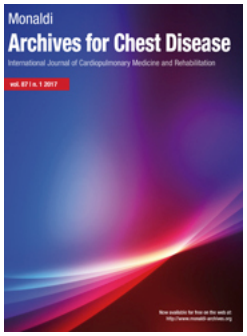

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Optimal treatment strategies for coronary heart disease in cancer patients: a complex clinical case

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Abstract

Coronary heart disease (CHD) remains a leading cause of mortality among cancer patients, primarily due to shared risk factors and the impacts of chemotherapeutic drugs, immune checkpoint inhibitors, and radiotherapy. Determining the optimal treatment strategy remains a challenging issue for patients with concurrent CHD and malignant neoplasms. In high-risk patients, managing CHD frequently takes precedence over addressing the oncologic disease. Myocardial revascularization, coupled with optimal medical therapy for CHD, can significantly enhance patient survival by reducing the risks of myocardial infarction and sudden cardiac death. However, selecting a surgical treatment strategy requires careful consideration of the indications, the complexity of coronary lesions, the risk of bleeding and thrombosis, and the overall prognosis of the malignancy. This clinical case demonstrates the importance of risk-benefit assessment, multidisciplinary discussion of cure strategy, and application of novel technologies to provide the most personalized and effective treatment.

Key words*:* coronary heart disease, cancer, myocardial revascularization.

Introduction

In 2022, there were over 20 million new cases of cancer globally, alongside 9.7 million deaths from cancer [1]. The prevalence of coronary heart disease (CHD) among cancer patients is high; for example, in lung cancer, the incidence of concurrent CHD ranges from 7.5% to 28% [2].

The presence of a malignant tumor leads to immunosuppression, chronic inflammation, endothelial damage, and activation of the thrombogenesis, all of which contribute to the

development and progression of atherosclerosis [3]. The manifestation of CHD, with the highest mortality, is more frequent in the first year after a cancer diagnosis. In patients cured of cancer, the risk of developing CHD remains 1.3-3.6 times higher compared to the general population [4,5].

Treatment of cancer significantly affects the process of atherogenesis. The development of CHD is closely linked to the effects of various chemotherapeutic agents, including anthracyclines, vascular endothelial growth factor inhibitors, antimetabolites, tyrosine kinase inhibitors, and immune checkpoint inhibitors [6]. For instance, in a study conducted by Laenens et al., 10.3% of patients undergoing immunotherapy experienced major adverse cardiovascular events within an average of five months of treatment [7]. Additionally, research indicates that chemotherapy can have delayed cardiotoxic effects, increasing the risk of developing CHD 10-20 years after the completion of treatment [8].

Research findings indicate that chest radiotherapy elevates the risk of myocardial infarction (MI) or sudden death by 5-10 times, correlating directly with the radiation dosage. The underlying mechanisms involve damaging the blood vessel walls, increased capillary permeability, and activating inflammation. These mechanisms lead to the proliferation of intimal tissue, formation and accumulation of collagen, and fibrosis, all of which expedite the development of atherosclerotic plaques [9].

In cancer patients, the "multiple impact" theory comes into play. Here, existing risk factors and chronic diseases are simultaneously influenced by chemotherapy, checkpoint inhibitors, radiotherapy, and surgical interventions. Such exposure may lead to the development or progression of CHD, making it difficult to effectively treat these related deceases [10].

When optimal medical therapy for CHD in cancer patients is ineffective, the decision on the surgical approach depends on various factors: the extent of coronary lesions, the patient's age, the presence of comorbidities, bleeding risk, cancer activity, and overall prognosis [5]. Unfortunately, current studies don't offer definitive answers about the best revascularization method. This is largely because cancer patients are frequently excluded from large randomized controlled trials, and the available data is often limited by small sample sizes and short follow-up periods [8].

Objective: Demonstrate the results of complex treatment of a patient with CHD and stage IV lung cancer. This is illustrated by a clinical case in which myocardial revascularization and antitumor therapy were performed during 18 months of observation.

Case Report

Patient K., born in 1950, applied to the oncology clinic with complaints of a dry paroxysmal cough and hoarseness of voice. Subsequent chest computed tomography revealed a solid mass with irregular, radiating contours, measuring up to 76x57mm, situated in the upper lobe of the right lung at the S1-S3 segment border and separate small foci in both lungs. No evidence of tumor spread to other sites was found. Histological examination confirmed the diagnosis of squamous cell lung cancer.

The patient had a five-year history of arterial hypertension, during which he did not consistently adhere to antihypertensive therapy. Based on the decision of the oncological consortium, which took into account the disease stage, tumor prevalence, histological type, it was decided to initiate systemic therapy as the first stage of specialized antitumor treatment. The chosen regimen includes pembrolizumab at a dosage of 200 mg, paclitaxel at a dose of 175 mg/m^2, and carboplatin with an area under the curve (AUC) 5, administered every 21 days.

Prior to the initiation of specialized treatment, the patient was administered combined hypotensive therapy consisting of valsartan at a daily dose of 80 mg and amlodipine at a daily dose of 5mg. Target blood pressure level was achieved within one week. Considering the presence of dyslipidemia, rosuvastatin therapy was commenced at a dosage of 40 mg/day. An echocardiogram showed no dilatation of the heart chambers, preserved myocardial contractility with an ejection fraction of 62%, and a global longitudinal strain of 18.5%. Additionally, there was moderate regurgitation on the tricuspid valve, first-degree pulmonary hypertension with a pulmonary artery systolic pressure of 40 mmHg, and type II diastolic dysfunction.

After three months of treatment, a follow-up examination using computed tomography of the chest revealed a reduction in the size of the left lung tumor and a decrease in the severity of paracancerous lymphostasis. Additionally, there was a noticeable decrease in both the size and number of metastatic lung foci, as well as a reduction in the size of the intrathoracic lymph nodes.

However, the patient began experiencing pressing chest pain with mild physical exertion, such as walking 200-300 meters. The pain resolved on its own when at rest. Due to these symptoms, the patient was urgently hospitalized in the cardiology department with suspected acute coronary syndrome without ST-segment elevation. Tests showed that myocardial

damage markers remained within normal limits, and no areas of local contractility disorders were detected.

Selective coronary angiography was performed, revealing a left-dominant blood supply, an unchanged left coronary artery trunk, and tandem stenosis of 80% and 75% in the proximal and middle thirds of the left anterior descending coronary artery (LAD), respectively. Additionally, there was up to 75% stenosis in the diagonal branch.

Despite these findings, considering the presence of active cancer and the associated risk of bleeding with dual antiplatelet therapy, the decision was made to continue with optimal medical therapy. The patient was advised to maintain a regimen including calcium antagonists (amlodipine 10mg/day), an angiotensin II receptor blocker (valsartan 80mg/day), statins (rosuvastatin 40mg/day), acetylsalicylic acid in enteric-coated form (100mg/day), and nitrates as needed.

Considering the tendency towards bradycardia observed in 24-hour Holter monitoring (average daytime heart rate of 58 beats per minute, nighttime rate of 40 beats per minute), episodes of atrial pacemaker migration, and transient first-degree atrioventricular block (PQ interval of 0.25 seconds), beta-blockers were not prescribed.

Due to persistent angina attacks, reduced exercise tolerance, the patient made multiple visits to the clinic at the Center to determine further treatment strategies. Based on the patient's symptoms, the progression of CHD, and the ineffectiveness of conservative therapy, it was decided to proceed with myocardial revascularization.

To aid in the stent selection and determine the optimal placement zone, intravascular ultrasound of LAD was performed. The minimum lumen area in the most critically narrowed zone was 2.5 mm^2, with a reference artery diameter of 3.25 mm and a proximal segment diameter of 4 mm. It was decided to perform LAD stenting with a Resolute Onyx 3.5x38 mm stent, followed by optimization of the proximal segment with a 4 mm balloon catheter (Figure 1).

The decision to select this particular stent was driven by the necessity to restrict dual antiplatelet therapy to just one month, due to the patient’s high risk of bleeding. Follow-up intravascular ultrasound confirmed optimal stent placement, with no evidence of malapposition or dissection, and an ideal minimum lumen area of 9.5mm^2. The myocardial revascularization procedure was executed without any complications, and the postoperative period proceeded uneventfully.

Upon discharge, the patient showed positive improvement, with no recurrence of angina pains. A regimen of dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) was prescribed for one month, followed by clopidogrel monotherapy for the next 12 months. Consequently, the surgical intervention for CHD allowed the patient to continue their specialized antitumor treatment without interruption.

At the follow-up examination conducted 18 months after starting chemotherapy, a significant regression of the tumor was observed. Computed tomography of the chest showed a fibrotic area in the upper lobe of the right lung. Additionally, a few subpleural and perivascular nodules were identified on both sides (Figure 2).

The plan was to maintain the patient's care under the oversight of a multidisciplinary team, consisting of an oncologist, cardiologist, neurologist, and radiotherapist.

Discussion

In the presented clinical case, we demonstrated the efficacy and safety of endovascular treatment of CHD in a patient with an cancer. Timely myocardial revascularization improved disease outcomes, reduced the risk of MI, and allowed for the continuation of full antitumor treatment.

Many large randomized controlled trials have shown no significant difference in treatment outcomes between invasive strategies and conservative therapy in patients with CHD, resulting in a lower recommendation grade for surgical treatment methods. Data on the clinical outcomes of myocardial revascularization in cancer patients with CHD are limited, as patients with active tumors were excluded from most studies [11]. These findings prompted us to analyze and highlight the complexity of treatment decisions in patients with coexisting CHD and oncologic disease, underscoring the need for further research in this area.

According to clinical guidelines, if conservative strategies prove ineffective in patients with CHD combined with malignant tumors, a minimally invasive procedure, such as percutaneous coronary intervention (PCI), is the preferred revascularization strategy for most patients, particularly when the tumor is widespread [8]. However, it is important to note that the presence of cancer in patients with CHD is a strong independent predictor of death, bleeding, and recurrent MI [12]. In a large database study of 1.9 million patients, re-hospitalization for MI after PCI was higher in patients with cancer (9.1% vs. 5.6%, $p<0.001$),

and a higher rate of bleeding was reported among cancer patients (1.6% vs. 0.6%, p<0.001) [13].

In study, Wei Guo (2021) demonstrated that patients with cancer have a higher risk of thrombotic and ischemic events following PCI. All-cause mortality was higher in cancer patients during the 5-year follow-up period (29.1% vs. 22.3%; p = 0.02), and the incidence of major adverse cardiovascular events was also higher compared to patients without cancer (48.6% vs. 33.0%, p < 0.001). The presence of malignancy led to an increased incidence of MI (16.1% vs. 8.0%; p<0.001), stent thrombosis (6.0% vs. 2.3%; p<0.001), repeat revascularization (21.2% vs. 10.0%; p<0.001), and bleeding (6.7% vs. 3.9%; p = 0.03) [14]. However, in a study by Ueki Y et al., the authors concluded that while patients with cancer had an increased risk of cardiac death and bleeding, they did not have a higher risk of ischemic events such as MI, stent thrombosis, or repeat revascularization [15].

A multicenter analysis utilizing machine learning techniques revealed that among women undergoing PCI with reproductive system tumors, mortality significantly decreased during CHD (OR 0.58, 95% CI 0.39-0.85; p = 0.006). Conversely, PCI was found to be less effective in reducing mortality in severe cases with metastatic lesions (OR 0.74, 95% CI 0.32-1.71; p=0.481) [16].

Interestingly, the outcomes of myocardial revascularization are influenced not only by the stage of cancer but also by its origin. Our patient, diagnosed with lung cancer, falls into one of the most challenging categories, marked by high in-hospital mortality and complications during PCI.

The primary reason for refraining from performing PCI in patients with CHD is the heightened risk of bleeding. This risk may stem from various factors, including local tumor infiltration, tumor angiogenesis, systemic effects induced by cancer, such as cytokine release, alterations in platelet function, or adverse effects of chemotherapy leading to thrombocytopenia [17]. Notably, 10-25% of patients with solid tumors may develop thrombocytopenia following chemotherapy, which, however, does not constitute an absolute contraindication for interventional therapy. Given that thrombocytopenia does not impede the occurrence of myocardial ischemia in cancer patients, it may, in fact, predispose them to thrombotic events [18].

Due to the elevated risk of bleeding in cancer patients undergoing PCI, meticulous planning of stent selection strategy is imperative. Recent randomized controlled trials have demonstrated the superiority of new-generation drug-eluting stents over bare-metal stents,

especially in patients at high risk of bleeding, where extended dual antiplatelet therapy is not feasible [19].

Ahmed T. et al. (2022) uncovered interesting findings in their study, revealing no significant differences in mortality or repeat revascularization among oncology patients when using stents from different generations. Additionally, it has been demonstrated that endothelialization of drug-eluting stents occurs similarly in both oncology and non-oncology patients [20]. Therefore, based on current evidence, in our clinical case, the patient underwent the safe implantation of a coronary stent system with a zotarolimus coating, along with dual antiplatelet therapy for one month.

The choice of cardiac surgical revascularization in cancer patients is still a matter of debate. Studies in this area are limited by small sample sizes, making it difficult to find homogeneous patient groups due to variations in tumor localization, stages, and degrees of differentiation.

Certainly, an accurate assessment of the stage of malignancy is pivotal in determining treatment strategies for CHD in cancer patients, especially considering the favorable long-term outcomes seen in those with early-stage cancer. Nonetheless, the possibility of myocardial revascularization should not be disregarded for patients with advanced cancer, particularly if it facilitates ongoing antitumor treatment and enhances prognoses related to both CHD and cancer.

Conclusions

Thus, in the presented clinical case of a patient with advanced lung cancer and concurrent CHD, myocardial revascularization has been shown to reduce the risk of cardiovascular complications and facilitate ongoing treatment of the malignant neoplasm. The placement of a drug-eluting stent and administration of dual antiplatelet therapy for one month were deemed safe alongside active antitumor therapy. Subsequent treatment resulted in significant regression of the malignancy and improvement in the patient's clinical status.

As the effectiveness of oncologic therapy continues to improve, an increase in ischemic events necessitating surgical intervention is anticipated. Therefore, further basic and clinical research is warranted to establish optimal treatment strategies for the combination of CHD and tumorigenesis and to formulate diagnostic and therapeutic guidelines.

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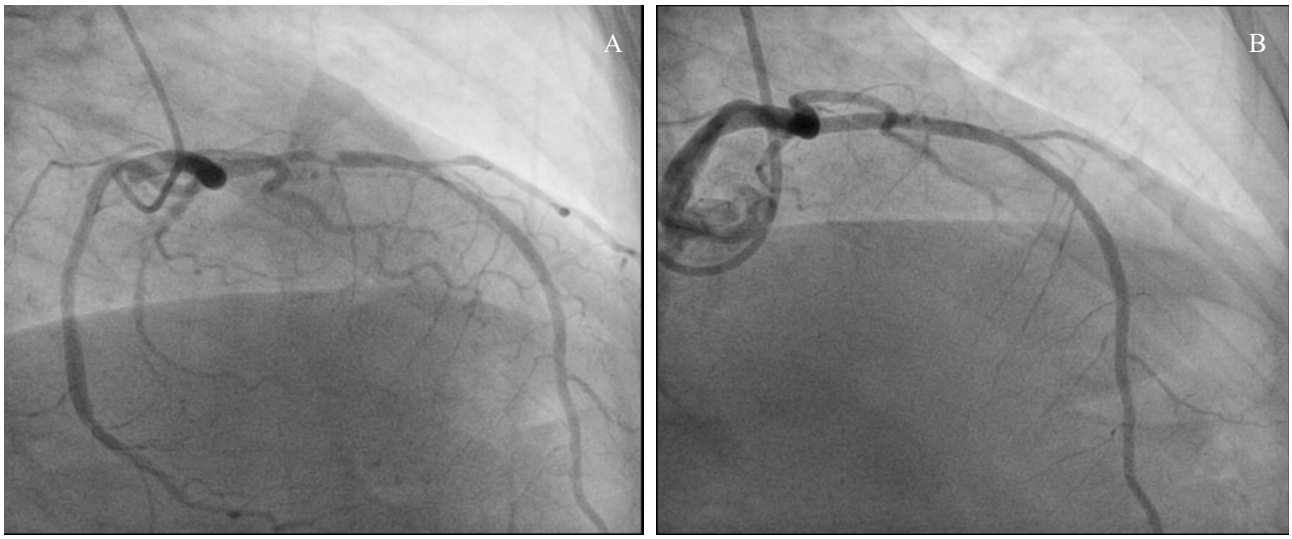

Figure 1. Coronary angiography showing initial LAD stenoses (A), and coronary angiography after placement of a Resolute Onyx 3.5×38 mm stent (B).

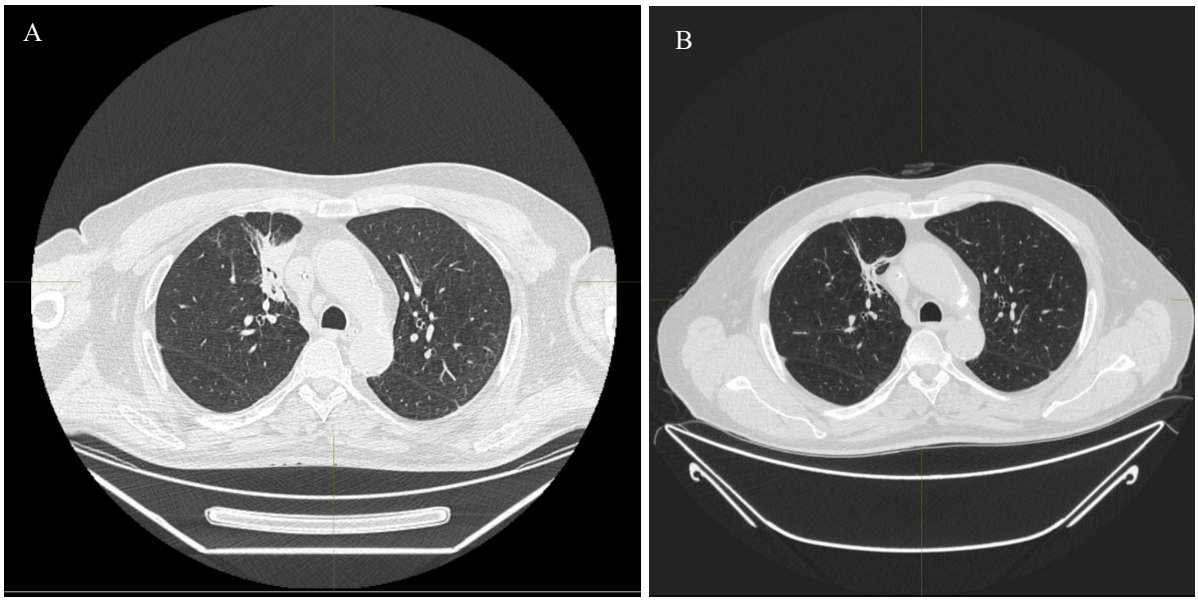

Figure 2. Computed tomography of the chest with in-vivo contrast: before treatment (A) and after 18 months of antitumor therapy (B).