



ORIGINAL ARTICLE

A retrospective study of do-not-do practice recommendations in metastatic breast cancer in Spain



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KEYWORDS

Metastatic breast cancer;
Low-value practices;
Overuse;
Patient safety

Abstract

Introduction: 34 722 incident cases of breast cancer were diagnosed in Spain in 2022. At the time of initial diagnosis, 5%–6% already presented metastasis. In 2007, The National Institute for Health and Care Excellence published a set of recommendations about low-value practices commonly known as “do-not-do” (DND), which lead to initiatives to decrease the overuse of health resources. The aim of our study was to collect, based on an expert consensus, DND recommendations for metastatic breast cancer and assess frequency of adherence in the real world.

Methods: Mixed analysis based on a literature review that combined a qualitative analysis (a panel of 10 experts reached an agreement on a list of criteria by consensus building) and a quantitative analysis (observational retrospective study assessing codified clinical information from electronic health records [EHRs] about the DND recommendations in 4 Spanish university hospitals).

Results: Consensus was reached on 12 recommendations based on the review of 826 EHR from the participating hospitals. The review revealed a 1.3%–28.1% range for improvement in the adherence to the recommendations. The DND recommendation with the higher non-adherence

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PALABRAS CLAVE

Cáncer de mama metastásico;
Prácticas de escaso valor;
Sobreuso;
Seguridad de pacientes

rate was do not start the locoregional metastatic treatment of the primary tumor, except in those with stable systemic disease.

Conclusions: DND recommendations for metastatic breast cancer provide an opportunity to reduce costs and unnecessary procedures, increasing patient safety and the sustainability of the healthcare system.

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Estudio retrospectivo sobre el no seguimiento de las recomendaciones prácticas para el cáncer de mama metastásico en España

Resumen

Introducción: En 2022 se diagnosticaron 34.722 nuevos casos de cáncer de mama en España. En el momento del diagnóstico inicial un 5%–6% presenta ya metástasis. En 2007, NICE publicó un conjunto de recomendaciones sobre prácticas de bajo valor, denominadas comúnmente «No Hacer» (Do-Not-Do, DND), que propició iniciativas para reducir el sobreuso de recursos sanitarios. El objetivo de este estudio fue agrupar, mediante consenso de expertos, recomendaciones No Hacer en cáncer de mama metastásico, y estimar su frecuencia en la práctica clínica real.

Métodos: Investigación mixta que parte de una revisión de la literatura y combinó una investigación cualitativa (un panel de 10 expertos llegó a un acuerdo de una lista de criterios mediante técnicas de búsqueda de consenso) y una cuantitativa (mediante un estudio observacional retrospectivo que revisó información clínica codificada en las historias clínicas electrónicas (HCE) sobre las recomendaciones No Hacer en 4 hospitales universitarios españoles).

Resultados: Se consensaron 12 recomendaciones que se revisaron en 826 HCE de los hospitales participantes. Esta revisión reveló que hay un rango de entre un 1,3 y un 28,1% de margen de mejora en el cumplimiento de las recomendaciones. La DND incumplida de forma más frecuencia señalaba la importancia de no realizar un tratamiento metastásico loco-regional del tumor primario en pacientes con cáncer metastásico, excepto en aquellos con enfermedad sistémica estable.

Conclusiones: Los No Hacer en cáncer de mama metastásico suponen una oportunidad para reducir costes y procedimientos innecesarios, contribuyendo a la seguridad de los pacientes y la sostenibilidad del sistema.

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Introduction

In Spain, 34 722 incident cases of breast cancer were diagnosed in 2022.¹ In 2022, breast cancer constituted 12% of all cancers diagnosed that year in Spain, which reached 280 100. The estimated global 5-year survival rate is over 44 million, being breast, colorectal, prostate, lung, and thyroid cancers the most prevalent ones. At the time of initial diagnosis, about 5%–6% of the patients already have developed metastasis. Furthermore, approximately 30% of women diagnosed with early-stage breast cancer will develop metastatic relapse throughout the course of their disease.² According to the literature, the overall costs for metastatic breast cancer in Spain will reach 200 000 euros per patient.³

Low-value practices can be difficult to identify. Overdiagnosis and overtreatment signal the need for improvement in healthcare.^{4,5} Low-value practices mean that the risks outweigh the benefits for a given intervention⁶ and they represent a threat to patient safety and the sustainability of the healthcare system.⁷

Almost 2 decades ago, in 2007, The National Institute for Health and Care Excellence (NICE) in the United Kingdom published a set of recommendations commonly known as “do-not-do” (DND),⁸ leading the way for studies on the overuse of healthcare resources.⁹ The NICE initiative was followed by others, such as Choosing Wisely, present in more than 30 countries¹⁰; the Less is More Medicine movement, which establishes that good clinical practices should be systematically repeated¹¹; and the *Right Care Alliance*, pursuing a safer, more effective, and patient-centered universal healthcare system.¹²

In Spain, the Ministry of Health made the “Compromiso por la Calidad de las Sociedades Científicas de España” public in 2013, preceded by the proposal of the Spanish Society of Internal Medicine (SEMI) of working towards the same goal. The initiative is coordinated by the *Subdirección General de Calidad y Cohesión del Ministerio* and the *Instituto Aragonés de Ciencias de la Salud* with the support of *GuíaSalud*. This initiative is part of the program of activities of the Red Española de Agencias de Evaluación de

Tecnologías y Servicios del Sistema Nacional de Salud.¹³ The repository of these DND recommendations can be found in the Minsitry of Health webpage.¹⁴ It currently includes more than 190 recommendations divided into 7 associations and 42 scientific societies, aimed at professionals in the fields of medicine, nursing, physical therapy, and nutrition, as well as patients, institutions, and healthcare authorities.¹⁴

DND recommendations for metastatic breast cancer cannot be easily identified in the literature. A recent study in Canada, from the Choosing Wisely initiative, did not recommend the screening of new primary tumors in patients already diagnosed with metastatic breast cancer. The study assessed the care received by 305 women with metastatic breast cancer. In this sample, 37.4% ($n=114$) underwent at least one screening test for the diagnosis of another primary tumor despite having already received a diagnosis of metastatic breast cancer (mammograms, Pap smears, fecal occult blood test, or even colonoscopies). Of the screening requests, 70% came from primary care doctors, 14% from oncology departments, and 12% from other departments.¹⁵ Given the high prevalence of breast cancer and metastasis in patients with a breast cancer diagnosis, it is advisable to compile low-value practices for breast cancer following the efforts to increase healthcare quality by reducing the overuse of resources.

The aim of our study was to identify, by expert consensus, relevant DND recommendations related to the care of patients with metastatic breast cancer.

Methods

Study design

This study was a mixed research. First, a literature review was carried out as a basis for a second phase, that consisted in a debate among experts that led to an agreement on DND recommendations for metastatic breast cancer. Thirdly, an observational retrospective study reviewed the clinical information codified in the electronic health records (EHRs) to assess adherence to DND recommendations in relation to their potential to increase healthcare quality and patient safety.

The panel of multidisciplinary experts proposed and prioritized DND recommendations. Finally, the recommendations that enjoyed a higher level of consensus were contextualized to assess their frequency in clinical practice and their adequacy with a retrospective review of EHR. This review was performed between April 2022 and September 2022 following the general criteria on the *Ley de Investigación Biomédica (14/2007, BOE n° 159)*. The study was reviewed and approved by the Ethics Committees of the Virgen de las Nieves Hospital and the General University Hospital of Valencia, codes: 1445-N-22 and 96/2022, protocol code: Versión 2, NH-27-07-22, respectively.

Literature review

The repository of Spanish DND recommendations,¹⁴ as well as the NICE⁸ recommendations were assessed. Additionally, a search of scientific literature was conducted using the PUBMED search tool at the MEDLINE Dabase in February 2022.

The keywords used were: “neoplasm metastasis” [MeSH Terms], “breast neoplasms” [MeSH Terms], and “choosing wisely”.

Quantitative analysis: DND consensus

This literature review fed into the work of the experts panel who, by consensus building in several rounds, proposed, and agreed on DND recommendations.

Firstly, each participant individually analyzed the information and proposed DND recommendations considering their impact on clinical practice, the prospect of improving patient care, and the possibility of identifying these low-value practices based on the clinical information available at the time of analysis. Secondly, the members of the panel actively engaged in an open debate about these recommendations with the aim of making them more specific, and provided relevant literature to support each of the recommendations shared, first on a face-to-face meeting, and then during 2 online meetings. In later rounds, different details and new recommendations arose that, following a methodology similar to the already described, were added to the panel of DND recommendations. Finally, all the recommendations were ranked by the experts using a 0–10 scale, where 0 meant “no relevance” and 10 meant “highly relevant”.

Participants

The multidisciplinary panel was composed of a total of 10 clinicians (3 medical oncologists, 1 nurse, 1 radio-oncologist, 1 radiologist, 1 OBG-GYN, 1 member of the board of directors, 1 hospital pharmacy head of department, and 1 head of clinical analysis) from 10 Spanish hospitals. The member selection for the panel (inclusion criteria) was based on a minimum of 5 years of experience in clinical practice, activity on scientific societies, and research experience assessed by publications, conferences, or research projects.

Quantitative research: Second phase. Field research

We assessed non-adherence frequency to DND recommendations that had been prioritized as the most relevant following the previously described criteria, see [Table 1](#). For the review of the EHR, DND recommendations were grouped into 3 categories ([Table 1](#), [Complementary Material](#)). For the codification of data from the review of EHR, DND recommendations were grouped by disease characteristic and patient profile (*i.e.*, screening, treatment). By following this procedure, subrogate review criteria were generated, which allowed the analysis of several DND recommendations within the same EHR simultaneously. Please see [Complementary Material \(Table 1, Complementary Material\)](#).

[Complementary Material Table 1](#). DND recommendations grouping for the field research:

- Chemotherapy treatment: 5 DND recommendations and 4 subrogated.
- Locoregional: 5 DND recommendations and 2 subrogated.
- Patients with advanced/terminal disease: 2 DND and 1 subrogated.

Table 1 Set of do-not-do (DND) recommendations selected and their score by the panel of experts.

DND recommendation	References supporting the recommendation
<i>Diagnosis/staging/follow-up</i>	
DND-MBC-01: Do not start the treatment in patients with metastatic cancer without a complete histopathological diagnosis and molecular biomarkers that would allow a correct evaluation and therapeutic decision. SCORE: 9.8 out of 10	Amir, Miller, et al. ¹⁸ ; Amir, Clemons, et al. ¹⁹ ; Colozza et al. ²⁰ ; Cardoso et al. ²¹ ; Chacón López-Muñiz et al. ²² ; de Dueñas et al. ²³ ; Dieci et al., 2013. ²⁴ ; Hammond et al. ²⁵ ; Foukakis et al. ²⁶ ; Gennari et al. ²⁷ ; Grupo Español de Investigación en Cáncer de Mama ²⁸ ; Torres et al. ²⁹
DND-MBC-03: Do not rely solely on tumoral blood markers for changes in care without clinical evidence of progression and/or on imaging tests. SCORE: 9.7 out of 10	Duffy ³⁰ ; García-Alegria et al. ³¹ ; L. Harris et al. ³² ; National Comprehensive Cancer Network ³³ ; Van Rossum et al. ³⁴
<i>Treatment</i>	
DND-MBC- 02: Do not administer high-dose or dose-dense chemotherapy to patients with metastatic breast cancer as no improvement in their survival has been observed and it significantly increases toxicity. SCORE: 8.3 out of 10	Chacón López-Muñiz et al. ²² ; Grupo Español de Investigación en Cáncer de Mama ²⁸
DND-MBC-04: Do not use combined cytotoxic chemotherapy (various agents) in patients with metastatic cancer unless the patient requires a rapid response to alleviate symptoms related to the tumor or to prevent an imminent organ failure. SCORE: 10 out of 10	Chacón López-Muñiz et al. ²² ; Dear et al. ³⁵ ; Gennari et al. ²⁷
DND-MBC-05: Do not place peripheral lines in patients with metastatic cancer and a central line. SCORE: 6.8 out of 10	Ortiz del Río et al. ³⁶
DND-MBC-06: Do not systematically perform a mastectomy in patients with metastasis, instead, adapt the intervention to their locoregional staging, opting for conservation surgery if possible. SCORE 7.4 out of 10	Galper et al. ³⁷ ; Halverson et al. ³⁸ ; Konkin et al. ³⁹ ; Petrelli & Barni ⁴⁰ ; Poodt et al. ⁴¹ ; Pfannschmidt et al. ⁴² ; Skinner et al. ⁴³
DND-MBC-07: Do not start the locoregional treatment of the primary tumor in patients with metastatic cancer, except in those with stable systemic disease who require local management of disease progression and in those with stable disease and long-time survival characteristics (young age, hormone-sensitive tumors, and limited bone disease). SCORE 9.9 out of 10	Badwe et al. ⁴⁴ ; E. Harris et al. ⁴⁵ ; Khan et al. ⁴⁶ ; Khan et al. ⁴⁷ ; Perez-Fidalgo et al. ⁴⁸ ; Rao et al. ⁴⁹ ; Ruiterkamp et al. ⁵⁰ ; Soran et al. ⁵¹ ; Gutiérrez ⁵²
DND-MBC-08: Do not start antiresorptive bone treatment in patients with metastatic breast cancer without bone metastases as a prevention strategy. SCORE 9 out of 10	Grupo Español de Investigación en Cáncer de Mama ²⁸ ; Wong et al. ⁵³
DND-MBC-09: Do not routinely consider long fractionation schemes for the palliative care of bone metastases in patients with metastatic cancer, instead consider schemes equals or shorter than 5 sessions. SCORE 7.4 out of 10	Fujino et al. ⁵⁴ ; Lutz et al. ⁵⁵ ; Maranzano et al. ⁵⁶ ; Shin et al. ⁵⁷
DND-MBC- 10: Do not use whole brain radiotherapy routinely with brain metastases in patients with metastatic breast cancer. SCORE 8.4 out of 10	Brown et al. ⁵⁸ ; Brown et al. ⁵⁹ ; Gil-Gil et al. ⁶⁰ ; Kaal et al. ⁶¹ ; Subbiah et al. ⁶² ; Tsao et al. ⁶³
DND-MBC-11: Do not prolong therapeutic effort in patients with metastatic breast cancer without an observed or expected clinical benefit, previously discussing it with the patient. SCORE 7.9 out of 10	Cardoso et al. ⁶⁴ ; Gennari et al. ⁶⁵
DND-MBC-12: Do not start oncological treatment in patients with metastatic cancer <i>de novo</i> or stage IV oligometastatic disease without consideration by the tumor committee. SCORE 9.8 out of 10	Chacón López-Muñiz et al. ²² ; Gennari et al. ²⁷ ; Malmgren et al. ⁶⁶

Since references included in this table, exceed Journals' limit, all references are presented as supplementary material 2.

After creating a form for data collection for each center, the retrospective observational study began. A systematic review was performed of the EHR of the patients who received care between April 2022 and April 2020 in 4 public university hospitals with the aim of assessing and quantifying the frequency of adherence to each of the DND recommendations. In those cases where not enough cases were found, the search was extended to previous years until the desired sample was obtained. EHR were selected by a simple

randomization, and each professional from the same department individually reviewed the EHR following the national legal framework for access to clinical information. In the present field research, the content of EHR up to 2-years old was reviewed.

Non-adherence to DND recommendations was assessed with the objective of quantifying further improvements in clinical practice in the centers participating in the study. Lot quality assurance sampling (LQAS, also known as acceptance

sampling) was considered the most adequate method as it allows the acceptance or the rejection of a lot only after a partial review. For the field research, it was stated that each center had to review 22 EHR that met the criterion specified in the denominator, and the lot would be rejected after 2 non-adherences to the numerator (see Table 1, Complementary Material). Only one non-adherence to DND-recommendations was considered for the lot to be valid with a 99% confidence.

If the number of cases meeting the criteria for a given denominator for a recommendation did not reach a threshold of 22 assigned to the size of the lot, the review of the EHR was included as well in the results shown, acknowledging that some of the contexts on which the DND recommendation was based on might not be common in everyday clinical practice. The results from the 4 participating centers were aggregated and are shown in Table 2, and each DND recommendation was assessed. Based on the DND recommendation, a numerator was determined. This numerator is the fraction that would indicate that an EHR does not adhere to the recommendation, and the denominator represents the total number of EHR that meet the criteria for a given recommendation.

Results

Literature review and first face-to-face meeting. Qualitative research

The literature review covered 2 DND recommendations repositories and a search of scientific literature using the PUBMED search tool from the MEDLINE database in February 2022. A total of 9 potentially relevant articles were found between 2020 and 2022. The review of this material produced a list of 23 DND recommendations that were grouped into diagnostic-related ($n=5$) or treatment-related ($n=18$). The list was shared with the panel of experts in a face-to-face meeting celebrated in March 2022 in Madrid.

Qualitative research: Second phase—first online meeting of the panel of experts

In this phase, experts provided 8 new DND recommendations. For each of the DND recommendations identified, bibliographic references supporting each recommendation were also provided. Table 1 shows the bibliographic references for DND recommendations.

Qualitative research: Second phase—second online meeting of the panel of experts

After the face-to-face meeting and the online meeting, the panel of experts produced a list of 31 evidence-based DND recommendations by consensus.

The list with the 31 recommendations was sent to the panel of experts and they were requested to assess the relevance of the recommendations for the quality of care and the safety of patients using a 0–10 scale for each of the recommendations.

Qualitative research: Second phase—Panel of experts consensus on DND recommendations

Using the individual score of each expert for of the 31 recommendations, a selection was made of those recommendations with an average score higher than 6.5 as long as none of the experts had scored that given recommendation with 0–2, which promoted homogeneity in the final criteria.

Field research

As established in Table 1 of the Complementary Material, we assessed non-adherence frequency to DND recommendations that had been prioritized as the most relevant following the previously described criteria in the previous section, see Table 1.

Table 2 Set of do-not-do (DND) recommendations assessed by each center and rate of appearance in EHR.

	Numerator	Denominator	Non-adherence to DND recommendation (%)	DND recommendation acceptance of the reviewed lot
DND-MBC-01	3	83	3.6	Accepted
DND-MBC-02	0	70	0.0	Accepted
DND-MBC-03	1	80	1.3	Accepted
DND-MBC-04	6	61	9.8	Rejected
DND-MBC-05	6	56	10.7	Rejected
DND-MBC-06	10	49	20.4	Rejected
DND-MBC-07	16	57	28.1	Rejected
DND-MBC-08	10	58	17.2	Rejected
DND-MBC-09	2	48	4.2	Accepted
DND-MBC-10	6	42	14.3	Rejected
DND-MBC-11	8	42	19.0	Rejected
DND-MBC-12	10	76	13.2	Rejected

[Numerator and Denominator]: These clauses can be consulted for each DND recommendation in Supplementary Material 1. [Accepted]: As the data represent an aggregate of all the EHR from the 4 participating centers, a lot is accepted when the numerator is equal or lower than 4. [Rejected]: A DND lot is rejected with a numerator of 5 or higher.

A total of 826 EHR from the 4 participant hospitals were reviewed (Table 2) meeting the sample size required. The review of the EHR showed opportunities for improvement in the adherence to the DND recommendations in a 1.3%–28.1% range for the centers participating in the study, see Table 2. The most frequent DND recommendation, DND-MBC-07, showed the importance of avoiding the locoregional treatment of a primary tumor in patients with metastatic cancer, except in those with stable systemic disease who require local management of disease progression and in those with stable disease and long-time survival characteristics (young age, hormone-sensitive tumors, and limited bone disease).

Discussion

Our study offers a series of recommendations following the “less is more” movement that aims to reduce the unjustified use of diagnostic or therapeutic resources as an alternative to optimize patient care quality and achieve higher efficiency. To the best of our knowledge, this is the first study so far that has gathered DND recommendations for metastatic breast cancer.

The study involved a panel of experts with diverse profiles and ample experience that, together, were representative of the team usually involved in patient care for metastatic breast cancer. Four centers in Spain participated in the field research which allowed—using acceptance sampling—the retrospective assessment of EHR of patients with breast cancer after 2 years. In this case, it was found that the non-adherence rate do not start the locoregional metastatic treatment of the primary tumor, except in those with stable systemic disease is the recommendation with the highest non-adherence rates. Other recommendations with high non-adherence rates are further discussed in the following paragraphs.

The rates for DND-MBC-04 could stem from the initial consideration of combined chemotherapy as the combination of various systemic treatments.^{22,27,35} For example: in patients with HER2-positive disease, combination therapy is used consisting of paclitaxel plus 2 monoclonal antibodies that target HER2, trastuzumab and pertuzumab, which are not strictly chemotherapy agents, therefore they were not considered as chemotherapy. In this case, the rate may be slightly different.

The high rates observed in DND-MBC-05 are relevant. There is an increased number of patients in whom, despite percutaneous catheter placement,³⁶ peripheral lines are also being placed for drawing blood or imaging tests with contrast, which is an unnecessary expense that may lead to complications (*i.e.*, ecchymosis, thrombophlebitis) and it is not justified by the safety data available either.¹⁶

Results for “DND-MBC-06: Do not systematically perform a mastectomy in patients with metastasis, instead, adapt the intervention to their locoregional staging, opting for conservation surgery if possible.” can be controversial because there may be a difference between the residual disease objectively determined by the pathologist in the surgical specimen in order to assess whether the surgery was appropriate for the post-treatment staging and the *a priori*

clinical suspicion based on imaging tests.^{37–43} Hence, the retrospective review of EHR may produce a bias about how information is stored and reviewed by other professionals.

The recommendation that would lead to a greater clinical practice improvement is DND-MBC-07, as it is the recommendation with the highest rate of non-adherence. This recommendation concludes that it is important to avoid the locoregional treatment of the primary tumor in patients with metastatic cancer, except in those with stable systemic disease who require local management of disease progression and in those with stable disease and long-time survival characteristics (young age, hormone-sensitive tumors, and limited bone disease).^{44–52} In this case, data supporting both strategies can be found in the literature, as some authors describe the possibility of increased survival in some patients. However, this care strategy is controversial and only applicable to certain patients¹⁷ as it is deleterious in triple-negative patients.

The rates of DND-MBC-08 could be justified by the administration of antiresorptive treatments in women with metastatic breast cancer as a prevention strategy without confirmed metastasis.^{28,53} As observed in the EHR of the patients participating in the study, many patients do not receive antiresorptive treatment despite presenting bone metastases. This may be interpreted as patients having a low burden of bone disease, accompanied by a low risk of a bone event (fracture, hypercalcemia, spinal cord compression) or by contraindications for the antiresorptive treatment.

The rates for DND recommendations related to palliative whole brain radiotherapy for the treatment of brain metastases were decided upon and discussed by the radiologists. Based on the individual characteristics of each patient, the radiosurgical or stereotactic management should be prioritized in order to avoid the long-term toxicity associated with whole brain radiotherapy.

Limitations

Data extraction was performed in 4 hospitals that voluntarily joined the study, which may result in a selection bias that should be considered during data interpretation. It is of utmost importance to consider different practice styles, information provision, and EHR structure as part of the variability observed, so in future studies, it would be advisable to increase the number of participating centers even when maintaining the sample size of EHR reviewed. In some of the results, a selection bias could be present since all the patients recruited have been part of the committees.

Conclusions

The main goal of DND recommendations is to reduce the number of unnecessary healthcare procedures to avoid iatrogenesis, decrease variability in clinical practice, and increase awareness among healthcare professionals about the adequate use of resources and their commitment to quality and efficiency of care.

A consensus was reached for a total of 12 DND recommendations for metastatic breast cancer, grouped by diagnosis, staging, follow-up, and treatment. In the pilot

study conducted, a high rate of non-adherence to some of the recommendations was found. These results warrant the need to share the study in order to reduce unnecessary costs and increase patient safety. More studies are needed to confirm the validity of the DND recommendations for metastatic breast cancer and extrapolate the results to real-life clinical practice at a national-level.

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Ethical considerations

The study was reviewed and approved by the Ethics Committees of the Virgen de las Nieves Hospital and the General University Hospital of Valencia, codes: 1445-N-22 and 96/2022, protocol code: Versión 2, NH-27-07-22, respectively.

Patients consent

Following the recommendations of the Ethics Committee Board, and according to the study design, no informed consent was required from participants.

Declaration of competing interest

The authors verify the absence of any conflict of interest.

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Appendix A. DNDs metastatic breast cancer group

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Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.senol.2024.100593>.

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