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Percutaneous coronary interventions in oncological patients

Shukurov F.B., Feshchenko D.A., Rudenko B.A., Vasiliev D.K., Mamedov M.N.

"National Medical Research Center for Therapy and Preventive Medicine
of the Ministry of Healthcare of the Russian Federation", Moscow, Russia.

AUTHORS:

Firdavs B. Shukurov*, MD. PhD, doctor of X-ray endovascular methods of diagnostics and treatment, senior researcher of the department of innovative methods of prevention, diagnostics and treatment of cardiovascular and other noncommunicable diseases, "National Medical Research Center for Therapy and Preventive Medicine", Moscow, Russia. ORCID: 0000-0001-7307-1502

Darya A. Feshchenko, doctor of X-ray endovascular methods of diagnostics and treatment, Head of the operating unit, junior researcher of the department of innovative methods of prevention, diagnostics and treatment of cardiovascular and other noncommunicable diseases, "National Medical Research Center for Therapy and Preventive Medicine", Moscow, Russia. ORCID: 0000-0003-3851-4544

Boris A. Rudenko, MD, PhD, doctor of X-ray endovascular methods of diagnostics and treatment, head of the department of innovative methods of prevention, diagnostics and treatment of cardiovascular and other noncommunicable diseases, "National Medical Research Center for Therapy and Preventive Medicine", Moscow, Russia. ORCID: 0000-0003-0346-9069

Dmitry K. Vasiliev, MD, PhD, doctor of X-ray endovascular methods of diagnostics and treatment, researcher of the department of innovative methods of prevention, diagnostics and treatment of cardiovascular and other noncommunicable diseases, "National Medical Research Center for Therapy and Preventive Medicine", Russia. ORCID: 0000-0003-2602-5006

Mehman N. Mamedov, MD, Professor, head of the secondary prevention of noncommunicable diseases department, "National Medical Research Center for Therapy and Preventive Medicine", Moscow, Russia. ORCID: 0000-0001-7131-8049

Cancer patients are both older and have many comorbidities, including CHD, which is often severe. Several cancer treatments, such as radiotherapy, chemotherapy and immunotherapy, increase the risk of cardiovascular events and mortality. Percutaneous coronary intervention (PCI) is often required, but the presence of procoagulant states, haematological disorders such as anemia and thrombocytopenia pose challenges in the management of these patients with anticoagulants, antiaplatelet drugs and PCI. PCI in cancer patients is associated with an increased risk of bleeding, in-hospital and long-term mortality, and the need for repeat revascularisation. Correct management

* Corresponding author. Tel. +7 (985) 610-07-61. E-mail: fshukurov@gnicpm.ru

of oncological patients with concomitant CHD will reduce the risk of periprocedural complications during PCI, at least partially by using the best surgical techniques.
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Introduction

The comorbidity of oncological and cardiovascular diseases (CVD) associated with atherosclerosis is a pressing problem in modern medicine. It is caused by a decline in the quality and duration of life in patients with combined pathology.

In recent years, an increase in new cases of malignant neoplasms has been observed in the Russian Federation. At the end of 2021, the number of patients under dispensary observation was 3,940,529 (2.7 % of the population of the Russian Federation) [1, 2]. The development and progression of coronary heart disease (CHD) can have a significant impact on patient survival. The prevalence of CHD in cancer patients is higher than in the general population [3]. Patients with current or previous cancer undergoing percutaneous coronary intervention (PCI) are at increased risk of CVD and mortality [4, 5]. Numerous studies have shown that the type of cancer and its stage are important determinants of outcomes, including in-hospital mortality and bleeding [4, 6–8].

Link between coronary heart disease and cancer

The inflammatory process is known to underlie pathological changes in cardiovascular and oncological diseases. The atherosclerotic process is characterised by low inflammatory activity [9], but at the same time, optical coherence tomography (OCT) studies of coronary arteries have shown that most atherosclerotic plaques that rupture and lead to acute coronary syndrome have significant macrophage infiltration and higher levels of serum C-reactive protein (CRP) [10]. Similarly, the role of inflammation in the pathogenesis of malignant cell transformation, carcinogenesis, invasion and metastasis [11] is well established in several forms of oncology, including breast cancer [12], cervical cancer (mediated by human papillomavirus), gastric cancer (mediated by Helicobacter pylori) and lymphoma (mediated by Epstein-Barr virus) [13]. Libby and Ebert proposed the modern concept of CHIP (clonal haematopoiesis of indeterminate potential) as an independent risk factor for CVD development in cancer patients [14]. CHIP refers to mutated stem cells in the peripheral circulation that are known to increase the risk of haematological malignancies. Interestingly, while most people with these cells in their peripheral blood never develop a full-blown malignancy, the presence of CHIP doubles the risk of CHD [15]. Even from an epidemiological point of view, smoking, diabetes and obesity are considered risk factors for both CVD and cancer (Fig. 1) [3].

Various cancer treatments such as radiotherapy, chemotherapy and immunotherapy also increase the risk of CVD and mortality [16]. Thoracic irradiation for lymphoma and breast cancer is associated with a higher incidence of obstructive CHD: an estimated 30 % of patients receiving radiotherapy have a severe multivessel lesion involving the left coronary artery and/or the right coronary artery. Ionising radiation causes the release of multiple inflammatory and profibrotic cytokines, resulting in endothelial damage both in the coronary arteries and in the microcirculatory bed [17]. The role of several chemotherapeutic agents in increasing the risk of developing CVD has been demonstrated: anthracyclines and trastuzumab are known to cause cardiomyopathy, whereas several other drugs such as cisplatin, fluorouracil, methotrexate, cytarabine, fludarabine, vinca alkaloids, interferons and interleukin-2 have been associated with an increased incidence of ACS [18]. The use of immunotherapy, such as rituximab [19] and bevacizumab [20], is associated with an increased risk of myocardial infarction and arterial thrombosis. Hormonal drugs used in the treatment of breast and prostate cancer are also associated with worsening

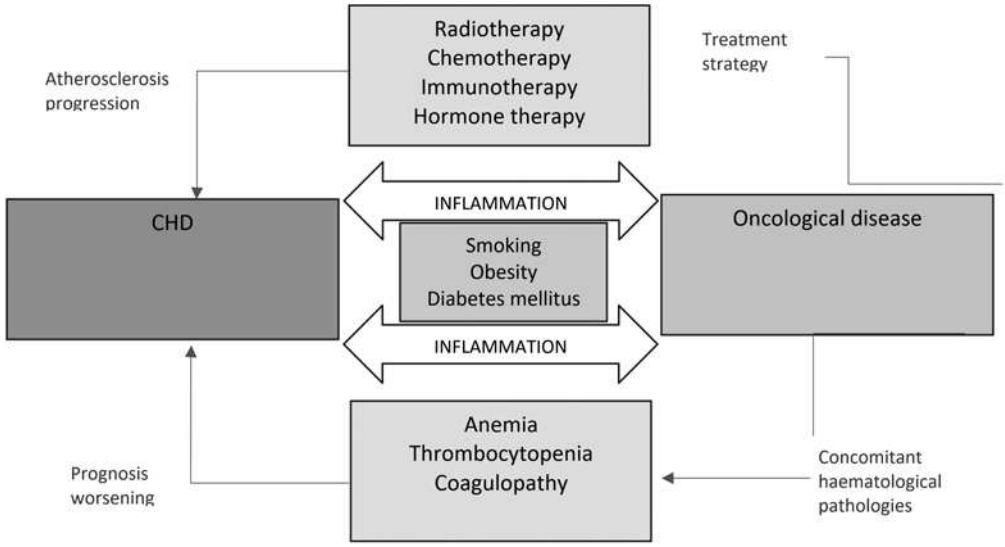

Fig. 1. Associations between CHD and cancer

of angina pectoris due to CHD progression and the development of ACS [21]. Therefore, clinicians need to be aware of the cardiovascular toxicity of anticancer drugs and screen patients prophylactically for CHD prior to initiation of these therapies and during long-term follow-up [22].

Challenges of PCI in cancer patients

Performing both planned and emergency percutaneous coronary intervention (PCI) in patients with cancer presents a number of challenges (Fig. 2).

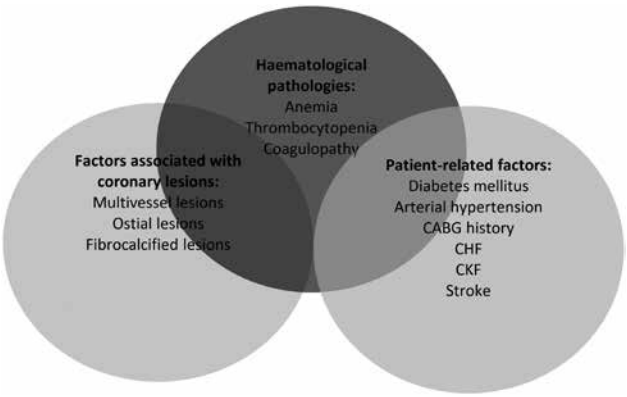

Fig. 2. Challenges of PCI in cancer patients разместить после рисунка

Firstly, these patients tend to be older and more likely to have severe comorbidities and a more severe course of CHD [4, 23, 24]. A study by Plotts J.E. et al on PCI outcomes in over 6 million patients showed that patients with oncology were generally older and had more comorbidities and often depended on the type of cancer process. For example, patients with lung cancer (compared to patients without cancer) had the highest prevalence of chronic lung disease (50.8% vs. 15.2%) and congestive heart failure (5.2% vs. 0.9%), patients with a history of lung cancer had: the highest prevalence of peripheral vascular disease (18% vs. 10.2%), smoking (52.4% vs. 35.5%), and prior PCI (23.8% vs. 18.7%). Patients with current colorectal cancer had the highest prevalence of anemia (34.1% vs. 8.3%) [4]. Subgroup analysis of the BleeMACS multicentre observational registry (n=14631) showed differences between patients with and without cancer among ACS patients and PCI survivors. Patients with cancer were older (70.8±10.3 vs. 62.8±12.6 years, p<0.001), more often female (28.7% vs. 22.8%, p<0.001) and had a higher prevalence of DM (28.7% vs. 23.5%, p=0.001), arterial hypertension (65% vs. 57.8%, p<0.001), stroke (8.3% vs. 5.4%, p=0. 001), congestive heart failure (5.4% vs. 2.9%, p=0.001), chronic kidney disease (CKD; 6.4% vs. 2.9%, p=0.001), history of ACS (15.4% vs. 11.5%, p=0.001), coronary artery bypass graft (CABG) (4.7% vs. 3.1%, p=0.01) and history of bleeding (11% vs. 4.9%, p<0.001) [24].

In addition, the presence of procoagulant states [25], haematological abnormalities such as anemia and thrombocytopenia pose challenges in the management of these patients with anticoagulants, antiaggregants and, if necessary, PCI. The Academic Research Consortium Consensus Document on High Bleeding Risk identified active malignancy, anemia (baseline haemoglobin level <11 g/dl) and thrombocytopenia (platelet count <100×109/l) as three independent predictors of high bleeding risk during PCI [26]. Bleeding risk is considered high if the occurrence

of future bleeding is Bleeding Academic Research Consortium (BARC) type 3 or 5 and its probability within one year is ≥4 % or the probability of intracranial haemorrhage ≥1 % [27]. Most patients with acute leukaemia, lymphoma and multiple myeloma have thrombocytopenia [28]. Its prevalence in patients with solid tumours receiving chemotherapy ranges from 10 % to 25 % [29].

A subgroup analysis of the HORIZONS-AMI trial showed that thrombocytopenia was associated with early and late adverse events, both bleeding and ischemia [30]. The presence of chronic thrombocytopenia in patients undergoing PCI was associated with a higher risk of haemorrhagic complications requiring blood or platelet transfusion, vascular complications, ischemic stroke and higher in-hospital mortality [31]. Anemia diagnosed in cancer patients is either a consequence of the disease or a complication of treatment. In a large meta-analysis of patients undergoing PCI, anemia was associated with a significant increase in postoperative mortality, major adverse cardiac events (MACE), reinfarction and bleeding [32]. An analysis of 6528 patients after PCI showed that severe anemia (mean haemoglobin level 98±11 g/L) was associated not only with an increased risk of death, cardiac death and myocardial infarction, but also with stent thrombosis [33]. In addition, patients with oncological processes often require invasive diagnostic and therapeutic procedures such as biopsy or resection, which raises concerns about their ability to receive continuous dual antiplatelet therapy.

Outcomes after PCI in cancer patients

Numerous studies (Table 1) have demonstrated that cancer patients undergoing PCI are at increased risk of bleeding [7, 24], hospital [5, 7] and long-term mortality [24, 35, 36].

Data from the BleeMACS registry showed that after one year of follow-up, patients with ACS and cancer who underwent PCI were more likely to have a combined endpoint of death or reinfarction (15.2 % vs. 5.3 %, p<0.001) and bleeding (6.5 % vs. 3 %, p<0.001) than those without cancer [24]. Results from large population-based registries suggest that cancer type may also play an important prognostic role. In a study by Plotts J.E. et al, lung cancer was associated with the highest risk of in-hospital mortality (odds ratio (OR) 2.81, 95 % confidence interval (95 % CI) 2.37–3.34), whereas colorectal cancer was associated with the highest risk of bleeding compared with those without cancer (OR 3.65, 95 % CI 3.07–4.35). In the same study, the presence of metastases, regardless of cancer type, was associated with an increased risk of in-hospital mortality and complications of PCI, including major bleeding [4]. A separate analysis focusing on patients with leukaemia undergoing PCI showed that these patients had an increased risk of in-hospital mortality and bleeding compared with the general population. In addition, the type of leukaemia also determined the prognosis: patients with acute myeloid leukaemia had a fivefold higher risk of in-hospital mortality after PCI than patients without leukaemia [7]. Another analysis of the NIS database, focusing only on cancer patients with ST-elevation myocardial infarction (STEMI), reported that patients with lung cancer had the highest in-hospital mortality (57.1 %). This study also showed that the use of primary PCI was 30.8 %, 20.2 % and 17.3 % in patients with breast, lung and colorectal cancer, respectively [8]. Valders et al, in their analysis of data from a multicentre registry in the Netherlands, reported that cancer patients with STEMI had higher all-cause mortality (17.4 % vs. 6.5 % in other patients) and cardiovascular mortality at 1 year (10.7 % vs. 5.4 % in other patients). A recent cancer diagnosis within the previous 6 months was strongly associated with early cardiac mortality [36]. In addition, PCI was performed according to a meta-analysis that included 5 studies that evaluating 1-year all-cause, cardiovascular, and non-cardiovascular mortality in patients with an active cancer or with the history of one. Patients in the cancer group had higher annual all-cause mortality [RR 2.22 (1.51–3.26; p<0.001)], including higher cardiovascular [RR 1.34 (1.1–1.65; p=0.005)] and non-cardiovascular mortality [RR 3.42] (1.74–6.74; p≤0.001). Notably, meta-regression analysis showed that the difference in annual all-cause and cardiovascular mortality between the cancer and non-cancer groups was not associated with baseline characteristics, PCI characteristics, or medications at discharge [37]. A retrospective observational study by Tabata et al. also showed that malignancy was an independent predictor of cardiovascular events in patients undergoing PCI, with an increased risk in patients with low ankle-brachial index/high brachial-ankle pulse wave velocity [38].

Studies have also shown that cancer patients who have undergone PCI are at increased risk of bleed-

Table 1. **The largest studies analysing PCI outcomes in cancer patients**

Authors	Studied population	Conclusions
Potts et al. [4]	National sample of inpatients, 2004–2014 yrs., N > 6 mln patients with PCI	— Active and past lung cancer increased the risk of in-hospital mortality; — Active colorectal cancer was associated with an increased risk of bleeding; — Current breast cancer was not associated with increased mortality or bleeding; — The presence of metastases was associated with an increased risk of bleeding and mortality, regardless of cancer type.
Potts et al. [7]	National sample of inpatients, 2004–2014 yrs., N > 6 mln patients with PCI	— The presence of leukaemia was associated with an increased risk of death and bleeding; — Acute myeloid leukaemia increased the risk of in-hospital mortality fivefold.
Pothineni et al. [8]	National sample of inpatients, N=3,7 mln patients with STEMI	— The performance of primary PCI was 30.8%, 20.2% and 17.3% in patients with breast, lung and colorectal cancer, respectively; — Patients with lung cancer had the highest in-hospital mortality.
BleeMACS registry [24]	BleeMACS registry of patients with ACS, N=15401	— The presence of cancer was the strongest independent predictor of the primary combined endpoint (death and reinfarction) and bleeding.
Valders et al. [36]	Multicentre registry of STEMI patients, N=3423	— Cancer patients with STEMI had increased all-cause and cardiovascular mortality at 1 year; — A recent cancer diagnosis within the previous 6 months was strongly associated with early cardiac mortality.
Shivaraju et al. [39]	National sample of inpatients, 1998–2006 yrs., N=1.2 mln	— The main independent predictor of gastrointestinal bleeding after PCI was malignancy (based on the odds ratio of rectal > gastric > oesophageal > colorectal cancer)
van Werkum et al. [40]	Dutch Stent Thrombosis Registry, 437 cases of definite stent thrombosis	— Active malignancy was an independent risk factor for stent thrombosis, OR 13.08 (CI 1.99–85.93, p=0.0074).
Tabata et al. [35]	Kumamoto University Registry for Malignant Tumours and Atherosclerosis (KUMA)	— Active malignancy or the history of malignancy was an independent predictor of TLR at 1 year; — The risk of TLR was highest in patients with ongoing cancer or recent cancer treatment.
Landes et al. [5]	Retrospective analysis in a single centre from Israel, N=12,785 consecutive patients who underwent PCI between April 2004 and October 2014.	— Cancer survivors (mean interval between cancer diagnosis and PCI 3.6±3.4 years) had a 40% increased risk of the combined endpoint of death, non-fatal myocardial infarction, target vessel revascularisation and coronary artery bypass graft surgery (mean follow-up 6.4±5.9 years).
Hess et al. [23]	Retrospective single-centre analysis (Duke Information Systems for Cardiovascular Care and the Duke Tumor Registry) N=15008	— The 3 study groups were «cancer before PCI» (any cancer treatment before PCI), «cancer after PCI» (received cancer treatment after the PCI), and «recent cancer» (cancer treatment within 1 year before PCI); — The adjusted risk of long-term cardiovascular mortality was not significantly different in patients with cancer before PCI compared with patients without cancer; — Patients with cancer after PCI (latent malignancy during PCI) had a significantly higher adjusted risk of cardiovascular mortality.
Wang et al. [41]	Retrospective analysis of a single centre from the Mayo Clinic PCI database, N=2346 STEMI patients from November 2000 to October 2010.	— Cancer patients had higher in-hospital non-cardiac mortality but the same cardiac mortality as the control group; — Recent cancer diagnosis (within 6 months of STEMI onset) had the highest risk of acute in-hospital mortality; — Even after a median follow-up of 6.2 years, the higher mortality observed in the cancer group was due to non-cardiac causes.
Quintana et al. [37]	Meta-analysis of trials evaluating all-cause, cardiovascular, and non-cardiovascular mortality at 1 year in PCI patients with active cancer or history of cancer, N=33175	— Cancer patients who underwent PCI had higher annual all-cause mortality, cardiovascular, and non-cardiovascular mortality; — Cancer patients had higher one-month all-cause and non-cardiovascular mortality, but no difference in cardiovascular mortality compared with non-cancer patients undergoing PCI.

ing, thrombosis, and repeat revascularisation. An analysis of the NIS database, which examined time trends in gastrointestinal bleeding after PCI, showed that the top four independent predictors of gastrointestinal bleeding were: rectal cancer (OR 4.64; 95% CI 3.20–6.73; p<0.0001), gastric cancer (OR 2.74; 95% CI 1.62–4.66; p=0.0002), oesophageal cancer (OR 1.99; 95% CI 1.08–3.69; p=0.0288) and colorectal cancer (OR 1.69; 95% CI 1.43–2.02; p<0.0001) [42]. The Dutch Stent Thrombosis Registry showed that current malignancy was an independent risk factor for stent thrombosis with an OR of 13.08 (CI 1.99–85.93, p=0.0074) [40]. Tabata et al. who studied the incidence of target lesion revascularisation (TLR) in cancer patients undergoing PCI, showed that current or recent history of malignancy was an independent predictor of TLR after 1 year. Time since completion of anticancer therapy also played a role, with the risk of TLR being higher in patients with a current or recent cancer history [35]. In a retrospective analysis in Israel, cancer survivors (mean interval between cancer diagnosis and the PCI was 3.6±3.4 years) had a 40%

increased risk of a combined endpoint consisting of death, non-fatal myocardial infarction, target vessel revascularisation and coronary bypass surgery (mean follow-up 6.4±5.9 years) [5].

However, researchers analysing PCI data in cancer patients from the Duke [23] and Mayo [41] registries showed opposite results. In this analysis, patients were divided into three groups: "pre-PCI cancer" (any cancer treatment prior to PCI), "post-PCI cancer" (patients receiving cancer treatment after the PCI), and "recent cancer" (cancer treatment within 1 year prior to PCI). The adjusted risk of long-term CVD mortality was not significantly different in patients with cancer before PCI compared with patients without one. However, patients with cancer after PCI (some of whom may have had underlying malignancy at the time of PCI) had a significantly higher adjusted risk of CVD mortality [23]. An analysis of data from STEMI patients undergoing primary PCI at the Mayo Clinic showed that cancer patients had higher in-hospital cardiac and non-cardiac mortality, similar to controls. A recent cancer diagnosis (within 6 months of STEMI) had the highest risk of acute in-hospital mortality. Even with a median follow-up of 6.2 years, the higher mortality observed in the cancer group was due to non-cardiac causes [41].

Special considerations for cancer patients undergoing PCI Indications for PCI

Revascularisation in patients with a history of oncology should be approached with a careful risk-benefit assessment, especially in planned clinical situations. Because of the high risk of bleeding, PCI should be reserved for absolute indications, even in patients with an acceptable oncological prognosis [42]. Patients with a life expectancy of less than 1 year and acute coronary syndromes (STEMI, high-risk non-STEMI, and unstable angina) should be offered revascularisation in the same way as patients without cancer. However, in stable angina, every effort should be made to optimise the patient's condition with conservative medical therapy, which may include treatment of concomitant oncological conditions such as anemia and hypoxia in addition to anti-anginal drugs [43].

Procedural specifics

According to the Society for Coronary Angiography and Interventions (SCAI) expert consensus document, careful caution should be exercised to minimise the risk of bleeding and optimise stenting outcomes when performing PCI in cancer patients [43]. Radial access should be one of the preferred routes for PCI given the significantly lower risk of vascular complications, bleeding and MACE compared to femoral access [44]. Notably, in patients with a history of breast cancer, the use of ipsilateral radial access does not increase the likelihood of developing lymphedema [45]. When radial access is not possible, the ulnar artery or attempted contralateral radial artery may be considered. In cases when radial/lateral access is not possible, to minimise periprocedural complications of the access site, the common femoral artery should be punctured under ultrasound and fluoroscopic control, and a suturing device should be used if possible. Case series and retrospective analysis of cancer patients with thrombocytopenia (including those with severely reduced platelet counts <30,000/mm^3) have demonstrated the safety of cardiac catheterisation and PCI as long as careful arterial access and post-procedural haemostasis are ensured [46, 47]. Intravascular ultrasound or optical coherence tomography should be used to assess the lesion and optimise stent implantation (location, apposition, dilatation and absence of marginal dissection) to improve short- and long-term outcomes in the event of early discontinuation or interruption of dual antiplatelet therapy. Data suggest that optical coherence tomography can also be used to identify low-risk patients (defined as those with adequate stent cell coverage, apposition and absence of stent restenosis or intraluminal masses) in whom dual antiplatelet therapy can be safely discontinued for cancer-related surgery [48]. During PCI, the use of bivalirudin may have an advantage over heparin because of the reliability of anticoagulation and the shorter half-life of the drug [43]. The SCAI consensus document also recommends that only coronary balloon angioplasty should be considered when a patient has a very low platelet count (<30,000/dL), when a platelet count is expected to decline, or when high-risk emergency surgery is warranted. When considering revascularisation in patients with platelet counts >30,000/dL who require an invasive procedure or chemotherapy that can be delayed >4 weeks, advanced drug-eluting stents should be considered over bare-metal stents. The polymer- and carrier-free BioFreedom stent (Biosensors Europe) [49] and the Endeavour Sprint stent with rapid release of zotarolimus (Medtronic Vascular,

Minneapolis, Minnesota) [50] have been shown to be superior to metallic stents, reducing the duration of dual antiplatelet therapy to 4 weeks. Similarly, a new generation drug-eluting stent should be considered in patients with platelet counts >30,000/ml who do not require immediate invasive procedures or chemotherapy. In addition, the X-ray endovascular surgeon should avoid complex bifurcation stenting, try to minimise the number of stents, the length of the stented area, and stent layering as this increases the likelihood of stent thrombosis and restenosis [43].

The role of the multidisciplinary team

The treatment of cancer with stable angina or ACS is often a complex scenario. Several factors must be considered, including the patient's life expectancy, the risk of bleeding, the anticipated need for invasive procedures (such as biopsy or surgical resection) in the near future, and the consequent interruption or complete withdrawal of antiplatelet therapy. These urgent decisions should be made in a multidisciplinary team discussion including surgical and/or medical oncology, X-ray endovascular surgery, radiation, palliative oncological basis of medicine and cardiology. In recent years, cardio-oncology has been considered an important field that specialises in CVD prevention and screening in patients with cancer pathology [51]. Finally, the risks, benefits and alternatives to any treatment should be thoroughly discussed with patients and their families, and their wishes should be taken into account.

Conclusion

PCI in cancer patients is associated with an increased risk of bleeding, in-hospital and long-term mortality, and the need for repeat revascularisation. The type of cancer and the presence of metastases also play a key role in determining outcomes. In addition, studies have also shown that recent cancer diagnosis and recent treatment predict worse outcomes after PCI. Older age, increased comorbidities and the presence of haematological and coagulation disorders pose challenges for PCI in this group of high surgical risk patients. These risks can be at least partially mitigated by using the best surgical operative techniques for performing interventions, and informed treatment decisions should be made with a multidisciplinary approach.

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