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Breast-conserving surgery and radiotherapy: a possible treatment for lobular carcinoma *in situ*?☆

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Abstract

Lobular carcinoma *in situ* (LCIS) is generally treated by conservative surgery alone and less often by mastectomy. We report our experience using conservative surgery and whole breast irradiation (WBI) for the treatment of patients with LCIS. From 1980 to 1992, 25 women with a median age of 54 years underwent lumpectomy (20) or quadrantectomy (5) and WBI (median dose: 52 Gy) for treatment of their LCIS. Five cases had palpable lesions, 19 were found by mammography alone and one case was found due to nipple discharge. Twelve women received tamoxifen at 20 mg/day for 2 years. With a median follow-up of 153 months (range 58–240), only one local recurrence was observed. The global rate of bilateral carcinoma was 17.6% (two synchronous and one metachronous). Until now, no case of LCIS treated by lumpectomy and radiation therapy has been reported in detail in the literature. After biopsy alone for LCIS, a subsequent infiltrating carcinoma occurs in approximately 15% of cases. Thus, classical radiosurgical therapy should represent an interesting alternative both for limited surgery alone and mastectomy, both of which have been proposed as sole treatments for LCIS.

Keywords: Lobular carcinoma *in situ*; Lobular neoplasia; Breast cancer; Radiation therapy; Conservative treatment; Local recurrence

1. Introduction

Since its identification in 1941 by Muir, Foote and Stewart [1], the exact significance of lobular carcinoma *in situ* (LCIS) has remained uncertain, ranging from a mere marker of subsequent invasive carcinoma to a real precancerous lesion [1–5]. Moreover, the histopathological distinction between LCIS and atypical lobular hyperplasia (ALH) is often very difficult. Thus, Haagensen, in 1978, redefined both lesions under the unique term 'lobular neoplasia' [6,7]. More recently, several authors have observed an increase in the incidence of LCIS [2,5,8–11], and others have detailed accurately the risk of subsequent invasive (and *in situ*) carcinoma in the ipsilateral or contralateral breast [2,5,12–21], identifying some cases of "aggressive" LCIS [2,10,16,17,22].

All of these facts, in association with its rarity, explain the persistent uncertainty with regard to the optimal treatment of this lesion. In the literature, therapeutic options used range from excision alone with regular follow-up to unilateral or bilateral mastectomy [2,5,10].

To our knowledge, classical radiosurgical therapy has been used in only 38 cases in three studies, but without any details being reported for outcome [15,23]. We report our results for 25 women treated with this approach

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and reported after a median follow-up of 153-months; 17 of these cases were previously published in 1998 after a 88-month follow-up [24].

2. Patients and methods

2.1. Epidemiological data

From January 1980 to December 1992, 25 women (17 from Strasburg and 8 from Toulouse) were treated by radiosurgical conservative therapy for LCIS. Their median age was 54 years (range: 47–74 years).

A central review of pathology was not performed, but all pathology forms were checked. Seventeen women (68%) were menopausal, 12 (48%) had a family history of breast cancer. Nine (36%) had undergone previous surgery for benign breast disease, such as cysts, fibroadenomas, ductal or lobular hyperplasia.

2.2. Diagnosis modalities

Nineteen LCIS were discovered only by mammographic and/or echographic abnormalities. The reasons for the biopsy leading to diagnosis are detailed in Table 1. Five women presented with a palpable lesion and one with nipple discharge.

2.3. Surgical treatment

All patients first underwent surgery: quadrantectomy was performed in five cases and lumpectomy or wide excision in 20 cases. Axillary dissection (AD) was carried out in nine cases (36%).

2.4. Histopathology

The histological specimens contained one (8) or several foci (17) of LCIS, almost always associated with complex lesions such as sclerosing adenosis, multiple cysts, fibroadenoma and/or atypical lobular hyperplasia. In two cases, a minimal (<1 mm) zone of ductal carcinoma *in situ* was seen.

Table 1
Radiological features leading to biopsy

• Asymmetric density	1
• Opacity alone	4
• Microcalcifications alone	8
• Microcalcifications + opacity	8
• Architectural distortion	1[a]
• Cyst	1[a]
• Cyst + microcalcifications	1[a]
• Normal	1[b]

[a] Radiological features associated with clinical palpable mass.
[b] With nipple discharge.

Two women underwent a contralateral synchronous mastectomy for an infiltrating lobular and a non-specified carcinoma.

2.5. Radiation therapy

All patients underwent whole breast irradiation using telecobalt photons at a median dose of 52-Gy (range: 45–56 Gy) in daily fractions of 2 Gy. In 20 cases, an additional boost was given by a direct electron field, with a median dose of 10-Gy (range: 6–15 Gy). No nodal irradiation was performed. Twelve women were given tamoxifen at 20 mg/day for 2 years.

3. Results

After a median follow-up of 153 months, only one invasive local recurrence (LR) has been recorded. This occurred after 179 months in a 74-year-old woman, in the same quadrant as the initial LCIS. The histology showed a grade two infiltrating ductal carcinoma (IDC). No *in situ* (lobular or ductal) recurrences have been observed and no further metastatic disease occurred. Another woman developed a contralateral IDC 20 months after her first surgery. All of the women are alive. Two second cancers have occurred.

4. Discussion

LCIS represents 1–2% of breast cancers and 15–20% of all *in situ* carcinomas [2,5,10,12,21]. Several authors found an incidence of 1.5–3.5% LCIS among biopsies for lesions of the breast considered as benign. In autopsy series, the frequency ranged from 0 to 4%. The median age at diagnosis of LCIS in most series varies from 45 to 50 years [2,10]. In Haagensen's large historical series [6,7], 88% of the women were premenopausal, but in more recent series, 40% of the patients were postmenopausal [2]. An increase in LCIS incidence has been observed in several reports [8,11,25,26]. The rate almost doubled from 1975–1979 to 1992 in the Vaud county [11], Detroit area [6,25] and Connecticut [26]. The highest incidence of LCIS occurs in middle-aged women around the age of menopause. The wide use of hormone replacement therapy (HRT) and mammographic screening could both explain this fact [8]. LCIS is generally considered an 'incidental finding', discovered after excision of a benign lesion, such as a cyst or fibroadenoma or mastosis [2,5,10]. Thus, although LCIS is generally not seen on mammograms, screening mammograms often reveal findings that lead to tissue biopsy [23,27–32].

All our patients had a clinical mass (5), nipple discharge (1) or mammographic and/or echographic abnormalities (19). In other reports, several authors also

found LCIS corresponding to clustered microcalcifications, mass alone or with calcification, added density or asymmetry of parenchyma [23,30–32]. Thus, LCIS can be revealed by a palpable mass or by a broad and unspecified variety of intraclinical lesions. Two authors (23, 31) observed an association of LCIS with mammographically dense breast tissue. In LCIS, microcalcifications are not 'specific' and they are often found in benign tissue adjacent to LCIS. However, in the pleomorphic LCIS, calcifications are associated with central necrosis, like in low-grade DCIS [27,29]. Several cases of LCIS are found adjacent to fibroadenoma and especially gross cysts [7]. The differential diagnosis of LCIS is sometimes difficult when trying to distinguish it from ALH, due to interobserver variability and the possible and frequent association of these lesions [2,3,33]. For this reason, some authors use the all-encompassing term 'lobular neoplasia', that was first suggested by Haagensen, with a three-tiered grading system to define the extent of the disease process [34], but without a certain correlation concerning the biological behaviour and especially the subsequent risk of development of invasive carcinoma. However, the recent report by Page and colleagues showed a 13% ipsilateral and 5% contralateral long-term risk of subsequent invasive breast cancer after biopsy for pure ALH [35]. Indeed, this fact is not surprising, because several recent data using molecular techniques have also shown that both ALH and LCIS are neoplastic proliferations [36–39] and that the genetic profiles of ALH and LCIS are similar to each other and to those of invasive breast cancer [40–43]. By contrast, the differential diagnosis between 'aggressive' pleomorphic LCIS and DCIS (especially low-grade) is also sometimes difficult, and both lesions can co-exist [33,35,41].

Multifocality and/or multicentricity are not accurately defined in many reports [2,5]. In fact, in most of the series, multicentricity is defined as residual lesion in the mastectomy specimen, often after a very small excision [2]; this is not the same definition as that used for DCIS (disease present in different quadrants of the breast).

Nevertheless, in Rosen's study [44], LCIS in quadrants other than the one in which the biopsy has been done was seen in 24 of 50 cases (48%). The same methodological problems can be seen for bilaterality, due to inclusion or not of metachronous lesions and systematic use of contralateral biopsy [2,5,44–47]. From the literature, the global rate of simultaneous bilaterality is approximately 20% [2,5,25]. In our series, we found two contralateral lobular infiltrating carcinoma (8%), but the systematic contralateral biopsy was not used.

The major problem for LCIS cases, as for DCIS, is the risk of the development of subsequent invasive carcinoma, bearing in mind that theoretically both lesions are initially totally curable [48–50]. Mastectomy was used by several teams to treat both LCIS and DCIS, with a cure rate of almost 100%. Radical surgery has frequently been considered an overtreatment, and conservative options have been proposed [48], but for LCIS almost always without irradiation [2,5,10]. Thus, the 'natural history' of LCIS treated by excisional biopsy alone is known and the rates of subsequent invasive and *in situ* ipsilateral breast relapses are described in Table 2. However, we noted again several important methodological problems, as well as the inconstant inclusion of previous/synchronous contralateral breast cancer, the variability in histological types of 'subsequent' accounted ipsilateral and contralateral breast cancer (invasive and/or *in situ*, both LCIS and DCIS) and the differences in mastectomy rates performed in the series.

With a wide range of follow-up durations, the rate of subsequent ipsilateral invasive carcinoma (ductal or lobular) varied from 2.2% to 23%, with an average of approximately 15%. These rates are higher if we also in-

Table 2
Risk of subsequent ipsilateral invasive or *in situ* carcinoma after treatment of LCIS by excision alone

Author (year) [references]	No of cases	FU	Invasive carcinoma				*In situ* carcinoma			
			Total (%)		IDC	ILC	Total	LCIS	DCIS	LCIS + DCIS
Carson (1994) [14]	51	50	3	5.9	1	2	7 (3.7%)	7[a]	–	–
Salvadori (1991) [20]	78	58	5	6.4	5	–	0	–	–	–
Ottesen (1993) [17]	69	61	8	11.6	4	4	4 (5.8%)	–	1	4
Page (1991) [18]	39	138	9	23	NS	NS	0	–	–	–
Fisher (2004) [16]	180	144	9	5	1	8	17 (9.4%)	10	6	1
Haagensen (1986) [7]	266	176	27	10.5	NS	NS	0	–	–	–
Andersen (1977) [47]	44	192	9	20.5	NS	NS	4 (9%)	4	–	–
Goldstein (2001) [37]	82	259	13	15.8	6	7	1	–	1	–
Rosen (1978) [19]	83	288	19	23	NS	NS	0	–	–	–
Ciatto (1992) [15]	32	NS	5	15.6	NS	NS	0	–	–	–

NS, not specified; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; FU, follow-up in months (median); LCIS, lobular carcinoma *in situ*.

[a] Subsequent biopsy.

clude subsequent non-invasive recurrences. For DCIS, the use of radiation therapy clearly reduces the rate of local recurrences, especially invasive. The updated results of the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B17 randomised trial (with a median follow-up of 129 months) shows 15.7% and 31.7% of LR with and without complementary irradiation (50 Gy on the whole breast), respectively [51]. All subgroups who received radiation therapy had a clear reduction in local recurrence rates. A similar 45–55% reduction in the LR rate was observed in another two randomised trials [52,53]. Even in two carefully selected series of DCIS discovered by mammography alone [54,55] and treated with large and complete excision alone, the 10-year LR rates were 22% and 27.7%, respectively.

In two large multicentric retrospective studies, the addition of RT (with or without boost) after DCIS excision led to a 11–13% overall recurrence rate at 10 years [48,56,57]. Quite surprisingly, the classical association of radiation therapy after limited surgery has to our knowledge almost never been used. Nevertheless, no data referring to the 'radioresistance' of LCIS can be found in the literature. We suppose that this is because LCIS is generally considered an 'indolent' disease [17,35], or even only a pre-cancerous lesion. As a matter of fact, this is not always true [2,5]. Unfortunately, until now, only very few papers have described some 'unfavourable' characteristics that may suggest a more aggressive treatment than biopsy alone is needed. Ottesen noted a high risk of subsequent infiltrating carcinoma in LCIS with 10 or more lobules involved (24% versus 8%) and/or large nuclear size (31% versus 11%) [17]. More recently, pathologists have begun to identify more aggressive variants of LCIS, such as pleomorphic (non-classic) LCIS. Pleomorphic LCIS has higher grade features than classical LCIS and may have a biological behaviour that is more typical of DCIS [2,22,41,42].

In our retrospective series, it is difficult to find LCIS criteria of note, except for the presence of several foci in 18 out of the 25 cases. With a 4% LR rate at 13 years, our results are encouraging. In several cases of LCIS, radiation therapy may have a role to play (perhaps in association with tamoxifen), because a long-term LR rate of 10–15% does not seem negligible, with a 5–7% subsequent risk of metastases and death, estimated from the literature [2,5].

In conclusion, we suggest that further studies should be undertaken to evaluate the potential benefit of radiotherapy, especially for LCIS with histological characteristics that suggest the disease is aggressive.

Conflict of interest statement

None declared.

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