Letter to the Editor

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European Guidelines Concerning the Transplantation of Organs from Donors with a History of Breast Cancer

Carole Mathelin[1], Beatriz Domínguez-Gil[2], Vahit Özmen[3], Massimo Lodi[4]

[1]Department of Surgery, ICANS (Institut de Cancérologie Strasbourg Europe), Strasbourg, France
[2]National Transplant Organization (ONT), Calle Sinesio Delgado, Madrid, Spain
[3]Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Istanbul, Turkey
[4]Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg Cedex, France

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Dear Editor,

The Council of Europe (CoE), based in Strasbourg (France), is an international organization that promotes cooperation among European countries in the areas of human rights, democracy, rule of law, culture and public health. Founded in 1949 by the Treaty of London, the CoE is composed of 46 member states. The CoE is a separate body from the European Union (EU), with 27 state countries, that have conferred some national legislative and executive powers to the EU, with the aim of achieving a high level of integration. In contrast, member states of the CoE maintain their sovereignty, but cooperate on the basis of common values and political decisions, and commit themselves through conventions. The CoE and the EU have a close collaboration in the field of transplantation of human organs*, tissues** and cells***, jointly promoting fundamental ethical principles, as the non-commercialization of substances of human origin, and common quality and safety standards. Within the CoE, work in the transplantation field is coordinated by the European Directorate for the Quality of Medicines and HealthCare (EDQM), which recently published the 8th edition of the Guide to the quality and safety of organs for transplantation (1), providing professionals and authorities with guidance to ensure a high level of protection for organ donors and transplant recipients.

In Europe, organ transplantation activities have steadily increased during the last few decades, except during certain periods of the Coronavirus disease-2019 pandemic (2). This increase, however, has been insufficient to cope with the transplantation needs of the European population. In 2021, 36,548 solid organ transplants were performed in CoE member States, an activity that lagged behind the volume of the transplant waiting list, estimated to include more than 138,0000 patients per annum. Approximately 20 patients have died each day on the waiting list because no organ became available (3).

There are different reasons for organ shortage, as failure to identify and refer possible organ donors, opposition to postumous donation, or medical unsuitability. One reason why possible organ donors are deemed ineligible is a past or present history of cancer, due to the risk of transmitting cancerous cells, the development of which may be facilitated by the immunosuppressive treatments required by transplant recipients. Given the increase in the number of indications for transplants and the shortage of organs, along with a decline in the incidence of brain death and the increasing evidence about the safety limits in the utilization of organs from donors diagnosed with a variety of diseases, the current trend is to expand criteria for donor eligibility, particularly regarding donors with a history of cancer. In the 8th edition of the EDQM Guide on the quality and safety of human organs for transplantation (1), the chapter concerning the risk of transmission of cancer has been entirely reviewed to provide current evidence for assessing the risk of transplanting organs from donors with a past or present history of cancer, and from donors with a genetic predisposition to develop cancer. Though not legally binding, this document supports professional decision-making according to the best available evidence.

A history of breast cancer (BC) has a prominent place in the debate concerning the transplantation of human organs. BC is the commonest cancer type among women in Europe, and its incidence continues to rise (with 531,086 new cases, 141,765 deaths and 2,138,117 five-years prevalence in 2020). The cumulative risk of BC (0–74 years) for a European woman is 6.28% in Central and Eastern Europe, 8.45% in Southern Europe, 9.35% in Northern Europe and 9.69% in Western Europe. Western Europe is placed third in the world in terms of prevalence of

Corresponding Author:
Carole Mathelin; c.mathelin@icans.eu

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BC, following Australasia (10.41%) and Northern America (9.71%) (4). In case of a donor with a history of BC, the risk of transmitting potentially fatal cancer cells to recipients of their organs is a major concern, notably depending on the type of BC. There is a wide variety of BC with the World Health Organization (5) describing 34 different histological BC subtypes. Some subtypes are associated with almost no risk of metastases, such as low-grade ductal carcinoma *in situ* (DCIS), while others are highly proliferative with a particularly unfavorable prognosis in the short term, such as triple negative BC, and others have a risk of late re-evolution, sometimes decades after the diagnosis, for example invasive lobular carcinoma. Therefore, before deciding on the clinical use of organs obtained from a woman with a past or current history of BC, it is essential to know the BC prognosis based on its histological subtype, molecular characteristics, including expression of hormone receptors, human epidermal growth factor-receptor 2 and proliferation index, together with stage, completeness of treatment, time since the diagnosis and regularity and normality of follow-up.

Tumor cell dormancy is a well-recognized phenomenon in BC. Tumor cells can spread to distant sites early during cancer progression. They can stay dormant and clinically undetectable after resection of the primary tumor for many years. Metastases in BC usually manifest asynchronously with the primary tumor and show variable time to become clinically detectable. For example, a large study (6) of 62,923 patients under 75 years of age treated for hormono-dependant invasive cancer [T0-2 N0-3 of the American Joint Committee on Cancer (AJCC) classification] showed the following risk of metastases at 20 years: T1N0: 13% (low grade 10%, intermediate grade 13%, high grade 17%), T1N1: 20%, T1N2: 34%, T2N0: 19%, T2N1: 26% and T2N3: 41%). Interestingly, the authors showed not only the importance of tumor size and lymph node involvement (stage), but also of tumor grade.

The EDQM has now reconsidered the criteria for acceptance of organs from donors with a history of BC, acknowledging the key role of medical teams in performing a risk-benefit assessment for each particular case. Since BC has high potential for late and aggressive recurrence and metastases, even after many years of complete remission, patients with BC should only be accepted as organ donors with the highest caution and for very selected recipients.

What Criteria Must be Checked Before Accepting an Organ Donation in Case of BC History?

First, an extended cancer-free period (generally more than 5 years) before accepting a donor with BC is recommended. Secondly, donor examination for BC recurrence and/or metastases, including careful clinical examination and imaging, is necessary even after a long disease-free survival. In patients with a history of BC, a whole-body computed tomography scan of thorax, abdomen, and pelvis, including cerebral scan in particular cases, should be carried out, if possible, to evaluate the current disease status and to ensure the highest possible safety for organ recipients. Any suspicious finding on imaging should be further evaluated for significance. If there are explicit features of active malignancy, organ donation should be discontinued. If there is doubt about a radiological diagnosis of malignancy, histopathological examination should be performed during organ recovery. In contrast, the routine screening of tumor markers (e.g., CA 15–3) is generally not recommended before donation, except for donors in whom tumor markers were previously used to monitor disease remission and with previous values available, to help assess the state of disease.

What are the Consensual Indications of Organ Procurement in Case of BC History?

Low and intermediate nuclear grade DCIS are considered as low risk for transmission. High nuclear grade DCIS (which can be associated with an occult invasive BC) and invasive BC stage 1A (T1N0, AJCC, 8th edition) with curative surgery and cancer-free period >5 years seems to be associated with low to intermediate risk of cancer transmission. All other invasive BC stages are considered as high-risk for transmission, independent of the presumed recurrence-free survival and treatment. Newly diagnosed invasive BC and past or present history of breast sarcoma are deemed to be of unacceptable risk for organ donation.

Different guidelines have been released in other regions outside the CoE. In the United States, the American Society of Transplant Surgeons estimates that, for lesions classified as pT1a or pT1b, organ donation would be possible after 10 years of remission, whereas it would no longer be indicated beyond pT1c, regardless of the time of remission (7). Conversely, the organ procurement and transplantation network/united network for organ sharing considers that the risk of transmission for invasive BC is high (>10%) due to the occurrence of late secondary lesions indicating that organs should not be used but only in exceptional situations (8). In the United Kingdom, the advisory committee on the safety of blood, tissues and organs (SaBTO) considers that donors diagnosed with a pT1a BC with a remission period of more than 10 years are associated with a low risk of disease transmission (0.1–2%) and pT1a BC with a remission period of 5–10 years with an intermediate risk (2–10%) (9). In France, the Agence de la Biomédecine (a state agency dealing with public health related issues regarding organ, tissue and cell transplantation) has established a list of breast specialists to perform a risk-benefit assessment for particular cases of donors diagnosed with a present or past history of BC.

In summary, in many countries, organs from donors with low risk of BC transmission are accepted for clinical use, while keeping in mind the theoretical risk of transmission due to possible late cell dormancy. Traceability (data to identify every organ from donor to recipient and *vice versa* must be kept for a minimum of 30 years) and biovigilance (reporting and management of serious adverse events and reactions) are legal requirements in the EU setting and in standards promoted by the CoE (10). For instance in France, to optimize transplantation security, the Agence de la Biomédecine has established a traceability system called "CRISTAL donor/recipient". Thus, if the recipient of a solid organ develops a cancer and there is suspicion of a donor-origin, the various medical teams in charge of patients who have received organs (and tissues) from the same donor must be alerted to activate a coordinated assessment, investigation and management of the case and take preventive and therapeutic measures on recipients affected and recipients at risk.

The number of organs accepted from donors with a previous or current history of cancer seems to be increasing, but the frequency of documented cancer transmission is low and estimated at 3–6 cases per 10,000 solid organ transplants (11). Under-reporting of transmission cases due to the previous lack of mandatory reporting cannot be ruled out. Within the EU legal framework, and with mandatory reporting to national health authorities (including suspected/confirmed cases of malignancy transmission), it should be possible in the future to more precisely assess the frequency of malignancy transmission through organ transplantation. Ideally, to better understand this risk, detailed donor cancer data should be included in national registries and efforts be made to define a basic data set to link international data.

Donors with a Genetic Predisposition to Cancer

Several genetic conditions (e.g., *BRCA1, BRCA2, PALB2, CDH1, PTEN*) predispose to BC. For EDQM, in a donor with a known genetic predisposition, two safety precautions must be considered. First, a careful examination of the organs known to be at risk of developing malignancy must be performed, to ensure no active cancer is present (e.g., breasts and ovaries for *BRCA1/2*, breasts and stomach for *CDH1*). Secondly, transplanting an organ with a genetic risk of malignancy is not advised (e.g., uterus for *PTEN*). When possible, a local expert in cancer genetics should be consulted. In France, the Agence de la Biomédecine has established a list of onco-geneticists to perform a risk-benefit assessment for particular cases of patients having a genetic predisposition of BC.

Specific Characteristics of Living Donors

Unlike the situation with a deceased donor, in the case of a living donor with a personal history of BC, it is possible to propose a complete workup to assess the individual risk of transmission. Indeed, there is more time to decide the eligibility compared to deceased donors, and there are no or minimal restrictions to perform a complete follow-up workup, including clinical examination of the breasts and complementary tests such as mammography, ultrasound or breast magnetic resonance imaging, CA 15–3 assay or positron emission tomography-computed tomography. However, the normality of a complete workup should not authorize organ donation in case of high-risk of transmission, and recommendations should also be applied in this context. Nonetheless, potential solutions in the case of living donors for reducing the risk of cancer transmission during transplantation are currently under investigation, such as circulating markers assays (tumor cells and tumor DNA), but to date they are not validated in clinical practice (12).

Treatment of Donor-transmitted Cancers and Future Perspectives

When diagnosed, donor-transmitted cancers are difficult to treat. Indeed, treatment may consist in cessation of immunosuppression, and/or explantation of the graft, and/or classical oncological treatments. This treatment is challenging and may cause several complications, including the need for re-transplantation in case of vital organs. Nonetheless, new possibilities are currently under investigation. For instance, mammalian target of rapamycin (mTOR) inhibitors, which have both immunosuppressive and antiproliferative properties, are increasingly being used after organ transplantation in clinical trials (13). Interestingly, they have potential advantages as anti-cancer agents for virus-induced malignancies but also for other types of cancers. Some authors have hypothesized that mTOR inhibitors could have a benefit for patients receiving an organ from a donor with a history of malignancy; however, at present further research is needed to evaluate the benefit (13). Moreover, some cases treated with immune checkpoint inhibitors to enhance immune response have been published, with positive outcomes (14, 15). In the treatment of donor-transmitted cancers, the link between immunity and cancer plays a central role. Within this rapidly growing field of research, scientific advances may provide new therapeutic leads in the future.

Footnotes

* Organs: Heart, lung, liver, kidney, pancreas, and small bowel

** Tissues: Cornea, bones, cartilages, heart valves, and skin

*** Cells: Hematopoietic stem cells

Peer-review: Internally and internally peer-reviewed.

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