

INTERNATIONAL PERSPECTIVES

Cardio-Oncology in Portugal

A Rising Tide



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*Neither floods nor plagues, famines nor
cataclysms, nor even the eternal wars of century
upon century, have been able to subdue the
persistent advantage of life over death*

—Gabriel Garcia Marquez in his acceptance
speech for the Nobel Prize for Literature, 1982

Cardiovascular and oncological diseases are the 2 most common causes of mortality and morbidity in developed nations. Patients with oncological disease have a significantly higher risk for cardiovascular events than the general population throughout their clinical trajectory. Approximately one-third of patients treated for oncological diseases will have cardiovascular complications. Cardio-oncology, the discipline that represents an interface between the 2 areas, is a rising tide in Portugal.

Blessed with a pristine coast and a temperate climate, Portuguese navigators discovered the maritime routes to 3 continents. Portugal is a country of 10 million people and a republican parliamentary democracy that evolved after the end of a decades-long dictatorship, through a bloodless revolution in 1974.

The national health service, Serviço Nacional de Saúde (SNS), was created in 1979 as an instrument of social justice. It is a tax-funded, single-payer system that affords equitable access to all citizens. For 25 years, care was delivered almost exclusively through the large network of hospitals and primary health care centers, with some fringe independent providers. In 2021, public sector spending on the SNS was

9.52% of the gross domestic product, slightly less than the European Union (EU) average, superseded only by 6 countries in the EU, all of which have considerably higher gross domestic products per capita.¹ In terms of life expectancy, Portugal is on par with the other EU nations, with 22% of the population older than 65 years.

Dovetailing with the SNS, several groups of private providers with their respective networks of hospitals and health units working in a classical spoke-and-hub pattern have emerged. There is an internal market for voluntary health insurance schemes, covering approximately 25% of the population. Patients with health insurance from these voluntary schemes can access both systems. The private sector has a different case mix, and the most complex cases are managed by the SNS. The SNS provides virtually all education and training of medical students and fellows in cardiology and oncology.

CARDIO-ONCOLOGY IN PORTUGAL

The major oncological diseases treated in Portugal are lung and bronchial (22%), colorectal (20%), stomach (12%), breast (9%), prostate (9%), pancreatic (8%), hepatobiliary (6%), bladder (5%), and others (9%).² A network of 47 hospitals within the SNS provides oncological care, including 3 comprehensive cancer centers named Instituto Português de Oncologia. Although patients can receive treatment from private providers, there is usually a ceiling of coverage imposed by the health insurance companies.

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Newer therapies are approved after clearance from the European Medicines Agency and local approval from the national regulatory agency, Infarmed. Recently approved medications with known cardiotoxicity include the immune checkpoint inhibitors durvalumab (2019) and pembrolizumab (2021), the epidermal growth factor receptor inhibitor osimertinib (2021), the proteasome inhibitor carfilzomib (2020) and the chimeric antigen receptor T-cell therapies axicabtagene (2021) and tisagenlecleucel (2021).

The pioneers who sowed the seeds of the discipline are Prof Manuela Fiuza, from the Department of Cardiology at North Lisbon University Hospital Center, and her departmental head, Prof Fausto Pinto, who is currently president of the World Heart Federation.^{3,4} The Portuguese Society of Cardiology (PSC) has a working group on cardio-oncology, which has education, training, research, academic, and clinical collaborations and international alliances with networks and societies as its aims.

Seven hospitals in Lisbon, 3 in Porto, 1 in Coimbra, and 4 others we contacted outside these areas have outpatient cardio-oncology consultation and surveillance imaging protocols in place. Although the SNS has an extensive network of hospitals with electronic health records, which allow cross-hospital access of clinic information under limited circumstances, very little is known in the public domain regarding the number of patients seen. Data on cardiovascular complications are also missing.

Every year at the annual meeting of the PSC, there are general courses on cardio-oncology and dedicated sessions on imaging and cardiotoxicity. In 2019, Prof Richard Kovacs, then president of the American College of Cardiology, spoke about the cardiovascular toxicity of targeted cancer therapies. One session during the 2022 meeting of the PSC recently addressed why cardio-oncology clinics are necessary. The fifth edition of the update in cardio-oncology course was organized by the Faculty of Medicine at the University of Lisbon this year. There have also been sessions at national oncology meetings on cardiotoxicity, and oncologists are now increasingly aware of cardiovascular side effects of therapy.

On the research front, Prof Fiuza and colleagues have described their experiences with the establishment of a clinic and have also conducted cost-benefit analyses of alternative strategies in managing left ventricular (LV) dysfunction. Our group has published on the echocardiographic and cardiac magnetic resonance evaluation of these patients.⁵⁻⁷

Investigators from Portugal are participating in the European Society of Cardiology/Cardiac-Oncology

Toxicity registry of imaging in patients with breast cancer presenting for evaluation of LV function. One Portuguese hospital is involved in the EARLY-HEART trial, which is studying cardiotoxicity after radiotherapy for breast cancer. A locally sponsored study will examine the impact of a cardiovascular rehabilitation program on cancer survivors with high cardiovascular risk.

A CALL TO ACTION FOR CARDIO-ONCOLOGY IN PORTUGAL

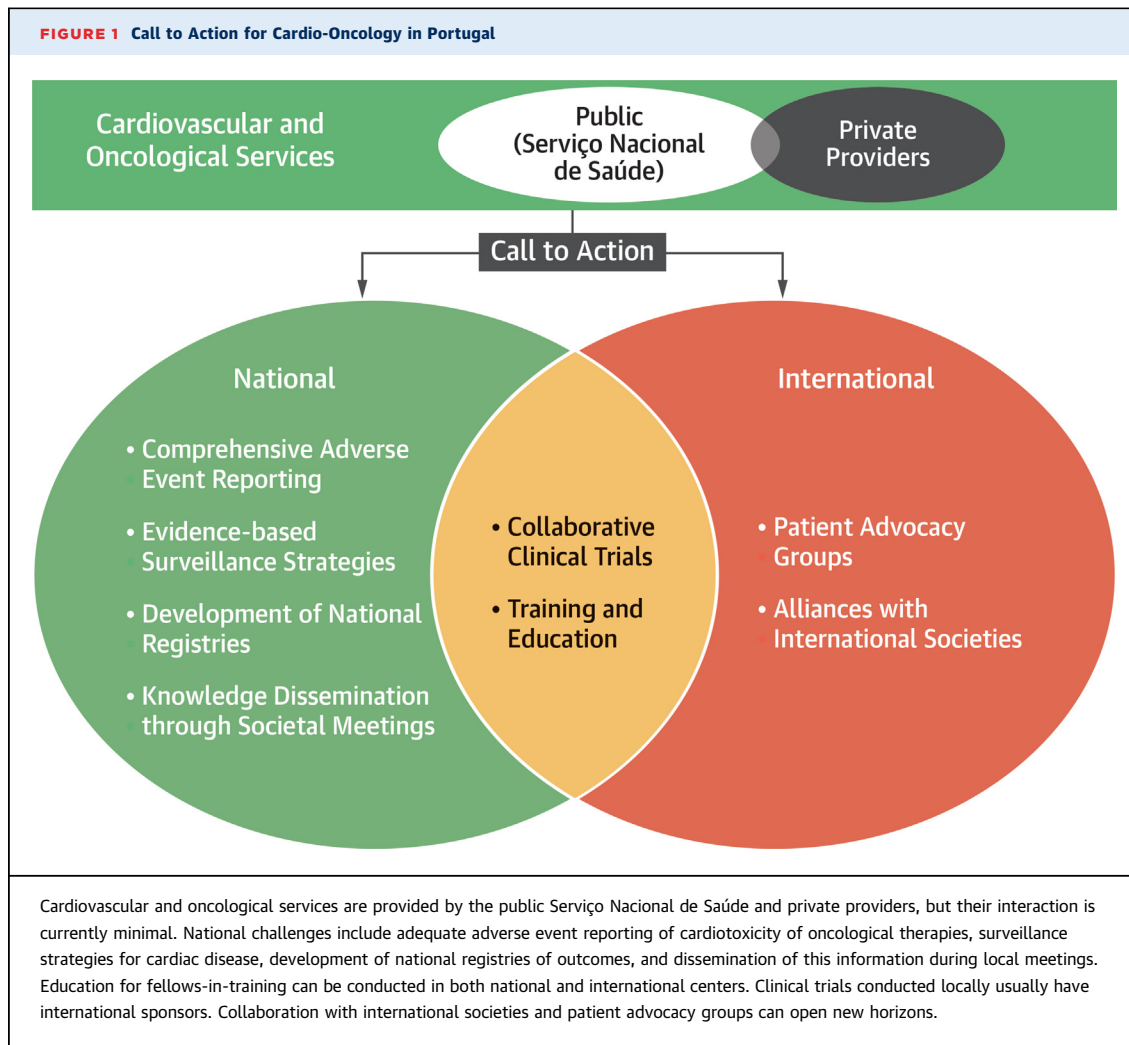
BUILDING CARDIO-ONCOLOGY PROGRAMS. Cardio-oncology programs enable risk stratification, treatment of established cardiovascular disease, early and late monitoring of cardiotoxicity, and adoption of cardioprotective strategies to complete treatment without the need to withhold appropriate therapy because of cardiac impairment.

We have prioritized our outpatient consultations for patients with significant clinical cardiac disease or established LV dysfunction, those undergoing therapy with specific cardiotoxic agents, those who become symptomatic during therapy, asymptomatic patients who develop indexes of LV dysfunction such as elevated biomarkers or abnormalities on imaging, and those with high-risk features on long-term follow-up (prior mediastinal radiation therapy, elevated anthracycline dose, and history of pediatric neoplastic disease). Databases with the reason for referral, exposure to cardiotoxic agents, cardioprotective strategies advised, and cardiovascular outcomes are maintained. In our experience, referral guidelines for specific clinical scenarios for oncologists need to be developed, because referral at a later stage is undesirable, portends poorer outcomes, and implies greater cost for the health system.

As surveillance for cardiotoxicity by imaging is resource intensive, it can be difficult to coordinate the imaging study before, during, and after treatment. Biomarkers, as a first step before imaging, are an option. Although cardiac magnetic resonance has an important role in cardio-oncology, demand outstrips supply.

A very heavy clinical load precludes opportunities for research. Since the pandemic, the SNS has been depleted of human capital, but research must be rejuvenated.

BETTER INTERACTIONS BETWEEN PROVIDER NETWORKS. Value in health care is achieved when the whole trajectory of care is secured seamlessly. Patients may receive surgery, chemotherapy, and radiotherapy through private providers using their voluntary private health insurance schemes, because



of waiting times in the public SNS. Subsequently, patients may have opted out of the purchase of insurance because of prohibitive increase in premiums and will have to be followed up in the public SNS. Transitioning from a private provider to the public SNS can present logistic hurdles. Patients are unaware of some aspects of coverage by health insurance and that their clinical trajectories may include both systems. Lack of capacity is a problem in the publicly funded system, and private providers have provided a yeoman service to these patients.

NATIONAL REGISTRIES THAT FOCUS ON OUTCOMES.

The overarching goal of cardio-oncology is the improvement of cardiovascular outcomes for patients who were treated for cancer. Currently, national registries exist for acute coronary syndromes, heart failure, electrophysiology, and percutaneous coronary intervention, all organized within the auspices

of the PSC, but none for cardio-oncology at the time of writing. Ideally, all centers in Portugal should participate in the Global Cardio-Oncology Registry, in addition to the national registry, which will certainly materialize shortly. Participation in clinical trials can improve outcomes because certain quality benchmarks are required for a center to be included. Data from registries can guide clinical trial sponsors to choose the most appropriate sites for the enrollment of patients. Improved reporting of cardiotoxicity related to recently approved therapies should be a key goal. Currently, there is no information in the public domain of cases of cardiotoxicity reported to the regulatory agency, Infarmed.

TRAINING. Cardio-oncology is not yet fully incorporated into the curriculum of fellowship in cardiology. As suggested by the American College of Cardiology Cardio-Oncology Section, level I training with a

4-week rotation of all cardiology fellows is possible at some centers in Portugal. Level II competency including a 3- to 6-month rotation in a well-established program within the EU through the directive for the free movement of professionals (2005/36/EC) should be encouraged. Oncology fellows should rotate through cardiology programs for 1 month, at least, to understand the interface between the 2 disciplines, cardiotoxicity, and when a referral should be made. Addition of a cardio-oncology module in the medical school curriculum ensures early awareness among students.

AWARENESS IN THE COMMUNITY. Although numerous campaigns exist in Portugal for improving cardiovascular health, we suggest one specific intervention that is most germane to our environment. Lisbon has consistently been in the top 2 cities in Europe, with almost 2,800 hours of sun per year. Combined with mild ambient temperatures, this provides an unparalleled opportunity for cancer survivors for outdoor physical activity. International Cancer Day can be used to promote awareness that increased physical activity can improve cardiovascular health in cancer patients.

Patient advocacy groups need to be engaged and empowered, as they may be crucial in advocating for the causes of cancer survivors with stakeholders, such as legislators. Tackling recalcitrant issues, such as adequate reimbursement from health insurance

companies and approval of newer treatments that may be deemed to be prohibitively expensive, is possible with the commitment of these groups. Our models of patient advocacy are not as developed as those that exist in the United States. International collaborations with these groups can be useful. Survivorship groups that promote models of mutual support should be encouraged by cardio-oncology programs to improve general well-being and health of these patients.

As highlighted in **Figure 1**, addressing the distinct elements in the panorama of cardio-oncology in Portugal is needed to improve outcomes. Our call to action makes specific context-appropriate recommendations. A rising tide raises all boats eventually.

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