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Review article

Axillary Treatment in Breast Cancer Surgery: Systematic Review of Its Impact on Survival☆

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ABSTRACT

Sentinel lymph node biopsy and ACOSOG-Z0011 criteria have modified axillary treatment in breast cancer surgery. We performed a systematic review of studies assessing the impact of axillary treatment on survival. The search showed 6891 potentially eligible items. Of them, 23 clinical trials and 12 meta-analyses published between 1980 and 2017 met the study criteria. The review revealed that axillary lymph node dissection (ALND) can be omitted in patients pN0 and pN1mic, without compromising survival. In patients pN1 it is proposed not to treat the axilla or replace ALND for axillary radiotherapy. The main limitations of this study are the inclusion of old tests that do not use therapeutic targets and lack of risk categorization of relapse. In conclusion, axillary treatment can be avoided in patients without metastatic involvement or micrometastases in the sentinel lymph node. However, there is no evidence to make a recommendation of axillary treatment in N1 patients, so individualized analysis of patient risk factors is needed.

Estado actual del tratamiento de la axila en la cirugía primaria del cáncer de mama: revisión sistemática de su impacto en la supervivencia

Palabras clave:
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Macrometástasis
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Radioterapia axilar
Tratamiento axilar

RESUMEN

La biopsia de ganglio centinela (BGC) y los criterios ACOSOG-Z0011 han modificado el tratamiento axilar en la cirugía primaria del cáncer de mama. Por esto se realiza una revisión sistemática de los estudios que valoran el impacto del tratamiento axilar en la supervivencia. La búsqueda mostró 6.891 artículos potencialmente elegibles, de los cuales, 23 ensayos clínicos y 12 metaanálisis publicados entre 1980 y 2017 cumplieron los criterios del estudio. La revisión desveló que la linfadenectomía axilar (LA) puede ser omitida en pacientes pN0 y pN1mic, sin comprometer la supervivencia. En pacientes pN1, se propone no tratar la axila o sustituir la LA por radioterapia axilar (RA). Las principales limitaciones de este estudio es que los ensayos son antiguos, no utilizan terapias dianas ni categorizan el

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riesgo de recaída. En conclusión, el tratamiento axilar puede ser suprimido en pacientes sin afectación metastásica o con micrometástasis del ganglio centinela. No obstante, no hay evidencia para establecer una recomendación de tratamiento axilar en las pacientes con afectación ganglionar N1, por lo que precisan de un análisis individualizado de sus factores de riesgo.

Introduction

In recent years, we have witnessed a change in decision-making for adjuvant treatment in women with breast cancer. Previously, disease staging based on tumor size and lymph node involvement were the elements that determined the choice of locoregional and systemic treatment. Currently, biological factors of the tumor are the basis for the selection of systemic treatment, and the choice of drugs is almost exclusively defined by the immunohistochemical or genetic characteristics of the tumor.[1–4] On the other hand, the decision of axillary treatment has not experienced this evolution and, consequently, axillary staging continues to be the key factor for the indication of axillary lymph node dissection (ALND) or axillary radiotherapy (ART). At present, this decision is controversial, for different reasons. The first, old clinical trials (CT)[5–10] with selected groups of patients have indicated that axillary treatment does not have an impact on overall survival (OS). Secondly, other trials[11–13] show that ALND can be suppressed in a select group of women with micrometastatic involvement of the sentinel lymph node (SLN), without compromising disease-free survival (DFS) or OS. Finally, some CT[14,15] have demonstrated the non-inferiority of ART versus ALND in women with metastatic SLN, with a lower incidence of lymphedema. These facts have resulted in modifications in axillary treatment strategy in women with N1 (1–3 lymph nodes) involvement.

The objective of this study is to develop a systematic review in order to analyze the impact of axillary treatment (ALND, ART) in primary surgery for breast cancer, with the aim to establish clinical recommendations.

Method

A bibliographic search was carried out in PubMed, the Cochrane Library and Academic Google with the search terms: ''axillary lymph node dissection'', ''axillary radiotherapy'' and ''micrometastasis'', in association with the words ''breast cancer''. The search was formulated according to the PICOS strategy where P was: women with breast cancer and primary surgery; I: axillary lymphadenectomy; C: ART or follow-up; O: OS and morbidity; S: clinical trials and meta-analyses. The PRISMA[16] methodology was used. A search of clinical trials presently underway was also done on www.clinicaltrials.gov.

Inclusion and exclusion criteria: included in the study were CT that have analyzed OS with a mean follow-up of at least 5 years, as well as quality meta-analyses that comparing axillary treatments published between 1980 and 2017 in Spanish or English. The study population was comprised of women with primary surgery for their illness (Tis-T4a, N0–N3, M0). Finally, this review included CT that are currently underway and are analyzing the impact of axillary treatment on survival, with the aim to discuss lines of future research. Excluded from the study were duplicate studies, those published in other languages and those that, due to their methodology, follow-up time or number of patients included, were not considered relevant. Similarly excluded were those CT and meta-analyses that either did not report OS or included patients with neoadjuvant chemotherapy or metastatic breast cancer (stage IV).

Two reviewers (BA and AGN) examined the titles and abstracts of the references uncovered in the search to identify potentially eligible publications. The full text of the selected articles was obtained after reading the title/summary, and the selection criteria were applied to review each trial. The 2 reviewers independently evaluated each of the trials that were potentially eligible for inclusion in the review, and discrepancies were resolved by discussion. By mutual agreement, those of greatest importance were chosen. The selected CT and meta-analyses analyzed axillary treatment in primary breast cancer surgery. Finally, a critical analysis was carried out to establish recommendations for clinical practice. The level of evidence and recommendation grades were established according to criteria of the US Preventive Service Task Force.[17]

Results

A total of 6891 articles were potentially eligible, and 359 of these were duplications. After reading the title or the abstract, we excluded 5873 studies as they were not related with the subject and 535 for the following reasons: 35 for being retrospective, 108 for being observational studies; 335 for opinion or with incorrect methodology; and 57 for being published before 1980. A total of 23 CT and 12 meta-analyses were included in the systematic review (Fig. 1). The search identified 13 CT in progress that studied axillary treatment in different clinical settings.

Axillary Lymph Node Dissection in Patients Without Lymph Node Involvement (N0)

Our bibliographic search identified 7 CT that analyzed the impact of ALND in the OS of patients with no clinical axillary involvement (cN0) prior to the introduction of sentinel lymph node biopsy (SLNB).[6,18,19] Four of them[9,10,18,19] compared ALND with the follow-up and did not show significant differences in the OS of both groups after a mean follow-up of at least 5 years. However, 2 of these CT[9,10] only included elderly patients. Another 2 CT compared ALND versus ART.[6–8] One of them, by Cabanes et al.,[7] reported a significant benefit of ALND; however, this benefit disappeared in the long-term follow-up