SHORT COMMUNICATION
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Breast cancer staging in population-based registries: an alert to the quality of information

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ABSTRACT

Objective: To discuss the practical difficulties associated with breast cancer staging, especially in the context of population-based cancer registries (PBCR). **Methods:** This is a short communication that discusses the importance and temporal evolution of breast cancer staging, as well as the limitations and new challenges associated with this process. **Results:** This study discusses the importance and temporal evolution of breast cancer staging, as well as the limitations and new challenges associated with this process. Minimal divergences in physical examination and disagreements in imaging tests can classify the patient in a higher or lower stage of the disease. In some population-based registries, up to 20% of the information regarding the clinical stage of breast cancer may be mistaken. **Conclusion:** We highlight the necessity for continuing education and constant training for all professionals involved in the breast cancer epidemiological context. The utilization of new technologies can help standardize the information and reduce the divergences related to cancer staging registry.

KEYWORDS: breast neoplasms; neoplasm staging; registries; evidence-based practice.

INTRODUCTION

Clinical staging plays an important role in the therapeutic planning and prognostic evaluation of patients with breast cancer[1]. This staging usually follows the TNM (primary tumor [T], regional lymph nodes [N], distant metastases [M]) system of the American Joint Committee on Cancer (AJCC), whose classification criteria are periodically updated based on scientific evidence[2,3]. However, only 23% of population-based cancer registries (PBCR) that participate in the Cancer Incidence in Five Continents, Volume IX (CI5-IX) have declared to collect TNM staging for all tumor sites[4-7].

The staging process is especially important in the critical assessment of survival curves and other epidemiological variables obtained from PBCR[2,7]. Lack of standardization hinders the epidemiological analysis of different populations and can interfere in the interpretation and development of public policies related to malignant neoplasms[6,8]. As an example, we can underline a recent divergence observed in breast cancer survival rates in the city of Goiânia, Brazil. In the CONCORD-2 study, the net survival rate for patients diagnosed with breast cancer was 79.4% between 1995 and 1999, 63.9% between 2000 and 2004, and 59.2% between 2005 and 2009[9]. However, using data from the local cancer registry, the time trends in 5-year overall survival rates were very different: 57.0% survival rate between 1988 and 1990[10], 65.4% between 1990 and 1994[11], and 72.1% between 1995 and 2003[12]. According to the authors of the CONCORD-2 study, the estimates for breast cancer survival in Goiânia were less reliable than would be preferred[13]. This divergence should not be a true epidemiological event but a methodological limitation[14].

In this context, PBCR must follow international good practice recommendations to ensure satisfactory performance quality, operationalization, and data quality[8,15,16]. These parameters range from the percentage of cases collected through histopathological tests[16] to the organization of flow diagrams for each neoplasm[17,18].

Each registry is responsible for the criteria employed to verify the quality of the clinical data collected, which are usually not reported adequately. In most registries, the person responsible for gathering information is a non-medical professional, advised by a multidisciplinary team of specialists. Despite the constant personnel training, some mistakes still occur due to the increasing

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complexity of the tumor staging process. Medical staff can also make mistakes in the staging, particularly when they gather and enter the data. This scenario may justify the high rates of "incomplete data" regarding tumor staging in different international series, usually ranging from 5% to 20%[19-21].

PRACTICAL DIFFICULTIES IN BREAST CANCER STAGING

Cancer staging estimates the extension of the neoplasm within the person's body. Despite the particularities of each tumor site, a report is usually issued after a physical examination. This report could include specific complementary tests, such as biochemical tests, computed tomography, among others[22]. However, in a real-world scenario, several factors can limit or hinder this staging process[6,8].

Concerning breast cancer staging, inter-observer variation must be highlighted in tumor measurement and clinical assessment of patients. In this context, if tumor palpation changes from 5.0 cm to 5.1 cm, cancer staging also changes, along with the prognostic classification. The assessment of lymph node status often shows divergences regarding small palpable axillary lymph nodes, which could represent a reactional inflammatory state (cN0) or one isolated axillary lymph node affected (cN1). Table 1 describes some situations that result from divergences in the staging process, with some considerations and good practice recommendations.

In most developing countries, the population can experience difficulties in accessing health services, which could extend the waiting time for complementary tests[23]. In these situations, the clinical staging of the patient is only concluded after two or three medical consultations and, occasionally, after cancer treatment begins. This fact hinders the staging process, as the patient can present significant variations in physical examinations during the investigation period, generally related to the progression of the disease. Effectively, choosing the best moment to register a variable can become a subjective decision: date of the first consultation? After the completion of complementary tests? Before starting treatment? Or should we always consider the most advanced staging?

Finally, another common situation in regions with hierarchical health systems is referring patients who received treatment from other services to reference centers after a breast cancer diagnosis. In this context, the dialog between the respective assistant professionals regarding the initial physical examination of the patient can prevent the use of the terms cTx and cNx, which would render the patient's initial staging as "unknown".

TEMPORAL VARIATIONS IN BREAST CANCER STAGING

The conceptual changes in breast cancer staging implemented over time have accompanied the evolution of scientific knowledge of the disease. The introduction of new

Table 1. Examples of divergences in the process of breast cancer clinical staging, with the respective recommendations.

TNM	Diagnostic question	Specifications	Recommendations
Evaluation of the "T" status	Tumor measurement	cT1 (≤ 2.0 cm) or cT2 (> 2.0 cm) cT2 (≤ 5.0 cm) or cT3 (> 5.0 cm)	Measurement with a caliper Two or more measurements, taken by the same observer Correlation with breast imaging tests
	Presence and extension of tissue involvement (cT4)	Localized (< 1/3 of breast tissue involvement, cT4b) or diffuse (inflammatory carcinoma, cT4d)	Ambient lighting and adequate breast exposure Percentage estimation of tissue involvement Correlation with tissue evaluation in imaging tests Tissue biopsy (punch), in case of doubt
	Chest wall and pectoral muscle involvement	Chest wall involvement (cT4a or cT4c)	Correlation with chest imaging tests (computed tomography and/or magnetic resonance)
Evaluation of the "N" status	Presence and extension of axillary involvement	cN0 (reactive lymph node, free axillary lines) or cN1	Correlation with imaging tests (ultrasound) Ultrasound-guided biopsy of atypical lymph node (fine-needle or core biopsy)
	Affected lymph nodes in the internal mammary, supraclavicular, or infraclavicular chain	cN2 or cN3, depending on the grade	Correlation with imaging tests (ultrasound, magnetic resonance, positron emission tomography-computed tomography – PET-CT) Ultrasound-guided biopsy of atypical lymph node (fine-needle or core biopsy)
Evaluation of the "M" status	Distant metastasis	cM0 or cM1	Correlation with laboratory and/or imaging tests (computed tomography, magnetic resonance, PET-CT) Cytological or histological evaluation (collection of material guided by imaging methods or surgically)

perspectives related to pathologic diagnoses, such as the identification of micrometastasis and isolated tumor cells in axillary lymph nodes, has also forced new concepts to be considered throughout time[24].

In January 2003, with the publication of the 6th edition of the cancer staging manual elaborated by AJCC, patients with affected lymph nodes in the supraclavicular chain were classified as cN3c staging and removed from the cM1 group[3]. Thus, statistics related to metastatic disease collected during this transition phase must be analyzed with caution due to the possibility of selection bias[25].

More recently, in 2018, the 8th edition of the manual removed lobular carcinoma *in situ* from the T*is* staging[26,27], which should affect the incidence curves of the disease in the next years. Reducing the number of T*is* patients might increase the proportion of diagnosed cases in stages II, III, and IV; however, this scenario could reflect an untrue epidemiological event.

Lastly, the situation of patients who achieved complete pathological response (pCR; ypT0ypN0cM0) after neoadjuvant therapies and of those with tumor cells circulating in peripheral blood [cM0(i+)] must be considered. According to the 8th edition of the cancer staging manual, the identification of circulating tumor cells does not classify the patient as cM1 in the absence of other signs of metastatic disease. Similarly, patients with pCR do not constitute a new specific group and remain in the group assigned at the moment of diagnosis. Nevertheless, with advances in the understanding of tumor biology and prognostic stratification of these patients[27,28], new concepts involving pCR and molecular techniques for cancer research might be incorporated into the next editions of breast cancer staging.

BREAST CANCER STAGING: 8TH EDITION

Traditionally, breast cancer staging was based on the anatomical extension of the disease and did not consider tumor biology. After 2018, the new staging (8th edition) elaborated by AJCC included biomarkers for the disease to improve the prognostic stratification of patients[26,27].

This inclusion was based on the retrospective evaluation of patients treated at the MD Anderson Cancer Center, in the USA, and posteriorly validated by the California Cancer Registry[7] and the National Cancer Database[29]. In this context, the inclusion of biomarkers resulted in better accuracy in the patient's prognostic evaluation regarding isolated anatomical staging[7,29].

Anatomical staging (AS) has also changed in relation to the 7th edition but maintains its practical value and remains an adequate instrument for the prognostic evaluation of patients. However, the main change was the creation of the clinical prognostic staging (CPS) and pathological prognostic staging (PPS), with the inclusion of tumor grade, HER2, and estrogen and progesterone receptors.

Genomic signatures can also be used in PPS as a potential modifier of staging, when available and indicated. In these situations, a low-risk genomic result indicates a similar prognosis to stage IA, which can affect the decision-making related to the adjuvant treatment of these women[30,31].

The greatest limitation of this new staging is the wide range of categories according to the combination of different criteria, with more than 1,400 possibilities of clinical staging and prognosis. In some circumstances, the combination of clinical and pathological variables can generate up to four staging classifications for the same patient, from the moment of diagnosis to the postoperative evaluation. These categories can be consulted in several specific tables available at the AJCC website (cancerstaging.org) or other platforms.

In the context of PBCR, the new version of the AJCC makes it even more difficult to collect information regarding breast cancer staging. Therefore, new studies involving this variable should state which type of staging was employed, how and when this assessment was carried out, and lastly, which instrument was used to interpret the obtained TNM. Nevertheless, we recommend caution when comparing studies conducted in different periods and geographic regions, with different or insufficiently described methodologies.

FUTURE PERSPECTIVES

An application developed by a Brazilian mastologist (TNM8 BREAST CANCER CALCULATOR®) was approved and licensed by AJCC for global use and is available at the Apple Store and Google Play at a reasonable price. This application allows the individualized inclusion of variables and automatically provides the corresponding staging[32]. In times of globalization and wide access to information, electronic instruments can help with the data collection process for population-based registries and improve the quality of information on breast cancer staging.

Finally, we emphasize the need for continuing education, along with constant training for all professionals involved in the breast cancer epidemiological context, from assistant medical doctors to the professionals responsible for gathering and registering this information. The utilization of new technologies can help standardize the information and reduce the divergences related to cancer staging registry.

AUTHORS' CONTRIBUTIONS

L.R.S.: Conceptualization, data curation, formal analysis, writing — original draft; M.P.C.: Formal analysis, writing — original draft; R.F.-J.: Formal analysis, writing — original draft.

REFERENCES

1. Beahrs OH. Staging of cancer of the breast as a guide to therapy. Cancer. 1984;53(3 Suppl.):592-4. https://doi.org/10.1002/1097-0142(19840201)53:3+%3C592::aid-cncr2820531303%3E3.0.co;2-9
2. Chavez-MacGregor M, Mittendorf EA, Clarke CA, Lichtensztajn DY, Hunt KK, Giordano SH. Incorporating Tumor Characteristics to the American Joint Committee on Cancer Breast Cancer Staging System. Oncologist. 2017;22(11):1292-300. https://doi.org/10.1634/theoncologist.2017-0116
3. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al. AJCC cancer staging manual. 6th ed. New York: Springer-Verlag; 2002.
4. Curado MP. Techniques of registration. In: Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al., eds. Cancer Incidence in Five Continents. Lyon: IARC; 2007. v. 9. p. 14-39.
5. Camargo Cancela M, Chapuis F, Curado MP. Abstracting stage in population-based cancer registries: the example of oral cavity and oropharynx cancers. Cancer Epidemiol. 2010;34(4):501-6. https://doi.org/10.1016/j.canep.2010.04.012
6. Curado MP, Voti L, Sortino-Rachou AM. Cancer registration data and quality indicators in low and middle income countries: their interpretation and potential use for the improvement of cancer care. Cancer Causes Control. 2009;20:751-6. https://doi.org/10.1007/s10552-008-9288-5
7. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, Yi M, Tadros A, Hortobagyi GN, et al. Validation study of the AJCC eighth edition prognostic stage compared with the anatomic stage in breast cancer. JAMA Oncol. 2018;4(2):203-9. https://doi.org/10.1001/jamaoncol.2017.4298
8. Valsecchi MG, Steliarova-Foucher E. Cancer registration in developing countries: luxury or necessity? Lancet Oncol. 2008;9(2):159-67. https://doi.org/10.1016/S1470-2045(08)70028-7
9. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. CONCORD Working Group. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015;385(9972):977-1010. https://doi.org/10.1016/S0140-6736(14)62038-9
10. Abreu E, Koifman RJ, Fanqueiro AG, Land MGP, Koifman S. Sobrevida de dez anos de câncer de mama feminino em coorte populacional em Goiânia (GO), Brasil, 1988-1990. Cad Saúde Coletiva. 2012;20(3):305-13.
11. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008;9(8):730-56. https://doi.org/10.1016/S1470-2045(08)70179-7
12. Freitas-Junior R, Nunes RD, Martins E, Curado MP, Freitas NMA, Soares LR, et al. Prognostic factors and overall survival of breast cancer in the city of Goiania, Brazil: a population-based study. Rev Col Bras Cir. 2017;44(5):435-43. https://doi.org/10.1590/0100-69912017005003
13. Allemani C, Coleman MP. Cancer survival: [corrected] the CONCORD-2study-Authors'reply. Lancet. 2015;386(9992):429-30. https://doi.org/10.1016/S0140-6736(15)61443-X
14. Freitas-Junior R, Soares LR, Barrios CH. Cancer survival: [corrected] the CONCORD-2study. Lancet. 2015;386(9992):428-9. https://doi.org/10.1016/S0140-6736(15)61441-6
15. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Instituto Nacional de Câncer. Coordenação de Prevenção e Vigilância. Manual de rotinas e procedimentos para registros de câncer de base populacional. 2nd ed. Rio de Janeiro: INCA; 2012 [accessed on 22 Jan 2019]. Available at: https://www.inca.gov.br/publicacoes/manuais/manual-de-rotinas-e-procedimentos-para-registros-de-cancer-de-base-populacional
16. Parkin DM, Whelan SI, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents. Lyon: International Agency for Research on Cancer; 2002. v. 8.
17. Freitas NMA, Freitas-Junior R, Curado MP, Martins E, Bandeira e Silva CM, Moreira MAR, et al. Tendência da incidência e da mortalidade do câncer de mama em Goiânia: análise de 15 anos (1988-2002). Rev Bras Mastol. 2006;16(1):17-21.
18. Moura L, Curado MP, Simões EJ, Cezário AC, Urdaneta M. Avaliação do registro de câncer de base populacional do município de Goiânia, estado de Goiás, Brasil. Epidemiol Serv Saúde. 2006;15(4):7-17. https://doi.org/10.5123/S1679-49742006000400002
19. Miller JW, Smith JL, Ryerson AB, Tucker TC, Allemani C. Disparities in breast cancer survival in the United States (2001-2009): Findings from the CONCORD-2 study. Cancer. 2017;123(Suppl. 24):5100-18. https://doi.org/10.1002/cncr.30988
20. Elkin EB, Hudis C, Begg CB, Schrag D. The effect of changes in tumor size on breast carcinoma survival in the U.S.: 1975-1999. Cancer. 2005;104(6):1149-57. https://doi.org/10.1002/cncr.21285
21. Lemos NAF, Freitas-Junior R, Moreira MAR, Silva TC, Oliveira JC, Silva CMB. Difficulties in collecting data on ductal carcinoma in situ at a population-based cancer registry. Mastology. 2019;29(2):86-9. https://doi.org/10.29289/25945394 20190000421
22. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Fort Washington: National Comprehensive Cancer Network; 2020 [accessed on Jun. 15, 2020]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
23. Tolêdo SRS, Almeida NAM, Souza MR, Minamisava R, Freitas-Junior R. Care flow of breast cancer patients in the public health care network. Rev Eletr Enf. 2016;18:e1201. https://doi.org/10.5216/ree.v18.39147
24. McCready DR, Yong WS, Ng AK, Miller N, Done S, Youngson B. Influence of the new AJCC breast cancer staging system on sentinel lymph node positivity and false-negative rates. J Natl Cancer Inst. 2004;96(11):873-5. https://doi.org/10.1093/jnci/djh142
25. Woodward WA, Strom AS, Tucker SL, McNeese MD, Perkins GH, Schechter NR, et al. Changes in the 2003 American Joint Committee on Cancer—staging for breast cancer dramatically affects stage-specific survival. J Clin Oncol. 2003;21(17):3244-8. https://doi.org/10.1200/JCO.2003.03.052

26. Hortobagyi GN, Connolly JL, D'Orsi CJ, Edge SB, Mittendorf EA, Rugo HS, et al. Breast. In: Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2016.

27. Giuliano AE, Edge SB, Hortobagyi GN. Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol. 2018;25:1783-5. https://doi.org/10.1245/s10434-018-6486-6

28. Luen S, Virassamy B, Savas P, Salgado R, Loi S. The genomic landscape of breast cancer and its interaction with host immunity. Breast. 2016;29:241-50. https://doi.org/10.1016/j.breast.2016.07.015

29. Li X, Zhang Y, Meisel J, Jiang R, Behera M, Peng L. Validation of the newly proposed American Joint Committee on Cancer (AJCC) breast cancer prognostic staging group and proposing a new staging system using the National Cancer Database. Breast Cancer Res Treat. 2018;171:303-13. https://doi.org/10.1007/s10549-018-4832-9

30. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016;375(8):717-29. https://doi.org/10.1056/NEJMoa1602253

31. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018;379(2):111-21. https://doi.org/10.1056/NEJMoa1804710

32. Andrade WP. TNM8 Breast Cancer Calculator [Internet]. Apple; 2018 [accessed on Jun. 15, 2020]. Available at: https://itunes.apple.com/us/app/tnm8-breast-cancer-calculator/id1294700966?mt=8