Eur J Cancer, Vol. 27, No. 1, pp. 35–37, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Risk of Invasive Cancer in Women with Lobular Carcinoma *in situ* of the Breast

Bruno Salvadori, Cesare Bartoli, Stefano Zurrida, Vincenzo Delledonne, Paolo Squicciarini, Dario Rovini and Lucilla Barletta

100 women underwent wide resection for palpable or mammographically detected breast lesions (1 woman had bilateral lesions). Histology excluded invasive cancer, but one or more foci of lobular carcinoma *in situ* (LCIS) were observed. There have been no recurrences in the 20 women who underwent total mastectomy. In the 12 patients who had a subsequent wide excision and the 68 who received no other treatment 5 presented with an invasive cancer in the same breast at some distance from the LCIS site (median follow-up 58 months). The (observed/expected) rate per 1000 per year is 10.3 for an untreated LCIS. LCIS is therefore a risk factor for invasive carcinoma. Nevertheless this risk does not indicate the use of mutilating procedures and a wait-and-see policy is appropriate.
Eur J Cancer, Vol. 27, No. 1, pp. 35–37, 1991.

INTRODUCTION

LOBULAR CARCINOMA *in situ* (LCIS) is one of three entities of "minimal breast cancer", the other two being intraductal carcinoma (DCIS) and invasive carcinoma of size less than 0.5 cm. However, the term minimal breast cancer, as intended by Gallager and Martin in 1971 [1], no longer seems appropriate and consequently the three entities should always be considered separately. Studies on LCIS are sparse and, due to the rarity of diagnosed non-invasive lesions, have often considered small series. Thus, the natural history of LCIS is far from known.

Our series of 101 LCIS cases, observed and treated at the National Cancer Institute of Milan from 1976 to 1988, allows some conclusions to be drawn on the risk of invasive cancer in women with a previous diagnosis of LCIS treated by local resection.

PATIENTS AND METHODS

100 consecutive female patients with pathologically ascertained LCIS were studied during 1976–1988. 1 woman presented with bilateral LCIS, so the number of breasts was 101. 62 women were premenopausal and 38 were postmenopausal aged from 25 to 72 years (mean 49). Age distribution was: 21–30 years (2), 31–40 years (10), 41–50 years (59), 51–60 years (21) and over 60 years (8).

LCIS diagnosis was always an unexpected finding and followed resection of the mammary gland for a palpable or mammographically evident lesion. In no case did histology demonstrate an invasive cancer but, within an area of breast dysplasia, one or more foci of LCIS were observed. Of the 101 specimens analysed, 40 were multicentric whereas in 61 one LCIS focus was observed.

Following pathological diagnosis of LCIS, 33 women underwent a second surgery. 21 had total mastectomy and 12 received a wider excision in the same area as the previous resection. The new excision was done to remove any small possible invasive lesions sited in the proximity of the LCIS. Surgical specimens of the 33 patients who received this second surgery were examined histologically. No lesions were observed in 23 cases, whereas in 10, residual foci of LCIS were reported. No other treatment was given.

1 of the 79 conservatively treated patients was lost to follow-up immediately after surgery, so that 78 women had regular follow-up (quarterly examination and annual mammography). Median follow-up has been 58 months (4–158).

No deaths were to be expected from LCIS, so that the end-point of the study was to identify the risk of invasive cancer in the breast that had harboured LCIS. This risk was calculated for the 78 women treated by local resection only and adequately followed up.

Statistical analysis

The null hypothesis to be tested was: the incidence rate of invasive carcinoma of patients with LCIS diagnosis is equal to that of the reference population (i.e. the population covered by the cancer registry of the region of Lombardy for 1978–1981) [2].

The number of expected events was computed by the person-years method [3] by assuming each patient at risk from the date of LCIS diagnosis to either the occurrence of invasive cancer or the last follow-up visit. Since the incidence per year of invasive breast cancer may be considered as a rare event, the Poisson distribution is suitable for fitting the occurrence of invasive breast cancer [4]. The number of expected events has been used as the parameter of the Poisson distribution. Therefore, the probability of observing a number of events equal to or greater than the observed events provides the significance level to test the null hypothesis.

RESULTS

No deaths so far have been recorded among 99 patients followed up. 5 of the 78 who received conservative treatment later presented with an invasive carcinoma in the same breast; these were diagnosed at 23, 37, 40, 62 and 94 months from

Correspondence to B. Salvadori.
B. Salvadori, V. Delledonne, P. Squicciarini and D. Rovini are at the Division of Surgical Oncology C; C. Bartoli and S. Zurrida are at the Division of Diagnostic Oncology and Outpatient Clinic; and L. Barletta is at the Division of Statistics and Biometry, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy.
Revised 29 Oct. 1990; accepted 31 Oct. 1990.

LCIS diagnosis. These cases had ductal carcinomas; no lobular carcinomas were observed.

The person-years at risk were 332 and the corresponding expected number of invasive carcinoma is 0.485; consequently the expected rate is 0.485/332 = 0.0014608, whereas the observed rate is 5/332 = 0.0150602. The rate ratio of developing an invasive cancer in women who had a LCIS compared with the reference population is 10.3 (per 1000 per year 95% confidence interval 3.4–24.0). The Poisson distribution with a parameter of 0.485 is less than 0.0001.

This allows us to reject the hypothesis that women with an LCIS have a risk of developing an invasive cancer equal to that of the reference population.

DISCUSSION

The behaviour of LCIS has been debated for many years. Observational studies on women with biopsied and untreated LCIS have provided information on the frequency, multicentricity and bilaterality of the condition and the risk of developing invasive cancer associated with it [5–8]. Since LCIS is usually detected by chance, the relation between the number of observed cases and actual frequency of the condition is not known; LCIS is probably more frequent than indicated from the reported series. Andersen [9] found LCIS in 1.5–3.5% of lesions of the breasts considered benign and biopsied. Giordano and Klopp [10] and Pope *et al.* [11] found LCIS in 2.5% and 1.4% of breasts biopsied, respectively. With regard to malignant lesions, LCIS represents 2.8–6.0% [11] of breast cancers and 18.5% of lobular carcinomas [12]. In our series of 100 cases, LCIS accounted for about 1% of the breast cancers observed and treated at the National Cancer Institute, Milan, over the past 10 years.

There is general agreement about the age of patients presenting with LCIS: mean ages range from 45 to 49 [12–17] and the ages of our patients were consistent with these. LCIS is hence more frequent in premenopausal women [16]. Rosen [18], however, reports 17 postmenopausal women out of 38 LCIS patients, and in our series 40% were postmenopausal. It is possible that LCIS is actually more frequent in postmenopausal women than previously thought: the lesion is always an unexpected finding of a biopsy and it should be remembered that benign lesions are more frequent in premenopausal than in postmenopausal women, who undergo breast biopsies less frequently. On the other hand, only 8 of 38 postmenopausal women in our series were over 60 years of age. Multicentricity is a peculiar characteristic of LCIS; a single focus was observed in 61 of the 101 surgical specimens, the remaining 40 were multicentric. Multicentricity in our series was lower than that reported by others [11, 16, 19], which can be as high as 70–90%. Since we never did contralateral biopsies in women with LCIS, we have no data on LCIS in the opposite breast. According to some reports, LCIS affects both breasts in 16–45% of cases [11, 15, 16, 20].

The main point that should inform the surgeon's attitude to women with a diagnosis of LCIS is the risk of developing invasive cancer. The rate of ipsilateral invasive carcinoma is 0.9% per year in biopsy-proven LCIS [21]. This figure is close to our results of about 1.5% for a total exposure of 332 person-years. For a group of 209 women with LCIS, untreated and exposed to risk for a total of 271 years, Haagensen [5] reported that the risk of developing an invasive carcinoma was seven times higher than the risk for women in the normal population. Similar figures have also been given by others [10, 17, 20, 22]. This figure agrees with our extimate of rate ratio and with the confidence interval.

This risk does not seem to justify aggressive treatment such as mastectomy. Neither should bilateral mastectomy be considered, given the low risk of contralateral breast involvement. Since LCIS can regress spontaneously, or remain as such without progressing to invasive cancer, a wait-and-see policy of close observation should be adopted. Such was the conclusion of the recent EORTC international forum on non-invasive breast tumours [21]. It is clear, however, that many investigators remain in favour of total mastectomy [23–27] not only to counter the risk of invasive cancer at a distance from the biopsy site, but also because of the possible existence (1–6%) of an invasive cancer in the proximity of the biopsied LCIS.

In this respect, 12 patients in our series were re-excised and 20 had the whole gland removed after the diagnosis of LCIS, so as not to leave behind an invasive cancer. But in no case was an invasive cancer discovered. No difference between the women who received biopsy and observation and those who had been re-excised immediately after diagnosis of LCIS was noted for the risk of occurrence of invasive cancer. Thus we feel that re-excision of the breast portion that contained LCIS is useless, since if an invasive cancer were found this would be purely by chance.

There is almost general agreement that axillary dissection is not worth performing, and in fact nodal involvement is practically nil for LCIS. Rosner [12] reported on a series of 120 radical mastectomies treated patients with LCIS: in no case were nodal metastases observed. Anderson [28] has discussed the reasons why observation only is an appropriate policy for women with LCIS. He noted that LCIS occurs more frequently in premenopausal women with a long life expectancy and that only a few of these will develop invasive cancer many years after LCIS. Since total mastectomy cures 100% of patients with LCIS, it is actually an over-treatment. Provided women with LCIS are adequately followed up, the diagnosis of invasive cancer should be early with a consequent good prognosis. We agree with these conclusions.

Clearly the breast presenting LCIS is to be considered at high risk of developing invasive cancer and careful follow-up is mandatory. According to their ability to understand, patients should be informed about the risk. We are convinced, however, that there is no reason to request mammography more frequently than once a year.

1. Gallager HS, Martin JF. An orientation to the concept of minimal breast cancer. *Cancer* 1971, **28**, 1505–1507.
2. Berrino F, Crosignani P, Gatta G, Macaluso M, Pisani P, Viganò C. Italy, Lombard Region, Varese Province. In: Muir C, Waterhouse J, Mack T, Powell J, Whelan S, eds. *Cancer Incidence in Five Continents*, Vol. 5 (IARC Scientific Publications No. 88). Lyon, IARC, 1987, 560–565.
3. Berry G. The analysis of mortality by the subject–year method. *Biometrics* 19, **39**, 173–184.
4. Vineis P, Duca PG, Pasquini P. *Manuale di Metodologia Epidemiologica*. Roma, La Nuova Italia Scientifica, 1988, 75–79.
5. Haagensen CD, Lane N, Lattes R, Bodian C. Lobular neoplasia (so called lobular carcinoma *in situ*) of the breast. *Cancer* 1978, **42**, 737–769.
6. Ozzello L. Carcinomi *in situ* e microcarcinomi: diagnosi morfoligica ed implicazioni cliniche. Corso Superiore di Aggiornamento su "I tumori della mammella", Istituto Nazionale Tumori di Milano. Milano, CEA, 1976, 57–63.
7. Newman W. *In situ* lobular carcinoma of the breast: report of 26 women with 32 cancers. *Ann Surg* 1963, **157**, 591–599.
8. Hutter RVP, Foote FW. Lobular carcinoma *in situ*: long term follow-up. *Cancer* 1969, **24**, 1081–1085.

9. Andersen JA. Lobular carcinoma *in situ*. *Acta Pathol Microbiol Scand* 1974, **82**, 519–533.
10. Giordano JM, Klopp CT. Lobular carcinoma *in situ*. *Cancer* 1973, **31**, 105–109.
11. Pope TL, Fechner RE, Wilhelm MC, Wanebo HJ, De Paredes ES. Lobular carcinoma *in situ* of the breast: mammographic features. *Radiology* 1988, **168**, 63–66.
12. Rosner D, Bedwani RN, Vana J, Baker HW, Murphy GP. Non invasive breast carcinoma. Results of a national survey by the American College of Surgeons. *Ann Surg* 1980, **192**, 139–147.
13. Rosen PP, Senie RT, Farr GH, Shottenfield D, Ashikari R. Epidemiology of breast carcinoma: age, menstrual status and exogeneous hormone usage in patients with lobular carcinoma *in situ*. *Surgery* 1979, 219–223.
14. Webber BL, Heise H, Neinfeld JP, Costa J. Risk of subsequent controlateral breast carcinoma in a population of patients with *in situ* breast carcinoma. *Cancer* 1981, **47**, 2928–2932.
15. Hutter RVP. The management of patients with lobular carcinoma *in situ* of the breast. *Cancer* 1984, **53**, 798–802.
16. Andersen JA, Schiodt T. On the concept of carcinoma *in situ* of the breast. *Path Res Pract* 1980, **166**, 407–414.
17. Curletti E, Giordano J. *In situ* lobular carcinoma of the breast. *Arch Surg* 1981, **116**, 309–310.
18. Rosen PP. Lobular carcinoma *in situ* and intraductal carcinoma of the breast. *Monogr Pathol* 1984, **25**, 59–105.
19. Tinnemans JGM, Wobbes T, Holland R, Hendriks JHCL, Van der Sluis RF, De Boer HHM. Treatment and survival of female patients with non palpale breast carcinoma. *Ann Surg* 1989, **209**, 249–253.
20. Kinne DW, Petrek JA, Osborne MP, Fracchia AA, De Palo AA. Breast carcinoma *in situ*. *Arch Surg* 1989, **124**, 33–36.
21. Van Dongen JA, Harris JR, Peterse JL, *et al*. *In situ* breast cancer: the EORTC consensus meeting. *Lancet*, 1989, **ii**, 25–27.
22. Andersen J, Buchert-Doft M, Dyreborg U. *In situ* carcinomas of the breast. Types, growth pattern, diagnosis and treatment. *Eur J Surg Oncol* 1987, **13**, 105–111.
23. Ashikari R, Hajdu SI, Robbins JF. Intraductal carcinoma of the breast. *Cancer* 1971, **28**, 1182–1187.
24. Brown PW, Silverman J, Owens E, Tabor DC, Terz JJ, Lawrence W Jr. Intraductal "noninfiltrating" carcinoma of the breast. *Arch Surg* 1976, **111**, 1063–1067.
25. Davis RP, Nora PF, Kooy RG, Hines JR. Experience with lobular carcinoma of the breast: emphasis on recent aspects of management. *Arch Surg* 1979, **114**, 485–488.
26. Farrow JH. Clinical consideration and treatment of *in situ* breast cancer. *Am J Roentgenol* 1968, **102**, 652–656.
27. Newman J. Lobular carcinoma of the female breast. *Ann Surg* 1966, **164**, 305–314.
28. Andersen JA. Lobular carcinoma *in situ* of the breast: an approach to rational treatment. *Cancer* 1977, **39**, 2597–2602.

Eur J Cancer, Vol. 27, No. 1, pp. 37–41, 1991.
Printed in Great Britain
0277–5379/91 $3.00 + 0.00

Treatment of Bone Metastases from Breast Cancer and Myeloma with Pamidronate

Daniel Thiébaud, Serge Leyvraz, Vladimir von Fliedner, Lucien Perey, Pierre Cornu, Sylviane Thiébaud and Peter Burckhardt

28 patients with progressing painful bone metastases (18 breast cancer, 9 myeloma and 1 low grade lymphoma) received pamidronate 60 mg by 24 h continuous infusion for at least 2 courses (range 2–12). In patients urinary calcium and hydroxyproline excretion significantly decreased in relation to diminution of bone resorption. 9 of 18 breast cancer patients and 8 of 9 evaluable patients with myeloma had symptomatic improvement. Sclerotic areas of previously lytic lesions appeared in 8 breast cancer patients and in 1 myeloma patient. Transient fever developed in 1 patient and local phlebitis in 2. Among the 28 patients, 15 did not receive any anticancer treatment or have any change of the anticancer therapy during pamidronate administration. Of 7 with breast cancer, 4 had an improvement of symptoms and 4 sclerosis on radiographs. Impressive control of symptoms was the major feature of 8 myeloma patients, but only 1 had radiographic sclerosis.
Eur J Cancer, Vol. 27, No. 1, pp. 37–41, 1991.

INTRODUCTION

BONE METASTASES are a frequent cause of morbidity and mortality in cancer patients, causing pain, pathological fractures and hypercalcaemia [1]. They result from accelerated bone resorption induced by the tumour and mediated through an activation of osteoclasts, stimulated by endocrine factors, such as parathyroid hormone related peptides, osteoclast activating factor (OAF), or by paracrine factors such as transforming growth factor alpha and tumour necrosis factor [2–4]. The frequency of bone metastases in breast cancer patients increases during the course of the disease, reaching 50–85% [5–7]. In myeloma, bone involvement is, by definition, 100%. The treatment of bone lesions is directed against the tumour itself (chemotherapy, hormonotherapy or radiotherapy).

Bisphosphonates are structural analogues of pyrophosphate, the natural regulator of bone mineral precipitation and dissolution. Their mechanisms of action are not completely understood. They alter surface hydroxyapatite, impairing osteoclast binding sites [8], and act directly on the mononuclear precursor of osteoclasts [9]. Bisphosphonates have been widely used in benign clinical conditions characterised by increased bone resorption, such as Paget's disease [10] or osteoporosis [11]. In

Correspondence to S. Leyvraz.
D. Thiébaud and P. Burckhardt are at the Department of Internal Medicine; S. Leyvraz, L. Perey and P. Cornu are at the Oncology Center; V. von Fliedner is at the Ludwig Institute for Cancer Research; and S. Thiébaud is at the Department of Radiology, University Hospital, CHUV-06, 1011 Lausanne, Switzerland.
Revised 17 Oct. 1990; accepted 5 Nov. 1990.