Review Article

Cardiopulmonary bypass and cancer dissemination and progression: myth reality, enigma, puzzle?

Li Siyuan[1], Danilo Tadao Wada[2], Paulo Roberto Barbosa Evora[1]

[1]Department of Surgery and Anatomy of Ribeirao Preto Medical School FMRP-USP, University of São Paulo, São Paulo, Brazil; [2]Department of Medical Imaging, Hematology and Oncology of Ribeirao Preto Medical School FMRP-USP, University of São Paulo, São Paulo, Brazil

Contributions: (I) Conception and design: PRB Evora, S Li; (II) Administrative support: PRB Evora; (III) Provision of study materials or patients: PRB Evora, S Li; (IV) Collection and assembly of data: S Li; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Paulo Roberto Barbosa Evora. Hospital das Clínicas da FMRP-USP, Av. Bandeirantes, 3900 – Campus Universitario, Monte Alegre 14048-900, Ribeirao Preto, Sao Paulo, Brazil; Department of Surgery and Anatomy of Ribeirao Preto Medical School FMRP-USP, University of São Paulo, São Paulo, Brazil. Email: prbevora@gmail.com.

Abstract: Cardiac disease (CD) and oncologic disease (OD) are among the most lethal diseases. Both share common risk factors and as a consequence, there are a substantial number of patients who need surgeries for problems related to both diseases. Treatments for OD should start as soon as possible, as the disease can progress and disseminate, reducing life expectancy for patients. At times, heart problems may need cardiac surgery (CS), which are sophisticated and peculiar, at many times needing a machine to do the lung and the heart function as the surgeon does his job. This is called cardiopulmonary bypass (CPB), a procedure that is known to be related to inflammation and immunosuppression syndromes, that could lead the cancer disease to disseminate. There is little information on this subject in the literature so, in this narrative review, we have made a literature review, trying to address whether this theoretical worry confirms at evidence-based medicine. We also described some considerations regarding the use of devices like Cell Saver® and autotransfusion in oncologic patients. Further, we have taken some considerations about what care should be taken when facing situations with patients of different stages of OD needing CS and what should be discussed multidisciplinary aiming a treatment that best fits patient's life-expectancy and clinical status.

Keywords: Neoplasms; thoracic surgery; cardiopulmonary bypass (CPB)

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Introduction

Cardiac diseases (CD) and cancer are among the ten most frequent causes of death in the world (1). Both share many risk factors, and so, many oncologic patients have concurrent CD. As within the general population, when looking closely at the noncancer causes of death in patients with an oncologic disease (OD), heart disease is still the first one (2). As so, it is reasonable that some patients with malignancy may need a cardiac intervention, including cardiac surgery (CS). Besides, with the progressive increment in survival rates seen in cancer treatment in the past years (3,4), part of then related to de development of modern therapeutics like molecular mutations targeting, immunotherapy, and cellular therapy, it is reasonable to expect increases in the number of people needing CS.

When facing cancer, time can be an urgent matter. As the treatment delays, the disease can progress and disseminate, worsening survival rates. However, many of the treatments used in cancer (chemotherapy, radiotherapy, immunotherapy, molecular target-therapy) can be toxic to the heart, worsening a coexistent CD (5-7). Due to this, in some selected cases, CS may be required before oncologic treatment.

Between the possible CS, some may need undergoing

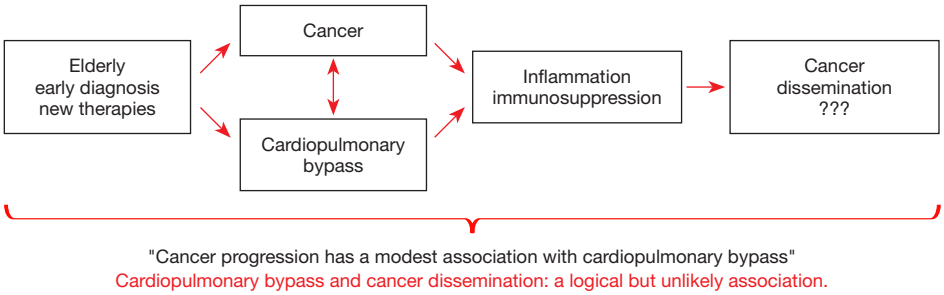

Figure 1 Cancer progression and cardiopulmonary dissemination (Visual Abstract).

a cardiopulmonary bypass (CPB), a procedure in which the patient's heart and lungs are temporarily bypassed and supplanted by machines (8,9). CPB is known to lead not only to a systemic inflammatory state but also to an immunosuppression one (10-12). So, theoretically, this could allow cancer to spread and recur (13). This relation is still unclear despite the advances in cardiac and oncologic treatments and the increase in publications about these themes.

Literature several questions occur when confronted with this problem. (I) Will the operative threat be more significant because the affected person has cancer? (II) Will the neoplastic disease enable sufficiently lengthy survival for the patient to revel in the result of the operation? (III) If cancer has been diagnosed recently, is it higher to the first function on the coronary heart or wait until the tumor has been treated? (IV) Will the systemic inflammatory response that frequently happens after surgery irritate the course of cancer? (V) Might there be some complications with the use of antithrombotic treatment? (14).

There is not any information that offers definitive evidence to these questions. Therefore, standards critiques of the international literature are extremely relevant justifying the "rationale" of the present text that are illustrated in the Visual Abstract (*Figure 1*).

CPB-related systemic inflammatory response syndrome (SIRS) and immunosuppression:

CPB is known to cause a transitory immunosuppression state by the elevation of cytokines (mainly IL-10 and TGF-β), leading to negative feedback of immunologic response mediated by T-cells (12,15). As so, it seems coherent to think that this immunosuppressor effect may compromise the capacity of atypical and cancerous cells, leading to its dissemination.

Surgical applications of CPB started in the 1950s. From that time on, many were the organic dysfunctions described in patients undergoing the procedure (12). The primary proposed mechanism seems to be related to an increase in capillary permeability, consequently leading to interstitial edema and impairing organs such as lungs, liver, and kidneys (16). Concurrently, there is an activation of the complement system's proteins, coherent with the systemic inflammatory state seen in these patients. Sometimes there can be an exaggerated inflammatory response, which we call SIRS (16).

Nowadays, CPB-related SIRS is known to be triggered by a multifactorial cause, mainly divided into two phases: acute and late. In the acute phase, the blood contact with non-endothelial cells leads to molecular release, including anaphylatoxins activated by the complement system, causing upregulation of pro-inflammatory cytokines like IL-1, IL-6, TNF-alpha, increasing the adhesion of neutrophils to myocytes and endothelial cells (10,15). They act synergically, stimulating the production of other cytokines by monocytes and leucocytes (IL-6 and IL-8). The reperfusion phenomena following CPB also upregulates the IL-1 and TNF-alpha expression by microvascular endothelial cells, causing a myocardial disfunction (17). Besides their direct role, the interleukins also trigger inflammatory cascades activations.

Simultaneously, we have inhibition of Toll-like receptors (TLR) activation (18) mediating an immunosuppression state. So, in CPB, we have activation of both: pro-inflammatory and anti-inflammatory cytokines. The antagonism of SIRS is called Compensatory Anti-inflammatory Reaction Syndrome (CARS) (16,19). In severe SIRS, there is an exacerbation of the innate pro-inflammatory system, causing organic dysfunction, while at CARS, there is an inhibition of the adaptative immunity

and apoptotic system through the production of anti-inflammatory cytokines (e.g., IL-4 and IL-10). Anti-inflammatory exacerbation leads to immunoparalysis, impaired cicatrization, a propensity to infections, and also to organic dysfunction (20). Genetic features mediate both SIRS and CARS, and the host environmental exposure may trigger then, with antagonistic phenotypes of organic reaction in patients with severe injuries (10).

As CPB is associated with SIRS and CARS, leading to inflammatory and immunosuppression state at the same time, it seems acceptable that it could predispose to tumor dissemination (21). Two are the primary mechanism proposed: tumor cell hematogenic dissemination from the reservatory thought the arterial cannula and disbalance of the inhibition of tumor cells by the host immunity.

Mechanistic biomarkers of cardiovascular disease and cancer

Cardiovascular diseases and cancer share several common pathophysiological mechanisms for the incidence and progression of the disease. In the recently published review by Narayan *et al.* (22), several markers common to both diseases were highlighted, in an attempt to understand the relationship between cardiovascular disease and cancer through fundamental biological processes common to cardiovascular diseases and cancer, including inflammation, cell proliferation, resistance to death neurohormonal stress, angiogenesis, and genomic instability. Papers of Interleukin 6, highly sensitive C-reactive protein (hsCRP), interleukin-33, suppression of tumorigenicity, galectin-3, growth differentiation factor 15 (GDF-15), cardiac troponin T, neurohormones such as NT-proBNP were reviewed, and regional intermediate pro-atrial natriuretic peptide (MR-proANP), neurotensin (NTS), placental growth factor (PlGF), and clonal hematopoiesis of undetermined potential (CHIP). As the era of personalized medicine advances, new biomarkers are expected to be used to inform and improve the prognosis of the disease in cardiovascular diseases and cancer. Understanding the role of these biomarkers can additionally inform the application of therapies. An example of this is canakinumab, an anti-IL1b monoclonal antibody, which improved the secondary prevention of important cardiovascular events in patients with elevated hsCRP after myocardial infarction (IM) (23-25) and showed a reduction in incident lung cancer, suggesting potential cancer benefit through an anti-inflammatory therapeutic intervention (26).

Surgical-related mortality risk in oncologic patients

It seems like there is no significant increase in surgical-related mortality for patients with OD undergoing CS with CPB, either in hematologic malignancies and solid cancers (14,27,28). Even when looking at heart transplantation, some experienced groups advocate that, in selected groups, the 1-year survival rate is comparable to overall rates (70% *vs.* 80%) (29,30).

Surgical morbidity

Despite not having a higher rate of early mortality, OD patients undergoing CS have an increased risk of morbidity (31,32). Mainly decurrent of a higher rate of blood transfusion, atrial fibrillation at post-operatory, pneumonia, sepsis, reintubation rate, and even cerebrovascular accidents.

Minimally invasive cardiovascular procedures in oncologic patients

Minimally invasive procedures rapidly developed in the last decades, allowing them to make aortic valve treatments without open surgery. Guided by X-ray radioscopy visualization, it is possible to make valvuloplasty by balloon inflation through a femoral vessel's catheter insertion. Even some valve replacements can be done by a minimally invasive whey, like transcatheter valve replacements (33) or even transapical mitral implants (34).

There are still small data regarding these procedures in oncologic patients, but even though high material costs and the need for specialized teams, the reduced recovery time and lower perioperative risks, when compared to open surgeries, are features to be considered. Even palliative patients can benefit from aortic balloon valvuloplasty if indicated (35).

CPB and risk of new cancers

By following 48,009 patients who undergo CS due to coronary artery disease (CAD), a multicentric cohort study (36) found an incidence of 6.8% of cancer at long-term follow-up. They also looked at the association of cancer development and CPB use and found that despite a marginally higher incidence (7.2% *vs.* 5.8%), it was not statistically significant. And so, concluded that even if there is an association between CPB and cancer development

that he could not prove, it is probably a little one. Hence, more research is needed to establish if transitory immunosuppression related to CPB may or not promote pre-existent cancer cell growth or dissemination.

CPB in OD patients

Long term follow-up of patients known to have OD who had a CS preceding the start of oncologic treatment also did not show a significant difference between those undergoing CPB and those who did not (23). Rates of oncologic recurrence, progression, or death were all similar between groups.

The urge for cancer therapy

Cancer treatment should be started as soon as possible after diagnostic confirmation, in most cases, before a CS. Only when facing patients at a high risk of major adverse cardiovascular events, the surgical procedure necessity superimposes the start of OD treatment (37). When facing patients with acute myocardial infarction, cardiac insufficiency, symptomatic cardiac valve disease, or risk of aneurysm rupture, one should consider CS before OD treatment.

It is important to remember that radiotherapy can lead to fibrosis and the development of adherence, which may put patients at more risks at surgical procedures, predisposing to vascular iatrogenic lesions and dehiscence. Furthermore, the liberation of chemotherapy or immunotherapy doses may also contribute to CD decompensations, by reducing ventricular ejection fraction by cardiotoxicity or autoimmune myocarditis.

Rapid cancer progression, recurrence, and CPB

Sometimes we see advanced stage OD cases, with a rapid cancer progression after a CPB (21). Even though, when comparing these patients with the ones going palliative treatments, the mortality is similar. So, maybe this rapid progression may not be related to the procedure itself. Concomitantly, there is no statistically significant difference in survival rates when comparing CS in patients who have treated cancer ten or more years before, with equivalent aged populations.

There is controversy in literature if the morbimortality and tumor recurrence related to CS can be higher in oncologic patients (32) ongoing extracorporeal circulation (ECC). About this fact, it seems like the time between the cancer diagnosis and CS also has a role in survival, with the best outcomes obtained when operating patients who had diagnosticated malignancy for more than two years (perhaps inferring a more indolent OD) (32).

Combined surgeries

Sometimes, given the duality of what urges most, patients are simultaneously operated for cancer and the CD (38,39). Despite feasible, the benefit of combined surgery is still controversial as there is an increased risk of pulmonary edema from CPB and bleeding by the heparinization required by CS. So, a rigorous selection of candidates must be made.

The use of Cell Saver® and autotransfusion in cancer patients

About the use of autotransfusion equipment such as Cell Saver® in cancer surgeries, Akchurin *et al*. (40) described eight oncologic patients who underwent operations using CBP and Cell Saver. All of the patients survived the surgery and were alive one year after. After each operation, researchers analyzed the filter system searching for neoplastic cells. Atypical cells and microthrombi were found on the physiological surface of the CPB arterial filters with 20 microns holes. On the outer surface of the filters and in the washed red blood cells, tumor cells were absent. The authors concluded that the potential possibilities of hematogenous metastasis when using special filters is minimal, but further investigation and the design of more effective filters for oncology patients are required.

CBP and some most frequent associate cancer

Lung cancer

Muralidaran *et al*. (41) in 2011 carried out a systematic review of the literature on lung resections in non-small cell lung cancer using CPB using PubMed. From January 1, 1990, to December 31, 2010, a total of 20 articles were found that fit the selection criteria. They observed that the survival of these patients is higher when the use of CPB is planned, compared to surgeries whose CPB was used in an emergency or an unplanned manner. The unplanned use of CPB was considered as a prognostic factor for worse long-term survival.

CPB and renal cell carcinoma and adrenocortical carcinoma

Among urogenital malignancies, adrenocortical carcinoma and renal cell carcinoma are highly aggressive, and their treatment is surgical. These tumors occasionally extend through the inferior vena cava and affect the right atrium, requiring the use of CPB for resection.

In 2015, Nguyen *et al*. (42) conducted a cohort study of 362 patients using data from 22 institutions in Europe and the United States on the impact of CPB on global and specific survival in patients undergoing level III-IV nephrectomy and tumor thrombectomy. Patients operated on using CPB did not observe a statistically significant difference in overall survival compared to patients operated without using CPB.

In 2019, Chaud *et al*. (43) carried out a retrospective cohort study with nine cases of renal and adrenocortical tumors with invasion of the right atrium through the inferior vena cava operated using CPB and deep hypothermic circulatory arrest, performed at our service. In the review of the existing literature, no publications were found directly correlating the type of neoplasia with the possible spread caused or favored by CPB.

CBP and digestive system cancer

We search PubMed (accessed 05/26/2020) using the words CEC, Cancer, gastric, digestive, colorectal, and only 1 article was found related to the use of CPB in a patient with gastrointestinal cancer. Platell *et al.* (44) compared the outcome of patients with colorectal cancer who underwent CS using CPB and those who did not. The 5-year survival rate specifically related to cancer was significantly lower in patients undergoing CPB surgery. However, considering only patients undergoing potentially curative resection, that is, excluding patients with stage IV cancer, there was no significant difference in the specific cancer survival rate. The author concludes that it was not possible to determine a causal relationship between the use of CPB in a patient with colorectal cancer and survival.

CBP and haematological cancer

In 2014, Plumereau *et al*. (27) concluded that the use of CPB surgery does not increase long-term mortality in patients with hematological neoplasia, and there does not appear to be a risk of malignancy progressing to a more aggressive form after CPB CS. He attributes these results to the routine use of leukocyte depletion filters and the cell protection technique during CPB surgery.

A logical but unlikely association

Despite those proposed mechanisms that could increase tumor dissemination when using CPB, it seems that the survival of cancer patients who undergo CS is more related to the progression of the tumor than the surgical procedure (27). CPB also does not seems to be a trigger that changes OD to a more aggressive form. The use of leukocyte depletion filters and cellular protection techniques employed at CPB, known to reduce the risk of hematologic malignancy dissemination, may have some role at that.

When looking at mortality causes in OD patients, CD is the most frequent noncancer cause of death (2). So, it seems reasonable that CS with or without CPB remains within the arsenal of therapies for this population, especially in treated or stable malignancy cases. Principally, given that there is no definitive proof that CS with CPB can either increase dissemination or survival (45).

Conclusions

In this article, we have pointed out the main mechanisms and principles that justify the worry of cancer spread and survival rates reduction in oncologic patients undergoing CS with CPB. Regardless of the public health importance and shared risk factors of both CD and cancer, publications about the subject are still scarce. Although the theoretical risk of cancer dissemination by CPB, it is not easy to prove it, as we can see by the articles already published about this theme. Overall, in our opinion, some extra care should be taken when considering CS in cancer patients. For patients with a remitted OD, given the potential life expectancy with new treatments, it seems like we are close to a consensus that CS should be promptly considered between the hall of treatment option, of course, following CD guidelines for his pathology. At high stage OD, there is a particular propensity to search for alternative non-surgical treatments as the morbimortality in CS is not negligible. For the remaining scenarios, a multidisciplinary approach pointing out oncologic, cardiac, and surgical teams' main worries can aid in decision making. The discussion should focus on whether the patient's significant risk of death in the short and mid-term would be related to CS, OD, or

CD. In a logical reasoning based on the paradigm "a logical but unlikely association", one can speculate why CPB is not associated with the spread of cancerous disease. CPB introduces at least three variables: massive heparinization, continuous flow and temperature variation. But, these speculative variables are not strong enough to confront the doubts mentioned in the title of this review: myth, reality, enigma, puzzle?

Concluding remarks

- Cardiac and OD are among the most lethal diseases. Both share common risk factors and as a consequence, there are a substantial number of patients who need surgeries for problems related to both diseases
- At times, heart problems may need CS, that is known to be related to inflammation and immunosuppression syndromes, that could lead the cancer disease to disseminate.
- This relation is still unclear despite the advances in cardiac and oncologic treatments and the increase in publications about these themes.
- The discussion should focus on whether the patient's significant risk of death in the short and mid-term would be related to CS, cardiovascular disease or the OD.
- The paradigm "a logical but unlikely association" (CPB associated with the spread of cancerous disease), remains a matter of speculation.

CPB introduces at least three variables: massive heparinization, continuous flow and blood temperature controlled variation. However, these speculative variables are not strong enough to confront the doubts mentioned in the title of this review: myth, reality, enigma, puzzle?

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Footnote

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