Severe aortic stenosis in a patient with breast cancer

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ABSTRACT

We present a case of 68-year-old female with severe symptomatic aortic stenosis and locally advanced breast cancer disqualified from mastectomy due to heart failure and from aortic valve replacement due to malignant neoplasm. The patient received neoadjuvant chemotherapy without anthracyclines. The aortic valve replacement was performed and then mastectomy and lymphadenectomy were made without hemodynamic complications. Adjuvant hormonotherapy was started. During 42 months of follow-up the patient remained free of recurrent cancer disease as well as no progression of heart failure was observed.

KEY WORDS: aortic stenosis, breast cancer, anthracyclines, aortic valve replacement, echocardiography

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INTRODUCTION

Breast cancer is the most common cancer among women worldwide. Each year over 1.6 million new cases are diagnosed across the world [1]. On the other hand, degenerative aortic stenosis is currently the third most common cardiologic condition diagnosed in Europe and North America, following arterial hypertension and ischaemic heart disease. It also remains the most common among the acquired valvular heart diseases. Development of a haemodynamically significant aortic stenosis worsens prognosis of oncological patients irrespective of the stage of disease [2]. In a great majority of cases, symptomatic stenosis of the left arterial ostium is an absolute contraindication to adequate anti-cancer treatment, both surgery and chemotherapy. According to the current guidelines, neoadjuvant treatment of locally advanced breast cancer is most efficacious in terms of long-term outcomes, when anthracyclines are combined with taxanes [3]. However, in the presence of heart conditions, the risk of anthracycline-related cardiotoxicity is increased, which is why anthracyclines are contraindicated [4]. The presented case is an example of a modification of the anti-cancer treatment algorithm, resulting from the presence of a cardiologic defect. The paper also touches upon the important issue of cooperation between different specialists. In the case discussed below, safe and efficacious breast cancer treatment would not have been possible, were it not for the tight collaboration involving oncology, cardiology and cardiosurgery specialists.

CASE PRESENTATION

In December 2011, a 68-year-old patient with ER-positive, PR--positive, and HER2-negative infiltrating ductal carcinoma (according to the terminology binding in 2011) reported to the Department of Oncology and Oncological Surgery of the European Health Centre in Otwock. The entire oncological diagnostics had been carried out in a different centre, which had failed to qualify the patient for mastectomy because of the simultaneous diagnosis of severe aortic stenosis. For several years, the patient had been suffering from exertion dyspnoea. When diagnosed with breast cancer, her physical performance had corresponded with NYHA functional class II, whereas at the moment of her admission to the European Health Centre Otwock, it was class III. The aortic stenosis, diagnosed after the detection of breast cancer, had not been managed for fear of cancer progression caused by an open heart surgery.

During the patient's stay in our centre, the physical examination revealed a small 1 × 1 cm ulceration in the lower outer quadrant (LOQ) at 5 o'clock. Under palpation, a large 4–5 cm tumour was felt in the area of the ulceration. Enlarged lymph nodes were not reported. The remaining abnormalities included tachycardia, loud systolic murmur (4/6 on the Levine scale) in the aortic region and radiating to the pulmonary arteries, and symmetric crepitation at the base of both lungs.

As the tumour grew rapidly, it was decided that pre-surgical chemotherapy be initiated immediately. However, the cardiologic conditions constituted a contraindication to the preferred regimens based on anthracyclines. Hence, the patient received 6 courses of TC therapy instead (docetaxel 75 mg/m^2 + cyclophosphamide 600 mg/m^2). For extended cardiologic diagnostics, and in order to decide on further treatment, the patient was then referred to the Department of Pulmonary Circulation and Thromboembolic Diseases at the Centre of Postgraduate Medical Education.

Upon admission to the Clinic, symptoms of heart failure corresponding with the NYHA class III were revealed. Slight ankle swelling was additionally reported in physical examination. Lab tests revealed a high NT-proBNP concentration of 1635 pg/ml (with the normal range of 0–177 pg/ml), and mild anaemia (haemoglobin 10.3 g/dl, haematocrit 31.5%). Transthoracic echocardiography confirmed the diagnosis of severe aortic stenosis. Large degenerative lesions of the trileaflet aortic valve were visualized (fig. 1), with annular calcifications and limited mobility of the thickened leaflets, as well as left ventricular hypertrophy, and mildly compromised diastolic function of the left ventricle (relaxation abnormalities), with normal systolic function. No signs of pulmonary hypertension were revealed. The maximum left ventricular ejection rate was 5.1 m/s, with aortic valve mean gradient of 65 mmHg (fig. 2). Aortic valve area was estimated planimetrically as 0.5 cm^2 (fig. 3), and as 0.8 cm^2 with the Doppler continuity equation method (fig. 4). Mild dicrotic wave, and mild ascending aorta distension (to 41 mm) were among the additional findings. Angiography did not reveal any significant lesions within the coronary vessels. The patient's risk of death related to the surgical aortic valve replacement was estimated as 1.01%. based on the EuroSCORE II logistic model. The patient's prior pharmacological treatment was modified to include ramipril, nebivolol, lacidipine, torasemide and simvastatin.

The patient was referred for cardiosurgical consultation, as a result of which decision was taken to surgically manage the aortic stenosis. On 18 April 2012, Medtronic Mosaic bioprosthetic valve, 19 mm in diameter, was implanted to replace the natural valve. Post-operative echocardiogram, performed on 30 April 2012, revealed a mean aortic valve pressure gradient elevated to

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FIGURE 1.
Parasternal long axis view. Examination preceding the cardiosurgical intervention. Ventricular systole phase. The thickening, hyperechogenicity and misalignment of the aortic valve leaflets indicate its degenerative stenosis. The valvular annulus, aortic bulb and sinotubular junction are not distended, which may play an important part, when selecting the size of prosthesis.

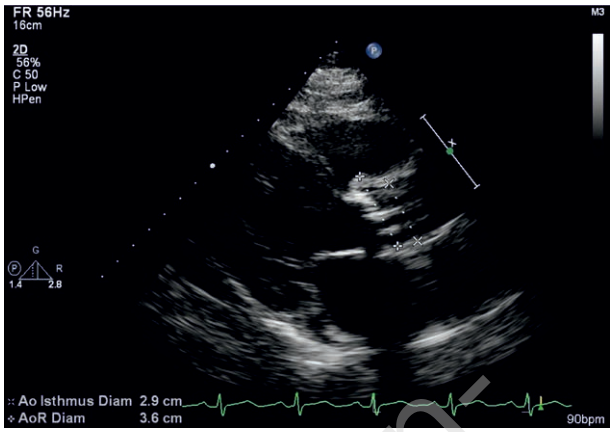


FIGURE 2.
Spectrum of flow velocity through the aortic valve – continuous wave Doppler measurement in apical five-chamber view. High maximum velocity (5.1 m/s) and high mean pressure gradient (65 mmHg) indicate valvular stenosis.

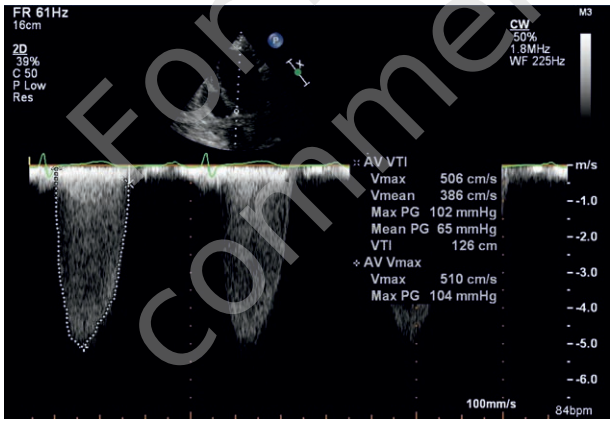


FIGURE 3.
Aortic valve surface area – planimetric measurement in parasternal vascular view. The small area of the valve ostium (0.45 cm^2) testifies to very severe stenosis, but the challenging technical conditions render accurate measurement difficult.

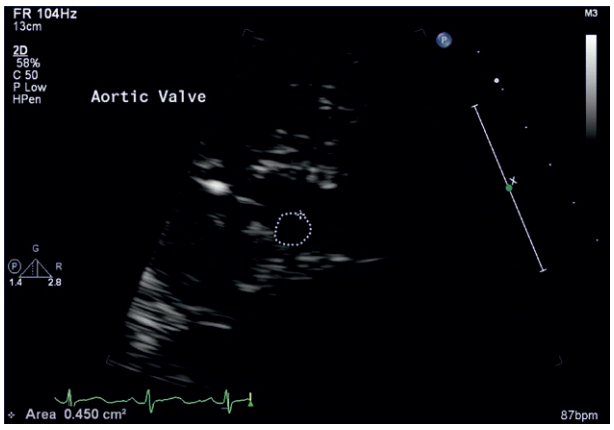
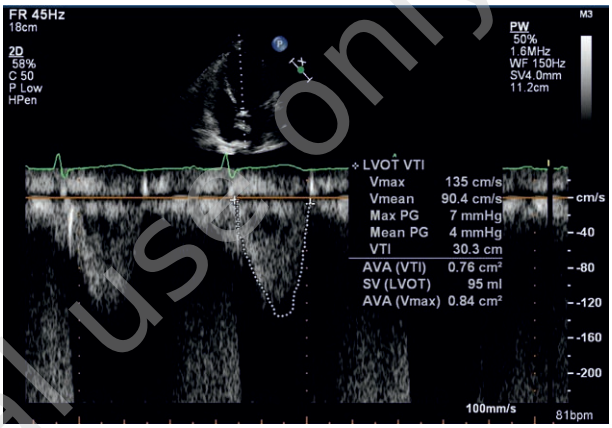


FIGURE 4.
Spectrum of flow velocity through the left ventricular outflow tract – pulsed wave Doppler measurement, with the Doppler gate in the left ventricle, ca. 1 cm inferior to the aortic valve. Aortic valve area calculated based on the continuity equation method amounts to 0.76–0.84 cm^2, i.e. a value significantly higher than the one obtained with planimetry (see fig. 3), but still indicative of severe (bordering on very severe) aortic valve stenosis.



34 mmHg, a larger than small paravalvular leak, normal (65%) left ventricular ejection fraction, and 11–13 mm layer of fluid in the pericardium, adjacent to the right ventricle and right atrium. Five months later, on 9 October 2012, the patient was readmitted on cardiology department for haemodynamic assessment before mastectomy. Her performance status had improved after the cardiosurgical procedure, going back to NYHA functional class II. Additionally, the peripheral oedema receded, as did the auscultatory signs of pulmonary stasis. The NT-proBNP concentration dropped to 935.5 pg/ml, the level of haemoglobin increased to 11.0 g/dl, and the level of troponin T was 0.008 ng/dl (normal range < 0.014 ng/dl). The bioprosthesis was positioned as expected in the aortic ostium (fig. 5), when examined by TTE, with suboptimal visualization conditions. The mean aortic valve pressure gradient was 35 mmHg, with the maximum aortic valve flow rate of 4.06 m/s (fig. 6). The calculated effective orifice area (EOA) of the left arterial ostium was 1.2 cm^2, while the aortic surface area indexed to body surface area (BSA) amounted to 0.7 cm^2. The left ventricular ejection acceleration time around 60 ms, while the Doppler velocity index (DVI) was 0.36. The paravalvular leak assessed by TTE was reported as moderate (fig. 7). The diastolic flow velocity in descending aorta was ca. 20 cm/s. Left ventricular contractility was assessed as good, with low probability of pulmonary hypertension, and no signs of right ventricular overload. Together with the team of cardiosurgeons who had performed the procedure, following an in-depth analysis of the patient's clinical situation and lab test results, and in light of the patient's satisfactory exercise tolerance, decision on transesophageal echocardiography was aborted, keeping the

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FIGURE 5.
Examination performed following the cardiosurgical procedure – apical 5-chamber view. The Medtronic Mosaic 19 mm bioprosthesis visualized in the aortic ostium.

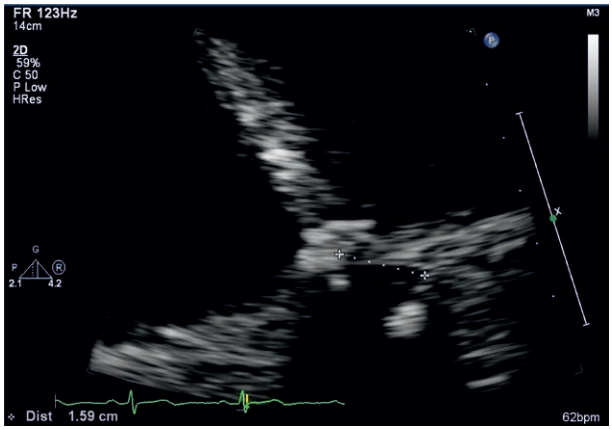


FIGURE 6.
Spectrum of flow velocity through the implanted bioprosthesis – continuous wave Doppler measurement in apical 5-chamber view, performed 5 months post-op. Compared with the pre-op examination, the maximum velocity is lower, but still remains high (4.06 m/s), as does the pressure gradient (35 mmHg).

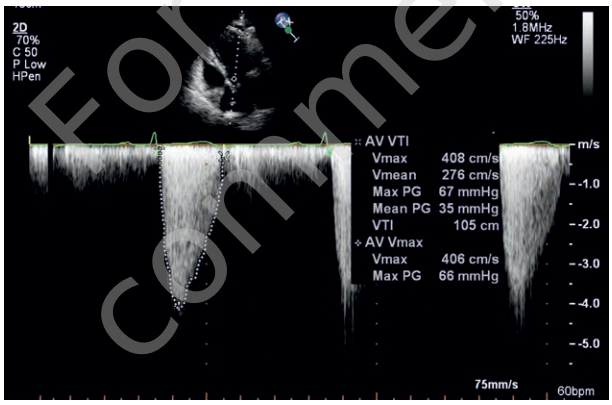
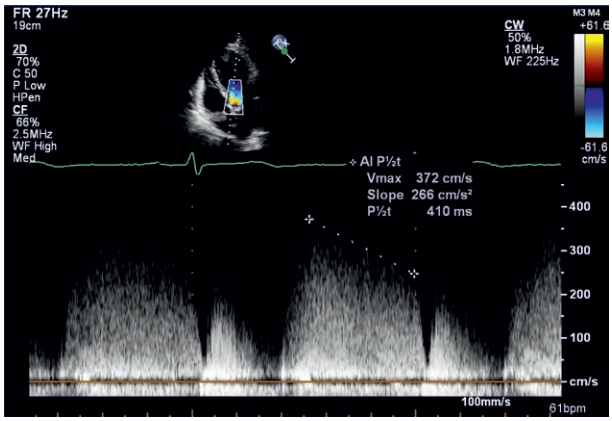


FIGURE 7.
Retrograde diastolic flow through the aortic valve orifice – paravalvular leak. Spectral Doppler measurement in apical 5-chamber view.



patient in follow-up. The patient was to continue on ACE-I, β-adrenolytic, torasemide, simvastatin, with an addition of spironolactone. Continuation of antithrombotic prophylaxis with vitamin K was recommended for a period of 3 months from the day of valve replacement, and antibiotics were prescribed to prevent infectious endocarditis.

Opinion was issued on the lack of contraindications to surgical anti-cancer treatment, thanks to which the patient could undergo radical mastectomy with lymph node dissection. There were no complications. As part of the perioperative antithrombotic prophylaxis, low-molecular-weight heparin (enoxaparin) was administered at full therapeutic doses. Due to the complete tumour response following the pre-operative chemotherapy, post-operative radiotherapy was not necessary. The patient was qualified for tamoxifen hormone therapy. 42 months (3.5 years) later, the patient reports no significant cardiologic symptoms, she is NYHA functional class I, and remains under continuous care of an oncology clinic.

DISCUSSION

Several clinical problems resurface in the above presented case description. The first one is the coexistence of two diseases with poor prognosis. In the case of breast cancer, 5-year survival depends on various factors, including age at diagnosis, histological type of cancer, stage of the disease, and the like. 1-year survival is around 92%, while 5-year survival is 75% [5]. On the other hand, in symptomatic severe aortic stenosis 2-year survival amounts to around 50% [6]. Analysis of the above mentioned data indicates that haemodynamically significant stenosis of the left arterial ostium is associated with poorer prognosis than malignant breast cancer.

In the presented case, due to the clinical advancement of the neoplastic disease (a large tumour > 4 cm), it was not possible to offer breast conserving surgery to the patient, with the adequate therapeutic option being mastectomy under general anaesthesia. However, the patient suffered from NYHA class III symptoms of heart failure, and the echocardiography examination revealed the maximum left ventricular ejection rate of over 5 m/s, the mean aortic valve pressure gradient of 65 mmHg, and aortic surface area of 0.8 cm^2. Both the European and American guidelines on valvular disease management [7, 8] classify such findings as severe symptomatic aortic stenosis, with the treatment of choice being aortic valve replacement (AVR).

In clinical practice, cancer disease may be a reason behind disqualifying a patient from AVR. In the retrospective analysis by

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Yusuf et al. [2], only 27% of patients from a university oncological hospital in whom severe aortic stenosis had been diagnosed underwent AVR. The group was not significantly different from the one receiving conservative treatment in terms of disease progression or other burdens. AVR turned out to be the only factor which statistically significantly reduced the risk of mortality (HR = 0.22; p = 0.028). The authors concluded that AVR in cancer patients with severe aortic stenosis improves survival irrespective of the type and stage of the tumour. Median survival in the AVR arm was 1148 days, while in the conservative treatment arm it was only 372 days, with mortality rates of 31% and 77% respectively.

According to the ACC/AHA guidelines, qualification to non-cardiologic surgical procedures should be a two-stage one [9, 10]. The first stage should involve the assessment of a given procedure, i.e. whether it is an urgent or elective intervention. At the second stage, cardiologic contraindications to surgery should be ruled out. A clinically significant aortic stenosis is a strong independent perioperative mortality risk factor in patients undergoing non-cardiosurgical procedures [11–13]. It is thus fundamental for the safety of the severe aortic stenosis patients undergoing surgical interventions that they are offered the best possible, modern and well-organized intra-operative and post-operative care [14].

In the case described above, transcatheter aortic valve implantation (TAVI) was taken into account. The procedure does not require sternotomy or extracorporeal circulation, but does not eliminate the risk of serious complications, including perioperative death, stroke, and complete atrio-ventricular block. High surgical risk patients, whose EuroSCORE is 20% or over, are qualified for TAVI, as are the patients following chest radiotherapy or those with porcelain aorta. Such indications were not present in the case of the discussed patient, though, which resulted in the selection of the classical method of aortic stenosis surgery. It is worth remembering that apart from the assessment of coronary arteries (angiography) and cephalic arteries (ultrasound), patients qualified for TAVI also require a detailed assessment of the iliac arteries and aorta, with the use of computed tomography with contrast and angio-CT, as well as the assessment of the aortic system, aortic bulb, and ascending aorta with the localization of the coronary artery ostia (angio-CT, and transesophageal echocardiography performed at a referential centre). A third method of treatment to be considered in such cases is balloon valvuloplasty for aortic valve stenosis. It is recommended [9] as a bridging procedure before an elective surgical aortic valve replacement or TAVI in patients who require an urgent and extensive non-cardiosurgical operation. Just like TAVI, the method is a transcatheter one, but it does not bring along lasting improvement, and it does not impact long-term prognosis, while it is associated with the risk of acute severe aortic incompetence, requiring immediate cardiosurgical management, which is why it is rarely applied in clinical practice.

AVR can never restore the normal haemodynamics of the heart. Due to the imperfection of both the valvular prostheses and the surgical techniques, it is not possible to reduce the resistance to blood flowing out of the left ventricle into the aorta to values found in healthy subjects. If the implanted valve is too small in diameter, there occurs an additional phenomenon of prosthesis-patient mismatch (PPM), which was exactly the case in the discussed patient. What indicated PPM was the persisting post-operative high left ventricular ejection rate reaching 4.06 m/s as well as the elevated mean aortic valve pressure gradient (35 mmHg). Amongst the arguments against restenosis, though, were the short time from AVR, and the echocardiography parameters, including the short transprosthetic flow velocity acceleration time, and the Doppler velocity index exceeding the value of 0.3. It is worth noting that the smallest manufactured Medtronic Mosaic bioprosthesis was implanted in the patient, which was most probably caused by the anatomy encountered by the cardiosurgeon during the replacement procedure. Apart from the patient prosthesis mismatch, there was another early complication in the form of the paravalvular leak. When preparing the patient for mastectomy, it was decided that the patient's condition and the moderate size of the leak do not justify the risk of potential reoperation. Modern techniques of interventional cardiology allow for percutaneous closure of significant paravalvular leaks, which should be considered in the course of the patient's further therapy.

It is also worth considering the type of an implantable prosthesis in the context of further anticoagulant treatment. Presently, cardiosurgery has two types of prostheses on offer, i.e. mechanical and biological ones. The main advantage of the mechanical prostheses is their durability. On the other hand, classical bioprostheses make it possible to discontinue anticoagulant therapy 3 months post-op. Transcatheter replacement valves (CoreValve, Sapien XT) are in fact bioprostheses, and require double anti-platelet therapy (acetylsalicylic acid 75 mg and clopidogrel 75 mg) for 3–6 months from implantation, followed by life-long treatment with acetylsalicylic acid). Both the double anti-platelet therapy as well as the treatment with vitamin K antagonists constitute important problems in patients undergoing mastectomy and other surgical procedures, increasing the risk of intraoperative bleeding. It should also be remembered that chemotherapy

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may impact the efficacy of vitamin K antagonists, leading to significant fluctuations of the INR value, which is associated with an elevated risk of bleeding on the one hand, and with prosthetic thrombosis on the other. The choice of a biological prosthesis eliminates those risks, but is associated with the risk of reoperation within the period of several years from AVR due to the progressing degeneration of the device.

A controversial issue is the use of extracorporeal circulation (ECC) in patients with active cancer or in remission. Two different mechanisms are indicated that may potentially lead to ECC-related cancer progression:

1. introduction of neoplastic cells to the systemic circulation, which may result in peripheral metastases [15]
2. temporary reduction in the cellular and humoral immunity, caused by ECC [16].

The first mechanism pertains mainly to patients with diagnosed lung cancer infiltrating large vessels of heart structures, whereas the second mechanism may potentially be true for all cancer patients. There are, however, no large prospective trials to confirm the thesis that temporary immunosuppression caused by ECC is of clinical significance and affects the development of a neoplastic process. An additional hindrance on the way to an objective solution of the problem is the relatively small number of open heart surgeries conducted in patients with concomitant oncological disease. Carrascal et al. [17] described 2146 patients operated on with the use of ECC, out of which only 89 suffered from a malignant tumour, with 33 patients (1.5%) in the course of an active neoplastic disease, and 56 subjects (2.6%) in complete remission. Among the operated cancer patients, there were 7 post-operative deaths related to tumour progression, and only one related to a relapse. In total, relapse was detected in 16 patients (18.8%), and the mean time from surgery to relapse was 6.7 months in the group of patients with active cancer, and 12.1 months in the remission group. The mean time from ECC to death due to cancer progression or relapse was 25.2 months. The authors concluded that the long period of time between the surgery and relapse fails to indicate a link between the relapse and ECC.

Similar conclusions stem from other retrospective analyses. Canver et al. analysed a group of 46 patients who had undergone surgery with the use of ECC, having previously been treated for malignant tumours, without reporting a single case of relapse following the open heart operation (mean follow-up time of 36.5 months, ranging from 26 to 47 months) [18]. Schoenmakers et al. examined 43 patients with lung cancer and coronary artery disease required surgical revascularization [19]. When comparing 28 patients subjected to lung resection followed by coronary revascularization with ECC with a group of 15 patients who underwent a beating-heart surgery for coronary revascularization first, followed by lung resection without ECC, they did not observe an increase in cancer-related mortality in the ECC group. The surgery involving ECC was found to be associated with a higher rate of 5-year survival than the beating-heart surgery (46% vs. 13%; $p < 0.01$). Kauffmann et al., on the other hand, analysed a group of 16 patients with non-small-cell lung cancer who underwent onco-cardiosurgical procedures with the use of ECC [15]. In 8 patients, an extensive mediastinal resection was performed, with the reconstruction of cardiovascular structures, because of a tumour infiltrating the heart or the large vessels (T4 tumour), and in the remaining 8 patients tumour resection (T1–T2) was combined with coronary artery bypass grafting. The median survival was 13.6 months in the advanced stage group (T4), and 21.1 months in the T1–T2 group. Local recurrence was reported after 3–31 months in the T4 group, with only a single patient from that group dying after 13 years with no signs of relapse. In the T1–T2 group, on the other hand, no case of relapse was reported, with deaths caused by cardiovascular incidents. Following ECC surgery, no clinically overt distant metastases were reported in either of the two groups.

When discussing different issues pertaining to the qualification of an oncological patient to a cardiosurgical procedure, it is worth observing that the commonly used European perioperative death risk model EuroSCORE and its updated version EuroSCORE II, just like the STS score used in the US, were elaborated based on patient populations in which cancer patients were only a small fraction. Among the 19 030 patients from the EuroSCORE database, only 106 (0.6%) were diagnosed with cancer at the time of the surgery, and only 80 of them (0.4%) were in the course of immunosuppressive treatment [20]. Not knowing whether the calculated surgical risk of oncological patients is the same as that of the general population addressed by the EuroSCORE II model [21], each individual case of a cancer patient qualified for cardiac reconstructive surgery has to be analysed separately. An optimum solution appears to be appointing a team of experts, including a cardiosurgeon, interventional cardiologist, anaesthesiologist and oncologist, provided it is possible in a given situation, and on condition that it will not significantly delay the initiation of treatment.

The presented case demonstrates the need to adapt neoadjuvant chemotherapy to a specific clinical scenario. Due to our patient's active cardiac condition, a chemotherapeutic regimen without anthracyclines was selected. For many years now, the mechanism of anthracycline-related cardiotoxicity has been extensive-

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ly studied [22]. Polish multi-centre observational studies, inter alia, indicate that the anthracycline-based neoadjuvant chemotherapy constitutes one of the most significant risk factors for the development of heart failure in breast cancer patients [23]. According to the ESMO 2015 guidelines (European Society for Medical Oncology), the most common chemotherapeutics in breast cancer are indeed anthracyclines. The addition of taxanes to the regimen improves treatment efficacy irrespective of the age, lymph node involvement, tumour size or steroid receptor expression, but it does so at the cost of increased non-cardiologic toxicity [3, 24]. An absolute contraindication to anthracyclines, however, is e.g. heart failure. In such cases, guidelines accept the use of modified regimens, without anthracycline antibiotics, but instead based on taxanes, like for instance 4 courses of docetaxel combined with cyclophosphamide (4 × TC) [25]. That very regimen was administered to our patient. Thanks to it, a very good therapeutic outcome was achieved (including pathological complete response), while avoiding the deterioration of the cardiovascular function.

It should be noted that left ventricular systolic-diastolic dysfunction may have a subclinical course in patients with aortic stenosis. It is related to the structural changes of the left ventricular muscle, which do not regress automatically after the valve replacement. Hence, even in the patients in whom a recent cardiosurgical intervention or TAVI removed the valvular defect, and who do not manifest any symptoms of heart failure, the risk of anthracycline-related cardiomyopathy appears to be elevated, which is why one should considering excluding that class of drugs from their chemotherapeutic regimen. The recommendation is especially valid in those patients in whom PPM was diagnosed after valve replacement, as in the case presented above.

The indications and benefits of neoadjuvant and adjuvant anthracycline-based chemotherapy are ever more frequently looked into these days. Following the last conference in St. Gallen, the expert panel adopted the position that in luminal B breast cancer anthracyclines combined with taxanes remain the recommended adjuvant chemotherapy regimen [3], while in the case of the luminal A cancer there is little evidence that such regimen is superior to the older protocols such as CMF [26]. In 2009, results of a relatively small study US Oncology 9735 were published, involving 1016 breast cancer patients. Over the 7-year follow-up, the study demonstrated the superiority of the docetaxel plus cyclophosphamide (TC) therapy over the regimen including doxorubicin and cyclophosphamide (AC) in terms of DFS and OS as well as in terms of treatment tolerance both in the younger and older population of patients [27].

We would also expect additional commentary on the use of the NT-proBNP concentration levels in the diagnostics and monitoring of heart failure related to aortic stenosis. Despite the fact that numerous studies demonstrated good correlation between NT-proBNP and the systolic/diastolic heart dysfunction, it should be emphasised here that the peptide does not form part of the canon of parameters that serve as indications for surgical valve replacement [8, 9], nor is it routinely used for the monitoring of the cardiotoxicity of anti-cancer drugs [28, 29].

SUMMARY

Coexistence of cardiac conditions and neoplastic diseases is ever more common. It may be expected that due to the aging of the society, and the longer life expectancy of our patients, the trend will only intensify. Thus, it will be a challenge of the coming years to elaborate and implement detailed guidelines on the cooperation of oncologists with the specialists from other disciplines, and cardiology in particular. In every case of coexisting cardiac disease and cancer, one should carefully agree on the management strategy, weighing the benefits and the risks related to cardiologic treatment preceding the anti-cancer therapy, and taking into consideration all possible involved complications. As demonstrated in the above presented case study, only tight collaboration between different specialists makes it possible to achieve good therapeutic effects, while ensuring the highest possible safety of the selected therapy. A neoplastic disease should not be treated as a contraindication to the surgical management of severe aortic stenosis. The available clinical data do not confirm the fact that ECC procedures are associated with faster cancer progression.

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The authors report no conflicts of interests.

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Authors' contributions:

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Sebastian Szmit: conception of the article, interpretation of oncologic surveys, discussion from the oncologic point of view, conclusions, selection and description of figures

Michał Wilk: case report, review of the manuscript

Anna Walaszkowska-Czyż: review of the manuscript

Michał Florczyk: review of the manuscript, selection and description of figures.

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