Editorial

Can we avoid treatment in patients with low-risk ductal carcinoma *in situ*?

Claudio Fuentes-Sánchez[1]^, Carmen González-San Segundo[2]^

[1]Department of Radiation Oncology, Hospital Universitario Candelaria, Santa Cruz de Tenerife, Spain; [2]Department of Radiation Oncology, Hospital Universitario Gregorio Marañón, Madrid, Spain

Correspondence to: Claudio Fuentes-Sánchez. Department of Radiation Oncology, Hospital Universitario Candelaria, Santa Cruz de Tenerife, Spain. Email: cfuentes98@yahoo.com.

Comment on: Poli EC, Chang C, Bleicher RJ, *et al*. Physician's comfort level with observing ductal carcinoma in situ of the breast: a survey of breast specialists at accredited breast centers in the United States. Ann Breast Surg 2022. [Epub ahead of print]. doi: 10.21037/abs-22-1

Received: 10 June 2022; Accepted: 23 June 2022.
doi: 10.21037/abs-22-21
View this article at: https://dx.doi.org/10.21037/abs-22-21

Since the use of mammography and early diagnosis programs became widespread, the diagnosis of ductal carcinoma *in situ* (DCIS) has increased dramatically in different percentages according to the country; from 9% in Finland to 25% in the US of all newly diagnosed breast cancers (1). Currently there are no reliable prognostic factors to predict which tumors will become invasive, this means that the majority of these patients are treated with conservative surgery and radiotherapy as if they had invasive tumors even though they have an excellent prognosis, with a specific cancer mortality at 20 years of 3.3% (2). This fact raises the concern over the possibility of overtreatment in these patients with the socioeconomic and health problems that this implies.

The percentage of DCIS progressing to infiltrating tumor can range from 28% (3) to 50% (4) in untreated patients when follow-up is long enough. In this last study, progression to invasive tumor was independent of tumor grade.

In the absence of published prospective randomised trials, we know that there are patients with CDIS who never progress and may not require treatment. One of the papers that support this fact and the most relevant because of the number of patients and years of follow-up is the retrospective study of Sagara *et al.* (5) using the database of the Surveillance, Epidemiology, and End Results (SEER) database which includes 57,222 cases of DCIS with known grade, of which 1,169 patients were managed without surgery. The main conclusion is that in patients with low-grade DCIS (230 patients) cancer-specific survival at 10 years was similar to those treated (98.8% *vs.* 98.6% respectively; P=0.95), although there was a difference for grades 2 and 3 in favour of treatment. Although the results are not definitive, we can conclude that there is a subgroup of untreated patients who, with long follow-up, obtain results similar to those treated in terms of survival. Some kinds of DCIS are very likely to remain indolent throughout the patient's life, while others have a greater propensity to progress to a life-threatening invasive disease.

The treatment of DCIS has been a controversial topic for years. As it happens in prostate cancer where active surveillance is an option in low-risk patients (6), in DCIS this option could be a viable alternative, although there are still no studies to support it.

Conservative treatment in infiltrating breast carcinoma has been well established since the 80s. However, in case of DCIS treatment with mastectomy was still a usual treatment during the 90 s. The indication for conservative treatment in DCIS was established after invasive carcinoma, which represents a contradiction, as it results in treating a less aggressive tumor with a more mutilating surgery. It was not until 1997 that breast-conserving treatment (lumpectomy plus radiotherapy) was established as a recommended treatment in DCIS at a consensus conference (7). However,

^ ORCID: Claudio Fuentes-Sánchez, 0000-0002-5578-7328; Carmen González-San Segundo, 0000-0002-5489-5327.

Table 1 Inclusion criteria in the trials for patients with DCIS

TRIAL	Age	Grade	Tumor size	Biopsy	Tumor	ER and PR
Loris (10)	≥46	1/2	Any size	VACBs	Not palpable	Any
Lord (9)	≥46	1	Any size	VACBs	Not palpable	Any
Comet (8)	≥40	1/2	Any size	VACB or core needle biopsy	Not palpable	+ >10%

VACB, vaccine assisted biopsy; ER, estrogen receptor; PR, progesterone receptor; DCIS, diagnosis of ductal carcinoma *in situ*.

mastectomy was still considered, in the absence of comparative studies, as the gold standard. The risk of relapse with transformation to infiltrating tumor in patients treated only with lumpectomy was considered to be 1% per year and surveillance without treatment was not considered as an alternative.

There are three ongoing trials to elucidate which patients can avoid surgery, COMET (United States of America, NCT02926911) (8), LORD (The Netherlands, NCT02492607) (9) and LORIS (United Kingdom, NCT02766881) (10). However, there are already publications that help determine which patients can be managed only with lumpectomy, without adjuvant treatment of hormone therapy or radiotherapy, such as patients with tumors smaller than 2 cm, free margins and low histological grade (11,12). Solin *et al.* (13) in the Oncotype DX breast cancer assay (Eastern Cooperative Oncology Group (ECOG) E5194 study) using genetic markers used in invasive breast cancer, establishes three risk groups for ipsilateral relapse as DCIS or invasive tumor. In 327 patients treated with lumpectomy alone, the risk of relapse as an invasive tumor was 3.7%, 12.3%, and 19.2% for low, intermediate, and high risk, respectively with no association with histological grade. Independent relapse factors were assigned risk group, tumor size, and menopausal status. The bottom line is that patients who meet the low-risk group criteria could be treated with lumpectomy alone without radiation therapy. Although the low-risk group shows a 3.7% of relapses as an invasive tumor and surveillance could be considered as an alternative, we have to be cautious because this percentage would be predictably higher if the tumor had not been resected.

Unfortunately, the three ongoing trials, COMET, LORD and LORIS (*Table 1*) do not include genetic risk factors within the selection criteria. An additional problem is that of upstaging risk; Pilewskie *et al.* (14) in the context of a study of patients diagnosed with DCIS and who meet the inclusion criteria of the LORIS trial, shows that in 20% of cases there is invasive tumor after lumpectomy. This discouraging fact suggests that the selection criteria, very similar in the three studies, may be insufficient.

Although we know that some DCIS have an indolent course and never progress to invasive life-threatening tumor, we do not know exactly which patients might be candidates for surveillance and thus avoid overtreatment. In this situation, Poli *et al.* (15) shows us what the opinion of professionals is, with a survey conducted among 948 doctors dedicated to the treatment of breast tumors in the US, Surgeons, Radiation Oncologist and Medical Oncologist. A 28.4% of respondents overestimate the risk of relapse when no treatment is done. There are also the majority who think that only 20% of the cases would be candidates for surveillance, being the majority (55.8%) those who believe there is weak or limited evidence to recommend observation; 76.5% think that there would be many difficulties in recruiting patients for the observation arm, indicating that the main concern would be the progression of the disease and the difficulty of predicting which patients are already invasive at the time of diagnosis. In no case would they recommend this procedure in patients with tumors of high histological grade. In general, the physicians surveyed recommend surveillance in patients with low-grade tumors and positive hormone receptors, factors required in the COMET trial, but would not feel comfortable in young patients or with tumors larger than 3 cm, criteria that are not limiting in this trial.

Facing this vision from the professional side, we also have to see the perspective from patient's point of view. Hawley *et al.* (16) concludes that a 45% of the patients diagnosed with DCIS overestimate the risk of distant relapse, which is associated with concern and decreased quality of life. These findings are in line with the survey results shown by Poli *et al.* (15); there is a clear lack of communication to the patients the true risks of local and distant relapse by physicians who also overestimate such risks. Likewise, Partridge *et al.* (17) shows in a study on psychosocial concerns in patients with breast DCIS, how patients tend to overestimate the risks of relapse as an invasive tumor.

In conclusion, there is an overdiagnosis and as a consequence there may be overtreatment in patients with DCIS. There is a group of low-risk patients in which no treatment may be recommended, or only lumpectomy, although they are not yet perfectly identified. The introduction of molecular criteria for their identification is necessary, as relying on histological, morphological and clinical criteria only is not sufficient. Selection based on molecular criteria, histological grade, tumor size, hormone receptors and menstrual status (age), as in invasive tumors, would help us define patients with low risk of microinvasion and progression, at least initially and in a safe way, with the possibility of increasing this group depending on the results. A jump from conservative surgery with radiotherapy to no treatment could be considered excessive without having determined properly this group of patients with a favorable prognosis. The paper of Poli *et al.* (15) shows the current problems in the treatment of patients with DCIS and the uncertainty when recommending no treatment without having this group of patients well identified. It is therefore mandatory to wait for the results of the ongoing trials with their subsequent analysis before recommending such a practice.

Acknowledgments

The authors thank to Jorge Fuentes Olea for his comments to improve the final text.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Breast Surgery*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://abs.amegroups.com/article/view/10.21037/abs-22-21/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Lynge E, Ponti A, James T, et al. Variation in detection of ductal carcinoma in situ during screening mammography: a survey within the International Cancer Screening Network. Eur J Cancer 2014;50:185-92.
2. Narod SA, Iqbal J, Giannakeas V, et al. Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ. JAMA Oncol 2015;1:888-96.
3. Page DL, Dupont WD, Rogers LW, et al. Intraductal carcinoma of the breast: follow-up after biopsy only. Cancer 1982;49:751-8.
4. Collins LC, Tamimi RM, Baer HJ, et al. Outcome of patients with ductal carcinoma in situ untreated after diagnostic biopsy: results from the Nurses' Health Study. Cancer 2005;103:1778-84.
5. Sagara Y, Mallory MA, Wong S, et al. Survival Benefit of Breast Surgery for Low-Grade Ductal Carcinoma In Situ: A Population-Based Cohort Study. JAMA Surg 2015;150:739-45. Erratum in: JAMA Surg 2015;150:820.
6. NCCN Guidelines for Prostate Cancer. Available online: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
7. Consensus Conference on the classification of ductal carcinoma in situ. The Consensus Conference Committee. Cancer 1997;80:1798-802.
8. Hwang ES, Hyslop T, Lynch T, et al. The COMET (Comparison of Operative versus Monitoring and Endocrine Therapy) trial: a phase III randomised controlled clinical trial for low-risk ductal carcinoma in situ (DCIS). BMJ Open 2019;9:e026797.
9. Elshof LE, Tryfonidis K, Slaets L, et al. Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ - The LORD study. Eur J Cancer 2015;51:1497-510.
10. Francis A, Thomas J, Fallowfield L, et al. Addressing overtreatment of screen detected DCIS; the LORIS trial. Eur J Cancer 2015;51:2296-303.
11. Early Breast Cancer Trialists' Collaborative Group

(EBCTCG); Correa C, McGale P, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010;2010:162-77.
12. McCormick B, Winter K, Hudis C, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol 2015;33:709-15.
13. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst 2013;105:701-10.
14. Pilewskie M, Stempel M, Rosenfeld H, et al. Do LORIS Trial Eligibility Criteria Identify a Ductal Carcinoma In Situ Patient Population at Low Risk of Upgrade to Invasive Carcinoma? Ann Surg Oncol 2016;23:3487-93.
15. Poli EC, Chang C, Bleicher RJ, et al. Physician's comfort level with observing ductal carcinoma in situ of the breast: a survey of breast specialists at accredited breast centers in the United States. Ann Breast Surg 2022. [Epub ahead of print]. doi: 10.21037/abs-22-1
16. Hawley ST, Janz NK, Griffith KA, et al. Recurrence risk perception and quality of life following treatment of breast cancer. Breast Cancer Res Treat 2017;161:557-65.
17. Partridge A, Adloff K, Blood E, et al. Risk perceptions and psychosocial outcomes of women with ductal carcinoma in situ: longitudinal results from a cohort study. J Natl Cancer Inst 2008;100:243-51.

doi: 10.21037/abs-22-21
Cite this article as: Fuentes-Sánchez C, González-San Segundo C. Can we avoid treatment in patients with low-risk ductal carcinoma *in situ*? Ann Breast Surg 2022.