© Curr Gynecol Oncol 2017, 15 (1), p. 87–90
DOI: 10.15557/CGO.2017.0008

Received: 27.10.2016
Accepted: 11.05.2017
Published: 31.05.2017

Ewa Śrutek[1], Tomasz Nowikiewicz[1,2], Wojciech Zegarski[1]

Current guidelines on the diagnosis and management of lobular carcinoma *in situ*

Aktualne zalecenia dotyczące diagnostyki i leczenia chorych z rozpoznaniem raka zrazikowego piersi *in situ*

[1] Surgical Oncology Clinic, Collegium Medicum Nicolaus Copernicus University Oncology Center, Bydgoszcz, Poland. Head of the Department: Professor Wojciech Zegarski, MD, PhD
[2] Department of Clinical Breast Cancer and Reconstructive Surgery, Oncology Center, Bydgoszcz, Poland. Head of the Department: Piotr Rhone, MD, PhD
Correspondence: Tomasz Nowikiewicz, Department of Clinical Breast Cancer and Reconstructive Surgery, Prof. Francis Łukaszczyk Oncology Center, dr I. Romanowskiej 2, 85-796 Bydgoszcz, Poland, e-mail: tomasz.nowikiewicz@gmail.com

[1] Klinika Chirurgii Onkologicznej, Collegium Medicum UMK w Bydgoszczy, Centrum Onkologii w Bydgoszczy, Bydgoszcz, Polska. Kierownik Kliniki: prof. dr hab. n. med. Wojciech Zegarski
[2] Oddział Kliniczny Nowotworów Piersi i Chirurgii Rekonstrukcyjnej Centrum Onkologii w Bydgoszczy. Koordynator: dr n. med. Piotr Rhone
Adres do korespondencji: Tomasz Nowikiewicz, Oddział Kliniczny Nowotworów Piersi i Chirurgii Rekonstrukcyjnej, Centrum Onkologii im. prof. Franciszka Łukaszczyka, ul. dr I. Romanowskiej 2, 85-796 Bydgoszcz, e-mail: tomasz.nowikiewicz@gmail.com

Abstract

Lobular carcinoma *in situ* of the breast is classified as non-invasive malignant tumor of the breast. Its diagnosis is a marker for an increased risk of developing other histological types of breast cancer. Lobular carcinoma *in situ* is usually asymptomatic, with no characteristic radiological features. The diagnosis is often accidental while diagnosing lesions found on screening mammography. The most important clinical issue associated with the diagnosis of lobular carcinoma *in situ* is the possible risk of concurrent breast cancer of another histological type. According to the current standards of managing patients with lobular carcinoma *in situ* of the breast, surgical biopsy of the mass is most commonly recommended. Specific principles of therapy depend on the circumstances surrounding the diagnostic process. The complete diagnosis requires histopathological study of tissue specimens from paraffin blocks. It is necessary to determine the histological subtype of the identified tumor as different subtypes present significant differences as to the course of the disease (classic lobular carcinoma *in situ*, pleomorphic, florid or *comedo* with necrosis ones). Contrary to the classic lobular carcinoma *in situ*, other subtypes are characterized by significantly higher risk of coexisting infiltrating breast cancer. In such cases, it is necessary to perform surgical excision of the tumor. Diagnosis of LCIS does not require surgical treatment (possible active surveillance of the patient).

Keywords: lobular breast cancer *in situ*, diagnosis and treatment, surgical treatment

Streszczenie

Rak zrazikowy gruczołu piersiowego *in situ* należy do postaci nieinwazyjnych nowotworów złośliwych o tej lokalizacji narządowej. Jego zdiagnozowanie jest markerem zwiększonego ryzyka rozwoju w przyszłości innych typów histologicznych raka piersi. Zrazikowy rak piersi *in situ* to najczęściej guz bezobjawowy, nieposiadający charakterystycznych cech radiologicznych. Do jego wykrycia dochodzi zwykle przypadkowo, w trakcie diagnostyki zmian uwidocznionych podczas skriningu mammograficznego. Najbardziej istotnym problemem klinicznym związanym ze zdiagnozowaniem tego nowotworu jest ryzyko współistnienia zmiany z innym rodzajem histologicznym raka piersi. Zgodnie z aktualnymi standardami leczenia chorych ze zrazikowym rakiem piersi *in situ* zalecana jest najczęściej biopsja chirurgiczna zmiany. Szczegółowe zasady postępowania terapeutycznego zależą od okoliczności zdiagnozowania guza. Rozpoznanie choroby wymaga oceny histopatologicznej preparatów tkankowych, pochodzących z bloków parafinowych. Niezbędne jest określenie podtypu histologicznego wykrytej zmiany, które wykazują znaczne różnice dotyczące przebiegu choroby (postać klasyczna, podtyp pleomorficzny, podtyp w stadium rozkwitu bądź podtyp *comedo* z martwicą). W odróżnieniu do typu klasycznego zrazikowego raka piersi *in situ*, pozostałe postaci cechuje istotnie wyższe ryzyko współistnienia form raka naciekającego piersi. W przypadku ich stwierdzenia konieczne jest operacyjne wycięcie zmiany. Wykrycie postaci klasycznej raka zrazikowego gruczołu piersiowego *in situ* nie wiąże się z taką koniecznością (możliwość aktywnego nadzoru chorych).

Słowa kluczowe: zrazikowy rak piersi *in situ*, diagnostyka i leczenie, leczenie operacyjne

GENERAL CONSIDERATIONS

Lobular carcinoma *in situ* (LCIS) of the breast is classified, along with ductal carcinoma *in situ* (DCIS), as a non-invasive malignant tumor of the breast. The first microscopic images of LCIS showing abnormal proliferation in the distal parts of the ductal-lobular system were first presented by Ewing in 1919[1]. Later, in 1941, it was possible to define LCIS neoplastic lesions and give their detailed description[2].

Diagnosis of LCIS is a marker for an increased risk of developing other histological types of breast cancer in the future. However, it is not considered a precancerous condition[3]. According to the observations by Li *et al.*, the presence of LCIS increases the risk of breast cancer 8 to 11 times compared to general population[4]. Hence, 10–20% of the patients will develop either an invasive breast cancer or DCIS within 15–25 years. The estimated risk of developing second cancer is three times greater in the breast in which LCIS was found, compared to the other side[5].

In contrary to ductal carcinoma, LCIS lesions are localized within terminal ductal lobular units (TDLUs). Similarly to DCIS tumor, LCIS neoplasms do not pass through epithelial basement membrane. Thus, they do not invade the surrounding stroma, excluding possible formation of metastasis.

For the LCIS diagnosis, it is necessary to assess pathologically tissue specimens from paraffin blocks. It is also necessary to expand the pathological assessment of the detected lesion. The examination should include the subtypes of LCIS. They are characterized by significant differences regarding the natural course of the disease (distinct biological features of the tumor). The classic type of LCIS should be diagnosed, or one of the other possibilities (*comedo* type with necrosis, florid or pleomorphic).

Contrary to classic LCIS, the other types are characterized by a significantly higher risk of comorbid infiltrating breast cancer. For the classic type, the risk is estimated to be ca. 1%[6,7].

The division of LCIS subtypes elaborated by Middleton *et al.* compiles a number of terminal ductal lobular units (TDLUs) involved by the cancer. Limited presence of abnormal lesions (1–2 ductal lobular units) makes it possible to diagnose "focal" LCIS. If greater number of TDLUs is involved (≥3), "extensive" LCIS is diagnosed[6]. However, the classification described above is of limited clinical use and does not influence the choice of therapeutic options thus far.

LCIS is usually asymptomatic with no characteristic radiological features. The diagnosis is often accidental while diagnosing lesions found on screening mammography[6]. Among lesions found in this way, the diagnosis of this type of cancer is made in 1% cases of pathological verification of tissue specimens obtained by core needle biopsy[8]. In 78% of the LCIS cases, microcalcifications can be found on mammography (similar to DCIS)[9].

Epidemiological studies show, similarly to more common types of breast cancer, a steady growth in LCIS incidence (although less dynamic). Based on the SEER data (Surveillance, Epidemiology, and End Results database) in the period of 2000–2009, an increase in the incidence rate from 2.0 to 2.75/100,000 was observed[10].

The most important clinical issue associated with the diagnosis of LCIS is the possible risk of concurrent breast cancer of another histological type (the so-called upgrade of diagnosis). According to the studies, such a problem affects 2–40% of all the cases[6,11–15]. Therefore, it requires the adoption of uniform standards for diagnosis and management of patients with LCIS.

CURRENT GUIDELINES ON DIAGNOSIS AND MANAGING PATIENTS WITH LCIS

Following the current standards for managing breast cancer patients with LCIS, therapeutic approach depends on the histopathological subtype of LCIS, and the circumstances under which the tumor has been diagnosed. Detailed recommendations are available in national (consensus agreed on by the Polish Society of Surgical Oncology, Recommendations of the Polish National Consultant in Surgical Oncology, Recommendations of the Polish Union of Oncology) and international (National Comprehensive Cancer Network – NCCN, American Society of Clinical Oncology – ASCO, Arbeitsgemeinschaft Gynäkologische Onkologie – AGO) expert guidelines[16–22].

"Incidental" LCIS

In the case of diagnosis that is based on the assessment of tissue specimens obtained after excision of the benign mass from the breast, and associated with concurrent lack of suspicious lesions in the radiological studies, we are facing the so-called "incidental" LCIS. When negative surgical margins following LCIS excision are achieved, active observation of the patient is recommended. It includes physical examination in 6- to 12-month intervals and mammography (at least once a year). There is no obligation for further surgical treatment. If resection of LCIS was not radical, further management depends on the histological subtype of the neoplasm. Surgical biopsy (surgical excision of the lesion) should always be performed, when either pleomorphic, florid or *comedo* with necrosis subtype has been identified on pathological assessment. Diagnosis of classic LCIS does not cause such a necessity (active surveillance of the patient is possible).

If the patient presents additional risk factors for breast cancer (especially *BRCA1/2* mutation, positive family history or diagnosis of LCIS at a young age), she can be qualified for primary prevention (bilateral mastectomy with simultaneous breast reconstruction). According to the studies by Middleton *et al.*, accidental diagnosis of LCIS

DOI: 10.15557/CGO.2017.0008 CURR GYNECOL ONCOL 2017, 15 (1), p. 87–90

is one of the most common diagnostic situations. The percentage of "incidental" LCIS may account for 66% of all the cases[6].

"Targeted" LCIS

Diagnosis of LCIS is based on pathological assessment of specimens obtained by core needle biopsy (including vacuum-assisted breast biopsy) of suspicious masses ("targeted" LCIS) and it requires the exclusion of coexistence of invasive cancer or DCIS. During qualification for surgical intervention (surgical biopsy of LCIS) rules described above for "incidental" LCIS do apply and should be followed. The necessity for surgical treatment (surgical biopsy of the lesion) is therefore dependent on the histological subtype. It is however not required after diagnosing the classic subtype of LCIS by core needle biopsy. It must be conducted whenever detecting any other subtype (pleomorphic, florid or *comedo* with necrosis).
In the case when LCIS of a subtype that increases the risk of coexisting other forms of breast cancer (pleomorphic, florid or *comedo* with necrosis subtype) is found in the margins of the specimen, it is necessary to radicalize the procedure (increase the excision margins). Identification of LCIS in such a case does not make such an approach necessary.

Management of other clinical conditions – after surgical excision of LCIS

Diagnosis of DCIS in a patient with LCIS (regardless of the subtype) requires further treatment as in the cases of DCIS. A similar approach holds for patients diagnosed with invasive breast cancer associated with LCIS.
Diagnosis of isolated LCIS lesions does not require verification of regional lymph nodes. It makes this group of patients distinct from other forms of breast cancer[23].

HOW PATIENTS WITH LOBULAR BREAST CARCINOMA *IN SITU* ARE MANAGED

Despite quite unambiguous and only slightly changing therapeutic guidelines, studies that analyze therapeutic approaches and outcomes in patients with LCIS prove that different available therapeutic options are frequently implemented. According to observations by Portschy *et al.*, treatment of LCIS of the breast can be based on completely different approaches[10]. In that study, data of 14,048 patients diagnosed with LCIS (based on the core needle biopsy) obtained from the SEER register between 2000 and 2009 were used. For the majority of patients (73%), surgical biopsy of the lesion was performed. In every tenth patient, conservative approach was chosen (active surveillance). However, even 16% of the patients underwent simple mastectomy (11% – one-sided, 5% – bilateral). For the rest (1%), combined treatment was chosen (surgical excision of the tumor with neoadjuvant radiotherapy). Despite the lack of objective clinical indications, surgical staging of the axilla was performed in 8% of the patients. During the studied period, an increase in the percentage of patients undergoing mastectomy was noted (from 12% in 2000 to 18% in the last year of observation).

OUTCOMES OF CONSERVATIVE TREATMENT IN PATIENTS WITH LCIS

The choice of conservative treatment in patients diagnosed with the classic subtype of LCIS by core needle biopsy requires introduction of active observation. During mammographic surveillance, a need for surgical excision of the lesion may arise in some cases. According to studies, it concerns 6–55% of confirmed LCIS cases[14,24]. However, studied groups are usually small (80–164 patients), which significantly hampers the formulation of straightforward conclusions.
Observations by Middleton *et al.* confirm the safety of possible conservative treatment of patients with LCIS. Among 104 patients undergoing mammographic observation, an additional different type of breast cancer was found in 5 patients throughout a 17–66 month follow-up period. However, in none of the patients did metastases or death due to breast cancer occur[6].
Similar results were obtained by Calhoun and Collins. In the analyzed groups, supplementary surgical biopsy was performed in some patients with LCIS confirmed by coarse needle biopsy of suspicious lesions. Out of 167 patients with this approach, another type of cancer was found in 10%. At the same time, poorer therapeutic outcomes were not observed in the compared group despite choosing the conservative approach (active surveillance after core needle biopsy). During the clinical observation (the follow-up period being 6–212 months), other types of breast cancer were found only in 2% of the patients after delayed surgical biopsy[25].
It has been proven in controlled randomized prospective studies that the risk of developing invasive breast cancer can be reduced in LCIS patients treated conservatively. According to the results of NSABP P-01 and Tamoxifen Prevention Trial studies, it is possible to achieve with chemoprophylaxis (tamoxifen). Due to this treatment scheme, the percentage of invasive cancer was reduced by 56% compared to patients receiving placebo[26,27].
In this paper, current guidelines on the diagnosis and management of patients diagnosed with LCIS were presented and systematized. Despite their worldwide availability, they are not fully implemented in clinical practice for this group of patients. It causes lack of complete consistence of therapeutic approach, like in managing other types of breast cancer[28].

Conflict of interest

The authors do not report any financial or personal association with other persons or organizations, who could negatively influence the content of this article or demands rights for this publication.

References

1. Ewing J: Neoplastic Diseases: A Textbook on Tumors. 1st ed., WB Saunders Company, Philadelphia, PA 1919.
2. Foote FW, Stewart FW: Lobular carcinoma in situ: a rare form of mammary cancer. Am J Pathol 1941; 17: 491–496.3.
3. Oppong BA, King TA: Recommendations for women with lobular carcinoma in situ (LCIS). Oncology (Williston Park) 2011; 25: 1051–1056, 1058.
4. Li CI, Malone KE, Saltzman BS *et al.*: Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988–2001. Cancer 2006; 106: 2104–2112.
5. Page DL, Schuyler PA, Dupont WD *et al.*: Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: a retrospective cohort study. Lancet 2003; 361: 125–129.
6. Middleton LP, Sneige N, Coyne R *et al.*: Most lobular carcinoma in situ and atypical lobular hyperplasia diagnosed on core needle biopsy can be managed clinically with radiologic follow-up in a multidisciplinary setting. Cancer Med 2014; 3: 492–499.
7. Morrow M, Schnitt SJ, Norton L: Current management of lesions associated with an increased risk of breast cancer. Nat Rev Clin Oncol 2015; 12: 227–238.
8. Menes TS, Rosenberg R, Balch S *et al.*: Upgrade of high-risk breast lesions detected on mammography in the Breast Cancer Surveillance Consortium. Am J Surg 2014; 207: 24–31.
9. Buckley ES, Webster F, Hiller JE *et al.*: A systematic review of surgical biopsy for LCIS found at core needle biopsy – do we have the answer yet? Eur J Surg Oncol 2014; 40: 168–175.
10. Portschy PR, Marmor S, Nzara R *et al.*: Trends in incidence and management of lobular carcinoma in situ: a population-based analysis. Ann Surg Oncol 2013; 20: 3240–3246.
11. Shah-Khan MG, Geiger XJ, Reynolds C *et al.*: Long-term follow-up of lobular neoplasia (atypical lobular hyperplasia/lobular carcinoma in situ) diagnosed on core needle biopsy. Ann Surg Oncol 2012; 19: 3131–3138.
12. Sullivan ME, Khan SA, Sullu Y *et al.*: Lobular carcinoma in situ variants in breast cores: potential for misdiagnosis, upgrade rates at surgical excision, and practical implications. Arch Pathol Lab Med 2010; 134: 1024–1028.
13. Brem RF, Lechner MC, Jackman RJ *et al.*: Lobular neoplasia at percutaneous breast biopsy: variables associated with carcinoma at surgical excision. AJR Am J Roentgenol 2008; 190: 637–641.
14. Renshaw AA, Derhagopian RP, Martinez P *et al.*: Lobular neoplasia in breast core needle biopsy specimens is associated with a low risk of ductal carcinoma in situ or invasive carcinoma on subsequent excision. Am J Clin Pathol 2006; 126: 310–313.
15. Nagi CS, O'Donnell JE, Tismenetsky M *et al.*: Lobular neoplasia on core needle biopsy does not require excision. Cancer 2008; 112: 2152–2158.
16. National Comprehensive Cancer Network: National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Breast Cancer. Version 1.2016. Available from: www.nccn.org [cited: 28 March 2016].
17. Lyman GH, Temin S, Edge SB *et al.*; American Society of Clinical Oncology Clinical Practice: Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2014; 32: 1365–1383.
18. Kozłowski L: Diagnostyka i leczenie raka zrazikowego *in situ*. In: Nowecki ZI, Jeziorski A (eds.): Chirurgiczne leczenie zmian nowotworowych piersi. Konsensus Polskiego Towarzystwa Chirurgii Onkologicznej. Via Medica, Gdańsk 2016: 46–47.
19. Jassem J, Krzakowski M (red.): Rak piersi. In: Krzakowski M, Warzocha K (eds.): Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych 2013 rok. Vol. I, Onkologia w Praktyce Klinicznej, Via Medica, Gdańsk 2013: 211–263.
20. Herman K, Marczyk E: Rak piersi – rekomendacje Konsultanta Krajowego w dziedzinie chirurgii onkologicznej. In: Zegarski W, Jastrzębski T, Nowikiewicz T (eds.): Rak piersi – postępy diagnostyki i leczenia. Medipage, Warszawa 2013: 1–6.
21. Guidelines of the AGO Breast Committee. Comission Mamma. Available from: http://www.ago-online.de/en/guidelines-mamma/march-2016/.
22. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.
23. Nowikiewicz T, Biedka M, Krajewski E *et al.*: Analysis of selected problems of sentinel lymph node biopsy in patients with breast cancer. Curr Gynecol Oncol 2012; 10: 296–306.
24. Murray MP, Luedtke C, Liberman L *et al.*: Classic lobular carcinoma in situ and atypical lobular hyperplasia at percutaneous breast core biopsy: outcomes of prospective excision. Cancer 2013; 119: 1073–1079.
25. Calhoun BC, Collins LC: Recommendations for excision following core needle biopsy of the breast: a contemporary evaluation of the literature. Histopathology 2016; 68: 138–151.
26. Nelson HD, Smith MEB, Griffin JC *et al.*: Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013; 158: 604–614.
27. Fisher B, Costantino JP, Wickerham DL *et al.*: Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005; 97: 1652–1662.
28. Nowikiewicz T, Śrutek E, Zegarski W: Current problems in diagnostic management and surgical treatment of breast cancer patients – a review of selected clinical issues. Curr Gynecol Oncol 2015; 13: 11–19.

DOI: 10.15557/CGO.2017.0008 CURR GYNECOL ONCOL 2017, 15 (1), p. 87–90