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Original Paper

Isolated Axillary Recurrences After Conservative Treatment of Breast Cancer

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This retrospective study presents the diagnostic, prognostic and therapeutic problems raised by axillary recurrences (AR). 1589 cases of breast cancer measuring less than 3 cm, treated at the Institut Curie between 1981 and 1987, were studied by a combination of surgery and radiotherapy. Treatment of the breast always included wide local excision associated with irradiation. The axilla was treated either by dissection (865 cases) or by irradiation (724 cases) and 159 patients received chemotherapy. 26 patients (2%) developed AR, confirmed by fine needle aspiration cytology in 92% of cases. None of these 26 patients had initially received chemotherapy. The treatment of the AR was variable, adapted to the initial treatment. 22 patients retained their breast during treatment of the AR and none subsequently developed a local recurrence. 4 mastectomies were performed and histological examination revealed a subclinical local recurrence in 2 cases. The TNM classification, menopausal status, size of the tumour and hormonal receptor status were not risk factors for AR. Young age ($P = 0.01$) and high histological grade ($P = 0.03$) were significant risk factors for AR. The AR rate was similar whether axillary dissection or axillary irradiation had been performed. The overall 5-year survival after initial treatment was 85% for AR and 95% for the reference population. The overall 4-year survival after recurrence was 69% and the incidence of metastasis was markedly increased ($P = 0.002$). 2 of the 26 patients developed lymphoedema of the arm after treatment of AR. We confirm that AR worsens the prognosis, but not significantly more than local recurrence. Young age and the modified histological grading of Scarff Bloom and Richardson were risk factors for AR. Although excision of the AR is necessary to ensure local control, mastectomy is unnecessary when clinical examination and mammography are normal. Copyright © 1996 Elsevier Science Ltd

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INTRODUCTION

CONSERVATIVE SURGERY and radiation for early stage breast cancer ensures a survival rate equivalent to that produced with mastectomy [1, 2]. The local recurrence rate is approximately 6% at 5 years and 10% at 10 years, and the risk factors are fairly well defined. Axillary lymph node recurrence is much rarer (1–3% at 5 years); it is considered to be more serious and the risk factors are less clearly defined. In this study, we present the diagnostic, prognostic and therapeutic problems associated with axillary recurrences (AR), with the exclusion of cutaneous recurrences in the axilla and, of course, recurrences of the axillary extension of the mammary gland.

PATIENTS AND METHODS

We studied 1589 cases of breast cancer, measuring less than 3 cm in diameter, treated at the Institut Curie between 1981 and 1987, by a combination of surgery and radiotherapy.

Initial treatment

All patients underwent wide local excision, extending 1 or 2 cm beyond the macroscopic limits of the tumour, associated with irradiation of the mammary gland at a dose of 50–55 Gy. Internal mammary irradiation was performed in cases with a central or internal tumour.

Axillary lymph node dissection was performed in 865 patients (54%). It included Berg's first two subpectoral and retropectoral levels, and an average of 10 lymph nodes were removed. When more than two lymph nodes were invaded, the infra- and supraclavicular region was irradiated.

724 patients (46%) received axillary irradiation, associated with supra- and infraclavicular irradiation. The mean irradiation dose was 45 Gy.

160 patients (10%) were treated by axillary lymph node dissection combined with axillary irradiation and 159 patients (10%), usually N⁺, received chemotherapy.

Surveillance consisted of clinical examination every 6 months and annual mammography. Aspiration cytology was performed when examination revealed a suspicious axillary lymph node.

Treatment of axillary recurrence

Treatment of axillary recurrence was usually multidisciplinary and adapted to the initial treatment. The surgical treatment of the 26 AR was as follows: axillary dissection or simple lymphadenectomy (16 cases); mastectomy and axillary dissection (4 cases); and no surgery (6 cases). Some patients received lymph node irradiation at doses and to regions adapted to the initial irradiation. All patients received systemic treatment by chemotherapy and/or endocrine therapy.

When the initial treatment included axillary dissection, simple lymphadenectomy was performed (7 cases). It revealed an average of 1.3 invaded lymph nodes out of the 2 removed. When initial treatment did not include axillary surgery, axillary dissection was performed (9 cases), revealing an average of 4.6 invaded lymph nodes out of the 11 removed. 4 patients underwent mastectomy in the context of treatment of AR. In 2 cases, histological examination of the breast revealed subclinical local recurrence.

The medical treatments for AR were as follows: radiotherapy (14 cases); chemotherapy (15 cases); and endocrine therapy (15 cases).

The doses and fields of irradiation were adapted to the initial treatment.

All patients received systemic chemotherapy and/or endocrine therapy.

The mean follow-up was 80 months after initial treatment of the tumour and 39 months after AR.

Statistical methods

Statistical analysis of the results was performed using the χ^2 test (significant for $P < 0.05$), associated with Yates' correction.

Survival curves were calculated according to the Kaplan–Meier technique and were compared by the log rank test.

RESULTS

At the end of the follow-up period: 26 patients had developed an isolated AR (2%); 158 had developed isolated local recurrences (LR) (10%); 10 had developed axillary and local recurrences (1%); 251 had developed metastases (16%). 1200 patients were free of any signs of recurrence (76%).

Risk factors for axillary recurrence

Table 1 shows the characteristics of patients with AR compared to the reference population. No significant difference was observed for the following characteristics: menopausal status, TNM classification, type of operation, size of the tumour, histology, the number of lymph nodes invaded, and oestrogen and progesterone receptor assays.

Young age was a predictive factor of AR, with the mean age of the AR group being 46.5 versus 51.5 years in the reference population ($P = 0.01$).

The incidence of AR was 2.3% in women younger than 50 years versus 1% in women older than 50 years ($P = 0.04$).

The high modified histological grading of Scarff Bloom and Richardson was also a predictive factor of AR. Patients with a grade I tumour had a significantly lower incidence of AR than grade III patients ($P = 0.03$), as well as grade II and III patients combined ($P = 0.042$).

20 of the 26 AR (77%) developed during the first 4 years following initial treatment. The risk of AR was not eliminated after this time, as the last AR in this study was detected during the tenth year of follow-up.

The AR rate after axillary dissection was 1.57 versus 1.71% after axillary irradiation; this difference was not significantly different ($P = 0.8$). The mean time to appearance of AR was 24 months (6–49 months) after irradiation versus 45 months (17–117 months) after axillary dissection. AR therefore appeared to occur earlier when the axilla had been irradiated, but the difference was not significant.

None of the 26 patients with AR received chemotherapy as part of the initial treatment, and none of the 159 patients initially treated by chemotherapy developed an AR, although they presented with more extensive lymph node invasion. This difference was not significant ($P = 0.08$).

Diagnosis of AR

The diagnosis of AR, suspected clinically, was confirmed by fine needle aspiration cytology in 92% of cases (24/26 cases). In one case, aspiration cytology was not performed and, in another case, it gave a false-negative result.

Course of AR

9 of the 26 cases of AR (34.6%) developed metastases versus 15.6% of patients in the reference population ($P < 0.002$) and 8 of them died. The breast was conserved in 22 patients during treatment of AR and none have developed a local recurrence. None of the 26 patients developed a second AR. 2 of the 26 patients developed lymphoedema of the upper limb following treatment of the AR. Both of these patients had undergone axillary dissection and irradiation during initial treatment of the tumour, followed by complementary irradiation during treatment of the AR.

Survival

Figure 1 shows the overall survival curves starting from initial treatment in the group of AR and in the reference population. The overall 5-year survival of patients with AR was 85 versus 95% in the reference population, which is significant ($P = 0.04$). The 4-year recurrence-free survival after AR was 65%.

Although AR occurred more rapidly when the patient had received initial axillary irradiation, the survival rate was not modified depending on whether or not axillary dissection was performed as part of initial treatment.

The survival rate was not significantly modified according to the time to onset of AR, as 2 of the 7 patients who developed AR during the 2 years following initial treatment died and 6 of the 19 patients who developed AR after 2 years of follow-up died ($P = 0.04$).

Table 1. *Description of the population and the group with axillary recurrences* (*AR*)

	Reference population 1563 patients		Axillary recurrence 26 patients
Mean age	51.5 years	P = 0.01	46.5 years
Premenopausal	59.7% (933)	NS	76.9% (20)
Postmenopausal	40.3% (630)	(P = 0.07)	23.1 (6)
TNM			
T0	8.5% (132)		7.7% (2)
T1	57.1% (893)	NS	50% (13)
T2	34.4% (538)	(P = 0.79)	42.3% (11)
N0	77.6% (1213)	NS	69.2% (18)
N1a	18.8% (294)	(P = 0.43)	23.1% (6)
N1b	3.6% (56)		7.7% (2)
Tumour size (mm)	20.6	NS (P = 0.15)	21.7
Histological N			
Unknown	44.2% (690)		46% (12)
N–	40.3% (631)	NS	27% (7)
N < 3	12.2% (191)	(P = 0.09)	27% (7)
N > 3	3.3% (51)		0 (0)
Histology			
L or C *in situ*	10.4% (162)		3.8% (1)
Invasive ductal	74.5% (1164)	NS	88.6% (23)
Invasive lobular	4.6% (72)	(P = 0.95)	0 (0)
Other	10.5% (165)		7.6% (2)
SBR			
Unknown	10.7% (167)	I and II–III	3.8% (1)
I	31.8% (497)	P = 0.042	15.4% (4)
II	47.1% (737)	I–III	61.5% (16)
III	10.4% (162)	P = 0.03	19.3% (5)
ER			
+	18.5% (180)	NS	17.4% (4)
–	81.5% (793)	(P = 0.89)	82.6% (19)
	(Total = 973)		(Total = 23)
PR			
+	26.5% (274)	NS	26% (6)
–	73.5% (757)	(P = 0.95)	74% (17)
	(Total = 1031)		(Total = 23)
Operation			
Lumpectomy alone	45.5% (711)	NS	50% (13)
Lumpectomy and axillary dissection	54.5% (852)	(P = 0.52)	50% (13)
Chemotherapy	10% (159)	NS (P = 0.08)	0 (0)

ER, oestrogen receptor; PR, progesterone receptor; SBR, Scarff, Bloom and Richardson grading. Numbers in parentheses are numbers of patients.

Figure 2 shows the various survival curves, from the time of recurrence, as a function of the development of AR, LR or a combination of the two.

The overall 4-year survival was 69% for AR, 83% for LR, and 60% for local axillary recurrences. The survival difference of these three groups was not statistically significant (P = 0.2), probably owing to the small sample size.

A bias was detected in the study population: in the group of patients treated by axillary dissection, the tumours were larger (22.4 versus 18.3 mm), with a higher histological grade and the patients more frequently presented with clinical lymph node involvement.

DISCUSSION

AR is a rare event in the course of breast cancer. In our study, the 5-year AR rate was 2%. The AR rate after retropec-

toral axillary dissection is low in tumours with no palpable nodes: 6% for Almaric and Spitalier [3], 4.5% for Fisher and associates [4], 3% for Verhaegue [3], 3% for Fowble and associates [5], 1.6% for Hery [3], 1.36% for Recht and associates [6] and 1.5% at 10 years for Pierquin and associates [7].

Fisher and associates [2] reported that the AR rate was the same after conservative treatment of the breast or mastectomy combined with axillary dissection.

In our study, we did not identify any risk factors for AR apart from age and high histological grade. Young women treated conservatively for breast cancer had a higher incidence of AR, but also a higher incidence of local recurrence. De La Rochefordière and associates [8] and Fourquet and colleagues [9] showed that the local recurrence rate was significantly higher and occurred earlier in younger women, particularly
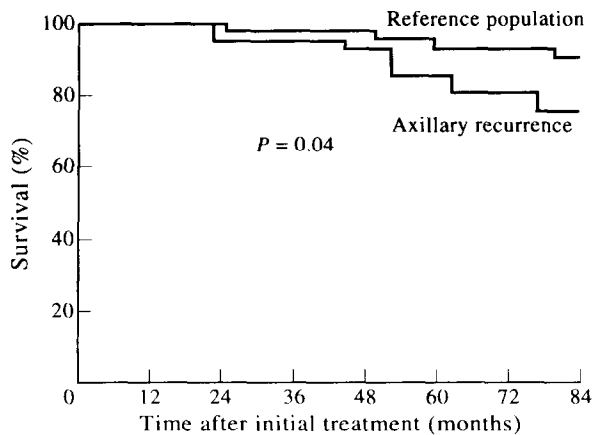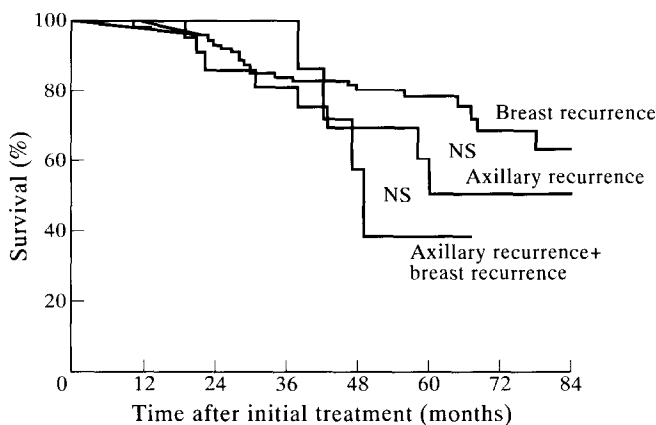
Figure 1. Overall survival (t0 = initial treatment).

Figure 2. Overall survival after local recurrence, axillary recurrence, local and axillary recurrence (t0 = recurrence).

before the age of 35 years. We did not observe this feature in women under the age of 35 years in our study, possibly because of the small number of patients (2 cases). However, we found a significant difference in women under the age of 50 years. We studied local and regional recurrences in 255 patients younger than 35 years and 1198 patients between the ages of 40 and 50 years (unpublished study), and found 3% of AR in women younger than 35 years versus 1.6% in women between 40 and 50 years. This difference was significant ($P = 0.003$). Fowble and associates [5] reported a significant difference in women younger than 35 years, for the incidence of supraclavicular lymph node recurrences, but not for AR. A high histological grade has not been reported in the literature to be a risk factor for AR. Clarke and colleagues [10], in a

series of 436 patients, did not reveal any predictive factors for AR, except perhaps for an interval exceeding 7 weeks between lumpectomy and axillary irradiation. Montbaron and colleagues [11] showed that the AR rate was not significantly modified when axillary dissection or irradiation was performed during initial treatment.

Chemotherapy would therefore appear to play a protective role against the development of AR, although we cannot formally confirm this hypothesis owing to the methodology of our study.

AR worsens the prognosis of breast cancer, as the 5-year survival after initial treatment falls from 95 to 85%.

In our study, the overall 4-year survival rate after AR was 69%, and the recurrence-free survival rate was 65%. Recht and associates [6] reported a recurrence-free survival of 50% at 45 months and Fowble and colleages [5] reported a 3-year recurrence-free survival of 57%.

In a previous study, Durand and colleagues [12] showed that the 5-year survival rate of patients with an isolated mammary recurrence was 72%, which was only slightly different from the survival of AR. Moreover, no significant survival difference was observed in our study between patients with AR or LR. Fowble and associates [5] also did not detect any significant survival difference between patients with AR and those with LR.

Fisher and associates [4], in NSABP trial 4, showed that the AR rate was 16% in patients with no clinical axillary lymph node involvement, in the absence of initial treatment of the axilla. It is therefore essential to treat the axilla either by dissection or by irradiation, as part of the initial treatment of stage I breast cancer [13]. The AR rate has not been shown to be the number of lymph nodes examined [3, 14, 15], except by Fowble and associates [5], who reported the resection of fewer than three lymph nodes to be a significant risk factor of AR and supraclavicular recurrence.

Table 2, comparing our results with those reported in the literature, shows that the lymph node invasion rate does not influence the AR rate. It should be noted that, in our therapeutic protocol, patients presenting with more than two invaded nodes received supra- and infraclavicular irradiation.

In the S4 randomised, prospective trial conducted at the Institut Curie [16], which compared lumpectomy and irradiation to lumpectomy and axillary dissection plus irradiation ± adjuvant therapy, the survival rate was better when axillary dissection was performed. However, it is difficult to determine whether the improved survival is due to adjuvant therapy or to axillary dissection. Reassessment of the trial at 6 years (not yet published) revealed 7.5% of local recurrences and 2.4% of isolated AR in the group without dissection versus 7.6% of local recurrence and 1.84% of AR in the group with dissection. These rates were not significantly different

Table 2. Axillary recurrences as a function of lymph node invasion

	Reference population	AR rate. (%)	N−% (no. of cases)	N+% (no. of cases)
Renolleau and associates (current study)	1589	0.0164	1.1% (631)	2.8% (242)
Mazeron and associates [17]	3353	0.02	0.01	0.02
Fowble and associates [5]	933	0.03	2.7% (642)	3% (291)
Durand and Hery [3]	1099	0.016	1.5% (807)	1.7% (286)
Dewar and associates [14]	592	0.012	1.02% (390)	0.5% (198)

between the two randomised groups. This confirms the results of our retrospective study, which is more open to criticism.

Mazeron and colleagues [17] showed that axillary irradiation associated with axillary dissection did not modify the AR rate, but markedly increased the incidence of lymphoedema of the arm.

AR occurs relatively rapidly after initial treatment: 77% of cases during the first 4 years. The time to onset of AR does not influence the prognosis of AR.

In Recht and associates [6], 66% of AR occurred within 3 years, while Pierquin and Mazeron [18] reported a mean interval to AR of 14 months. AR, either isolated or associated with local recurrence, appear to occur earlier than supraclavicular recurrences [5, 18].

During treatment of AR, 4 of our 26 patients underwent mastectomy. In 2 cases, histological examination of the breast revealed a subclinical breast recurrence. However, none of the 22 patients in whom the breast was conserved developed local recurrence following the AR. In a series of 31 lymph node recurrences studied by Fowble and associates [5], only one subsequently developed local recurrence. Durand and colleagues [12] did not detect any histological local recurrences in a series of 11 mastectomies performed in a group of 25 isolated AR. It therefore appears reasonable to conserve the breast during treatment of AR, provided that clinical examination of the breast and mammography are strictly normal.

Durand and colleagues [19] showed that lymphoedema of the arm depends on the type of surgery and irradiation. The axillary dissection technique, removing the first two Berg levels, is associated with a low incidence of lymphoedema of the low arm, while allowing almost certain determination of the lymph node status [20, 21]. Dewar and colleagues [14] showed that the complications of axillary dissection did not increase with the number of lymph nodes removed, but with the number of lymph nodes invaded, and with combined surgery-irradiation. 2 of our patients developed lymphoedema of the arm after treatment of the AR. Both cases concerned patients who had received axillary surgery and radiotherapy as part of the initial treatment, followed by irradiation of the AR. Moreover, according to Pierquin and Mazeron [18] and Fowble and associates [5], local control of AR appears to be easier to achieve when the AR is excised.

Axillary recurrence is a rare event after conservative surgery and irradiation for breast cancer. It worsens the prognosis, but not to a significantly greater extent than local recurrence.

Young age and high histological grade are risk factors for AR, while adjuvant chemotherapy appears to exert a protective role on AR.

Surgical treatment of AR must include excision to facilitate local control; and, when clinical examination of the breast and mammography are normal, mastectomy can probably be avoided.

1. Veronesi U, Banfi A, Salvadori B, et al. Breast conservation is the treatment of choice in small breast cancer: long term results of a randomized trial. Eur J Cancer 1990, 26, 668–670.

2. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1989, 320, 13, 822–828.

3. Durand JC, Hery M. Comité d'experts sur les cancers du sein; Atelier chirurgical. Bull Cancer Radiother 1991, 78, 89–94.

4. Fisher B, Wolmark N, Bauer M, et al. The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. Surg Gynecol Obstet 1981, 152, 765–772.

5. Fowble B, Solin LJ, Schutz DJ, et al. Frequency, sites of relapse, and outcome of regional node failure following conservative surgery and radiation for early breast cancer. Int J Radiat Oncol Biol Phys 1989, 17, 703–710.

6. Recht A, Pierce SM, Abner A, et al. Regional nodal failure after conservative surgery and radiotherapy for early-stage breast cancer. J Clin Oncol 1991, 9, 988–996.

7. Pierquin B, Otmezguine Y, Lobo PA. Conservative management of breast carcinoma. Acta Radiol Oncol 1983, 2, 101–107.

8. De La Rochefordière A, Asselain B, Campana F, et al. Age as prognostic factor in premenopausal breast carcinoma. Lancet 1993, 341, 1039–1043.

9. Forquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. Int J Radiat Oncol Biol Phys 1989, 17, 719–724.

10. Clarke DH, Le MG, Sarrain D, et al. Analysis of local-regional relapse in patients with early breast cancers treated by excision and radiotherapy: experience of the Institut Gustave Roussy. Int J Radiother Oncol Biol Phys 1985, 11, 137–145.

11. Montbaron X, Radiet JM, Chassard JL, et al. Traitement conservateur du cancer du sein: experience lyonnaise 1963–1983. Bull Cancer 1990, 77, 917–923.

12. Giard C, Asselain BL, Clough KB, et al. Les récidives mammaires après traitement conservateur radiochirurgical du cancer du sein. Chirurgie 1995, 4, 186–190.

13. Hoskin PJ, Rajan B, Ebbss, et al. Selective avoidance of lymphatic radiotherapy in the conservative management of early breast cancer. Cancer Radiother Oncol 1988, 25, 83–88.

14. Dewar JA, Sarrzin D, Benhamou E, et al. Management of the axilla in conservatively treated breast cancer: 592 patients treated at the Institut Gustave Roussy. Int J Radiat Oncol Biol Phys 1987, 13, 475–481.

15. Fisher B, Palekar A, Rockette H, et al. Pathologic findings from the national surgical adjuvant breast projejct (protocol n°4). Cancer 1978, 42, 2032–2038.

16. Cabanes PA, Salmon RJ, Vilcoq JR, et al. Value of axillary dissection in addition to lumpectomy and radiotherapy in early breast cancer. Lancet 1992, 339, 1245–1248.

17. Mazeron J, Pierquin B, Otmezguine Y. Résultats de l'analyse de 5225 traitements des aires ganglionnaires axillaires et susclaviculaires faits dans le cadre de la thérapeutique conservatrice d'un adénocarcinome mammaire. 6° Journées de la Société Française de Sénologie. Paris, Maloine, 1984.

18. Pierquin B, Mazeron J. Conservative treatment of breast cancer in Europe report of the group european of curietherapy. Radiother Oncol 1986, 6, 187–198.

19. Durand JC, Poljicak M, Lefranc JP, et al. Wide excision of the tumor, axillary dissection, and postoperative radiotherapy as treatment of small breast cancers. Cancer 1984, 53, 2439–2443.

20. Contesso G, Rouesse J, Genin J. L'envahissement ganglionnaire loco-régional dans les cancers du sein. Bull Cancer 1975, 62, 359–372.

21. Boova RS, Bonanni R, Rosato FE. Patterns of axillary nodal involvement in breast cancer. Ann Surg 1982, 196, 642–644.