [47–51].

Repeated sit-to-stands (STS) have been validated as both a measure of frailty and a predictor of mortality in a variety of patient populations [52–55]. In our experience, STS can be easily administered to a hospitalized patient as the primary work load. Exercise safety is assured as the seating surface can be adjusted for height (controlling the muscular effort) and is directly behind the patient in case of lost balance. Finger pulse oximeter allows monitoring of heart rate in real time. For patients with congestive heart failure, exercise periods of 30 s and 60 s rest are recommended [50].

Role of Physiatry in the Post-acute Care

For those patients who are unable to function in the community as the result of their disease and its treatment, the importance of appropriate post-acute care cannot be overstated. Achieving functional status can often mean the difference between curative treatment and palliative care only. Inpatient and outpatient cardiopulmonary rehabilitation must be pursued for cancer patient who develops new heart failure and angina and suffers a myocardial infarction (MI), or significant lung volume loss. In our experience, it is often the consultant physiatrist who can most effectively advocate for the patients and overturn denials of rehabilitative care by insurance companies. As in general population, the primary barrier to structured cardiopulmonary rehabilitation is access and all members of the patient care team must be educated to ensure timely referrals.

Safety Considerations During Active Cancer Treatment

Acute coronary syndrome (ACS) remains an important cause of early chemotherapy-related cardiac disease. Classic agents, such as paclitaxel, cisplatin, and 5-fluorouracil, cause ACS in about 1% of chemotherapy recipients [56]. Some groups, such as African-Americans or patients with pre-existing cardiac risk factors, may be at a higher risk. Newer agents, such bevacizumab (Avastin), have been associated with a more than fourfold increase in cardiac ischemic events, including 0.6% incidence of MI [56, 57]. More alarmingly, up to one third of patients receiving anti-angiogenic tyrosine kinase inhibitors, such as sunitinib, sorafenib, and cediranib, have been reported to have an elevation in cardiac enzymes, EKG changes, or ACS symptoms [58]. Furthermore, uncontrolled hypertension due to high volumes of intravenous fluids, associated with classic chemotherapy agents, or renovascular dysregulation, caused by the newer medications, such as bevacizumab or TKIs, can result in ACS or acute congestive heart failure (CHF) [56, 58, 59]. Grade 3 HTN (systolic blood pressure > 180 mmHg, or diastolic pressure > 110 mmHg) can happen as early as the first 1–3 days, which may be found in up to 92% of patients with renal cell carcinoma receiving a combination of sunitinib and bevacizumab, or in 1 of every 17 patients receiving a single TKI [58, 60].

Table 1 summarizes frequently encountered cardiopulmonary toxicities of neoplastic agents.

Additionally, there may be other patient-specific barriers to exercise, such as impaired venous return, increased limb weight due to edema, pain, fever, anemia, and skeletal pain from metastatic bone lesions. Many of these factors can be effectively and safely addressed by appropriate national guidelines, such as venous thrombosis prophylaxis and timely mobilization [75, 76], while other may be helped by the modifying exercise program or employing adaptive equipment, orthoses, mobility aides, compression garments, or other tools of rehabilitation trade.

Table 2 summarizes various exercise exclusion criteria used in patients undergoing active cancer treatment.

Exercise After Active Treatment

Similarly, exercise in the post-treatment period showed numerous benefits for major cancer diagnoses [45, 77–85]. Typical resistance regimen is exemplified by a protocol outlined by Segal et al.: warm-up, followed by 2 sets of 8–12 repetitions of nine exercises targeting major muscle groups—leg extension, calf raises, leg curl, chest press, latissimus pulldown, overhead press, triceps extension, biceps curls, and modified curl-ups, performed at 60–70% of 1-repetition maximum 3 times weekly for 12 weeks [82]. Aerobic programs typically utilize a brief warm-up, followed by 30 min of cycling, walking, or jogging at 65–80% of cardiac reserve [83]. Even high-impact aerobic activity (soccer) in prostate cancer survivors with known asymptomatic bony metastases showed improved lean body mass and VO_{2max} without observed pathologic fractures [86]. Simple, easily accessible eccentric exercise, such as descending stairs, has proven effective in decreasing heart rate and systolic blood pressure and increasing bone mineral density in healthy obese women [87], though it is yet to be validated in cancer survivors. Most recently, HIIT has been shown to reduce CVD risk factors in testicular cancer survivors by as much as 20% [88].

Exercise Adherence

Continued adoption of physical activity is a challenge in both general US population and cancer survivors, particularly those with lower baseline function [89]. Various approaches, such as group therapy [90–94], telephone follow-up [44], and team sport activities [86, 95], have proven to be helpful.

Table 1 Selected cardiopulmonary complications of chemotherapy

Adverse effect	Commonly implicated agents
MI/ACS	*Paclitaxel*, *bevacizumab*, cisplatin, 5-fluorouracil, sunitinib, sorafenib, axitinib, regorafenib, cabozantinib, cediranib
CHF	*Doxorubicin* (> 550 mg/m^2), *trastuzumab*, daunorubicin, epirubicin (> 900 mg/m^2), idarubicin, sunitinib, sorafenib, pazopanib, dasatinib, trametinib, bortezomib
HTN	*Bevacizumab*, *sorafenib*, trastuzumab, aflibercept, sunitinib, ponatinib, imatinib, pazopanib, axitinib, regorafenib, lenvatinib, everolimus
Atherosclerosis	Class effect of selective estrogen receptor modulators (e.g tamoxifen), aromatase inhibitors (e.g., anastrozole), antiandrogen therapies (e.g., leuprolide, enzalutamide), dasatinib, nilotinib, ponatinib
Acute pulmonary edema	*Bleomycin**, gemcitabine, trans-retinoic acid, cytosine-arabinoside, methotrexate, docetaxel, decitabine, dasatinib
Acute diffuse alveolar damage	*Bleomycin*, *busulfan*, carmustine mitomycin
Infusion hypersensitivity	*Paclitaxel*, bleomycin, carmustine
Acute pneumonitis	*Mitomycin*, *paclitaxel*, *docetaxel*, gemcitabine + taxane, methotrexate, cyclophosphamide, gold salts, minocycline, oxaliplatin, fludarabine, bortezomib, lenalidomide
Chronic pneumonitis	Mitomycin, actinomycin—may provoke "radiation recall"
Chronic pulmonary fibrosis	*Bleomycin*, *busulfan*, *carmustine*, tamoxifen + cobalt-60 rt, cisplatin with RT, methotrexate, cyclophosphamide, ifosfamide, chlorambucil, melphalan
	Afatinib, *alectinib*, *ceritinib*, *crizotinib*, *erlotinib*, *gefitinib*, *lapatinib*, *osimertinib*, *pazopanib*, *trametinib*, *vandetanib*, imatinib, dasatinib, nilotinib, sorafenib, sunitinib

Italic designates most frequently reported chemotherapeutics. Adapted from [8, 9, 56–74]

MI myocardial infarction, *ACS* acute coronary syndrome, *CHF* congestive heart failure, *HTN* hypertension

*Supplemental oxygen greater > 30% concentration has been reported to provoke acute pulmonary edema in patient with remote bleomycin exposure

Early Recognition of Late Treatment Toxicity and Exercise Safety

Physiatrist taking care of a patient with remote history of cancer may be the person best positioned to detect early symptoms of CPD. Assessing treatment-related cardiopulmonary risk factors and communicating with cancer care providers can greatly facilitate timely diagnosis and safe rehabilitation. Another important role for a cancer rehabilitation physiatrist is ensuring exercise safety. When a survivor plans to engage in an exercise program that may include a high cardiac workload, physiatrist should elicit important historical risk factors, such as family history of sudden cardiac death, high left chest radiation exposures, anthracycline doses, or a combination of the two modalities. One trial (HF-ACTION) demonstrated higher all-cause mortality at 35 months (84 vs 66%) in the cancer survivors with heart failure, if they could not tolerate > 90 min of exercise per week, likely indicating that special attention is needed to guide aerobic exercise in such cases [96]. Indeed, a more recent report showed that women with heart failure due to the effects of breast cancer treatment demonstrate similar gains and same dropout rates as controls with ischemic cardiomyopathy [97].

Table 2 Contraindications to exercise during active cancer treatment

Hemodynamic	DBP decrease of >10 mmHg or SBP decrease of >20 mmHg from baseline
	60 mmHg<DBP>115 mmHg, 90 mmHg<SBP>160 mmHg
	MHR>(180−age), RHR>115 bpm
	MHR>RHR+(220 − age−RHR)×75%
Hematologic	Hemoglobin <8 mg/dl, WBC <10^3/μl, PLT <25–50×10^3/μl
Systemic	Fever >38 °C (101 °F), severe illness, confusion, impending pathologic fractures or cord compression, day of cardio- or neurotoxin administration
Reported symptoms	Angina, fatigue, dyspnea, wheezing, skeletal pain, claudication

DBP diastolic blood pressure, *SBP* systolic blood pressure, *MHR* maximum heart rate, *RHR* resting heart rate, *WBC* white blood cell count, *PLT* platelet count

Radiation therapy is a major contributor to the development or progression of coronary artery disease. While newer treatment modalities, such as breath holding and prone positioning, greatly reduce or eliminate cardiac irradiation, patients treated prior to the last decade are likely to have received more than the recommended maximum of 30–35 Gy to the cardiac region. The risk of events, such as MI, cardiac revascularization, or death from ischemic heart disease, increases by 7.4% for every 1 Gy delivered to the heart [98]. Similarly, radiation-induced valvular disease (RVD) is becoming less frequent—when calculated dose to valve is < 30 Gy, the increase in valvular disease risk is only about 1.4% at 30 years [99]. However, any modifiable risk factors (smoking, DL) must be managed as more than half of the patients with RVD will progress [99].

Stretching exercise, one of restorative therapy mainstays, has already been shown to benefit head and neck cancer patients before and during radiotherapy [100–102]. One mechanistic explanation for this is the stretch-induced production of nitric oxide (NO). It acts both as a free radical scavenger, protecting muscle stem cells [103], and as a signaling molecule, stimulating muscle repair [104]. Thus, there is good reason to counsel patient to engage in both general stretching routines and regular aerobic exercise to promote NO elaboration by cardiac muscle and surrounding tissues that happens in response to increased filling with activity.

Advanced Management of the End-Stage Cardiopulmonary Dysfunction

Ventricular Assist Devices in Cancer Patients

Physiatrist taking care of cancer survivor with cardiac disease can be an effective advocate in pursuit of advanced CPD management—ventricular assist devices (VADs) [105, 106]. Recent report from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) suggests that patients with cancer treatment-related heart failure represent about 2% of VAD recipients. They are more likely to be younger and female and have fewer comorbidities, but higher incidence of right ventricular failure [107, 108]. Survival appears to be similar to that of VAD recipients without history of cancer (73, 63, and 47% respectively at 1, 2, and 3 years), although cancer patients often require more additional cardiac surgeries, such as tricuspid repair (approximately one-half vs one-third in other etiologies), and those with more severe restrictive cardiomyopathy may fare worse [106, 109]. Interestingly, in the cancer cohort recovery of cardiac function allowing explanation of the VAD has been reported in 4.1%, up to 21% of them show improvement of LVEF to greater than 40% [110].

Since VADs have been approved as a bridge to transplantation, two major scenarios have been described in oncologic population. There have been 32 new cancer diagnoses in VAD recipients, either during pre-transplant workup or while awaiting an organ, with at least 12 patients being able to undergo cancer treatment owing to VAD support [111–114]. Additionally, there are three cases of VADs implanted specifically to facilitate cancer treatment in patients with active disease [113, 115]. Furthermore, in several of the cases, VADs facilitated home discharge, which can be of great importance at the end-of-life [114, 116–118].

Heart and Lung Transplantation in Cancer Survivors

As with VAD use, physiatrist can serve as the interface between the oncology and solid organ transplant service for patients who may need heart and lung transplantation. Current guidelines no longer recommend the arbitrary 5-year waiting period following completion of cancer treatment. Indeed, there is at least one case report of a successful double-lung transplant for acute bleomycin toxicity 5 weeks following testicular cancer treatment [119]. The decision regarding the feasibility and timing of the transplantation in a cancer survivor should depend on the tumor type, treatment response, recurrence, and metastatic risk [120]. According to United Network for Organ Sharing (UNOS), cancer patients represent about 0.8% of those listed for an orthotopic heart transplant (OHT) and have comparable outcomes following the procedure without significant increase in secondary malignancies [105, 106]. Despite having more infections (22 vs 14%), fewer cancer patients had rejection at 1 year (28 vs 38%) and survival at 1, 3, and 5 years was similar to OHT recipients without oncologic history—86, 79, and 71% respectively [121].

Lifestyle Changes

Physiatrists often have close and lasting therapeutic relationships with their patients. In our opinion, that privilege makes it possible to successfully tackle such difficult problems as smoking cessation, weight control, and dietary changes. Since cancer survivors are prone to accelerated atherosclerosis due to effects of hormonal deprivation, radiation, and other forms of oxidative stress, risk-free interventions, such as plant-based diets, can provide same amount of CVD risk reduction as intense exercise and reduce risk of cancer by 8–15% [122–124]. Similarly, a physiatrist can also be more effective in helping patients quit smoking, citing immediate benefits and involvement during a pulmonary rehabilitation program while emphasizing benefits such as reduced pain and faster recovery following lung cancer surgery [125].

Conclusion

As physicians tasked with maintaining a person's function across time and different settings, physiatrists are uniquely positioned to supplement the efforts of the oncology team and help patients tolerate some of the most morbid treatments. Physiatrists' focus on interdisciplinary care and ability to navigate insurance barriers and social issues can help a cancer patient at any stage of the cancer journey, from prehabilitation to hospice. By taking into account co-existing diseases, anticipating adverse treatment effects, and utilizing adaptive equipment, physiatrists can help prepare patients for taxing cancer care, avoid unnecessary immobilization during hospitalization, guide appropriate post-acute care services, and provide sustainable restorative care until the very end. Regardless of the diagnosis or treatment phase, cardiopulmonary fitness of a cancer survivor can be improved through exercise [126], even to the point of being able to complete a full marathon during chemotherapy [127]. Additionally, by promoting healthy lifestyle changes, such as smoking cessation, weight control, and dietary interventions, physiatrists can literally alter the course of morbidity and mortality in a cancer survivor with cardiopulmonary dysfunction.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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