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The value of radiotherapy on metastatic internal mammary nodes in breast cancer. Results on a large series

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The 'regional nodal mapping', is a fundamental step to stage breast carcinoma. In addition to the axillary nodes status, the involvement of internal mammary nodes is an important prognostic factor. Six hundred and sixty-three patients with breast carcinoma, mainly in the inner quadrants, underwent a biopsy of internal mammary nodes. Positive internal mammary nodes were found in 68 out of 663 cases (10.3%) representing 27.2% of all cases with regional node metastases (250). When histologically proven metastases were detected, radiotherapy was administered to the internal mammary nodes chain. In 254 cases, the surgeon's exploration was guided by a gamma probe. Out of these cases, 28 (11.0%) showed metastatic involvement. Out of the other 409 cases, not radioguided, 40 showed positive nodes (9.8%). Patients with internal mammary metastases treated with radiotherapy and appropriate systemic treatment showed an excellent survival (95% at 5 years), a result which is in opposition to the previous experience, which stated that invasion of internal mammary nodes is an ominous prognostic sign. We assume that this excellent result is due to radiotherapy to internal mammary nodes and we propose that exploration of internal mammary nodes should be part of the staging process of carcinomas of the medial part of the breast.

Key words: axillary lymph nodes, breast cancer, internal mammary nodes

introduction

The 'nodal mapping' defining the extent of regional nodes involvement is considered a fundamental step to plan appropriate local and systemic treatments, but is generally limited to the axillary lymph nodes, while many data [1–16] show that the internal mammary nodes should equally be considered. Moreover, as the involvement of the internal mammary nodes may lead to the spread of cancer to the pleura and the thoracic cavity [17], an appropriate treatment to the involved internal mammary nodes should be considered. Several studies found that in large series of breast cancer cases, those patients with a primary carcinoma located in the inner portion of the breast had a prognosis significantly worse than in patients with tumor in outer quadrant [18, 19]. The interpretation was that the over-mortality in this subgroup of patients may be the result of under treatment due to undetected metastases at the internal mammary nodes.

With the aim to investigate the involvement of the internal mammary nodes and to explore a specific therapeutic program, 663 patients with carcinoma of the breast, mainly located in the medial part of the breast were submitted to biopsy of internal mammary nodes. In case of positivity, the internal mammary chain was submitted to radiotherapy and the adjuvant systemic treatment was adjusted to meet the modified prognostic condition.

patients and methods

From September 1998 to April 2006, 663 patients with a primary carcinoma of the breast were submitted to internal mammary node biopsy. Women with a recurrent disease, women submitted to neoadjuvant chemotherapy or treated for a previous carcinoma in other organs and pregnant women were not considered eligible to the study. The average age was 50.2 years (minimum 22 and maximum 80). The majority of the patients (520) had a carcinoma of the inner quadrants, 24 had a carcinoma of the areola region, while 112 had the primary carcinoma in the supraareolar or underareolar portion of the breast. In the remaining seven patients, the carcinoma was located in the outer part of the breast. The majority of the patients had a ductal carcinoma (547) and a lobular carcinoma (47),

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the remaining either being mixed (23) or of different histology (46). The average size of the primary carcinoma was 18.9 mm (Table 1).

surgery of internal mammary nodes

In the great majority of the patients, one intercostal space was surgically explored. The second space was examined in 405 patients, the third space in 240 and the first and fourth space in seven and seven patients, respectively. In four cases, the second and third spaces were explored simultaneously. The exploration of the internal mammary chain (IMC) occurred in the course of breast-conserving surgery (quadrantectomies) in 597 cases and of mastectomies in 66 cases.

In 254 cases, the surgeon's exploration was guided by a gamma probe after the radiotracer injected close either to the primary tumor or to the pectoralis fascia was uptaken by one or more internal mammary nodes. In the cases that did not show hot nodes, the policy to decide which intercostal space to explore was on the basis of the anatomy of the lymphatic flow to the internal mammary nodes. It was decided in fact to explore the second interscostal space when the carcinoma was located at the superomedial quadrant and the third intercostal when it was located in the inferomedial quadrant of the breast.

In all patients submitted to breast-conserving surgery, the intercostal space to be explored was reached through the surgical incision utilized for the removal of the primary carcinoma. In 431 cases (65.0%), one lymph node was removed, in 111 cases (16.7%) two nodes, in 35 cases (5.3%) three nodes and in eight cases (1.2%) four nodes were removed. In a limited number of cases (78, 11.8%), no nodes were found. These cases were classified as negative.

With the surgical technique herewith described, the number of surgical complications was very limited: eight cases of small pleural lesions and one case of transitory costal osteomyelitis.

Table 1. Patients' characteristics and stratification for internal mammary chain (IMC) lymph nodes status

	Classification	Total, *n* (%)	IMC+, *n* (row%)	Univariate *P* value[a]	Multivariate odds ratio and 95% CI[b]
All patients		663	68 (10.3)		
Age (years)	<35	48 (7.2)	8 (16.7)	0.046	NS
	35–50	314 (47.4)	38 (12.1)		
	≥51	301 (45.4)	22 (7.3)		
Laterality	Right	337 (50.8)	30 (8.9)	0.243	–
	Left	326 (49.2)	38 (11.7)		
Size of tumor (cm)	≤1	103 (15.6)	2 (1.9)	0.004	1.2 (1.0–1.5)
	1.1–2	353 (53.3)	33 (9.3)		
	>2	206 (31.1)	33 (16.0)		
Tumor location	Inner quadrants	520 (78.4)	54 (10.4)	0.116	–
	Areola region	24 (3.6)	5 (20.8)		
	Supraareolar or underareolar region	112 (16.9)	8 (7.1)		
	Outer quadrants	7 (1.1)	1 (14.3)		
Axillary status	Negative	430 (64.9)	17 (4.0)	<0.001	4.1 (2.2–7.7)
	Positive	233 (35.1)	51 (21.9)		
No. of positive axillary nodes	1	125 (18.9)	26 (20.8)	0.877	–
	2–4	63 (9.5)	14 (22.2)		
	≥5	45 (6.8)	11 (24.5)		
Histotype	Ductal	547 (82.5)	58 (10.6)	0.653[c]	–
	Lobular	47 (7.1)	4 (8.5)		
	Mixed	23 (3.5)	3 (13.0)		
	Other	46 (6.9)	3 (6.5)		
Estrogen receptors	Negative	112 (16.9)	11 (9.8)	0.868	–
	Positive	551 (83.1)	57 (10.3)		
Progesterone receptors	Negative	163 (24.6)	16 (9.8)	0.831	–
	Positive	500 (75.4)	52 (10.4)		
Grading	G1	122 (18.7)	7 (5.7)	0.153	–
	G2	286 (43.7)	31 (10.8)		
	G3	246 (37.6)	30 (12.2)		
Ki-67 (%)	<20	325 (49.2)	26 (8.0)	0.057	NS
	≥20	336 (50.8)	42 (12.5)		
Vascular invasion	Present	180 (27.1)	41 (22.8)	<0.001	2.6 (1.4–4.5)
	Absent	483 (72.9)	27 (5.6)		

[a]Univariate analysis: associations between IMC lymph nodes status and other clinicopathologic features are tested using the chi-square test or the Fisher's exact test.

[b]Multivariate analysis: clinicopathologic features statistically significant on univariate analysis are tested using a multivariate logistic model, with age, size of tumor and Ki-67 considered as continuous variables; CI, confidence interval; NS, non significant.

[c]Only ductal and lobular histotypes are compared.

pathology

Forty-four percent of the patients had a primary carcinoma of grade 2, 38% of grade 3 and 18% of grade 1. The proliferative index, evaluated with the Ki-67 test, showed values of 25.6% as average with a median of 21%. Estrogen receptor-positive tumors were 83% and progesterone positive 75%. The axillary sentinel node biopsy was done in 567 patients, which was negative in 408 patients (72%).

lymphoscintigraphy

The great majority of the patients (623, 94%) were submitted to lymphoscintigraphy with 99Tc to identify the sentinel lymph node at the axilla or other different sites. In 348 cases, the injection of the radiotracer was carried out either in the peritumoral region or in a deep position close to the pectoralis major fascia and in 188 was done in the subdermal space. In 80 cases, the injection was carried out both in the peritumoral region and in the subdermal space. In seven cases, the injection was done in the areola region, while in 40 cases no lymphoscintigraphy was carried out. In 254 cases, the internal mammary biopsy was radioguided, having the radiotracer visualized the uptake in a specific internal mammary node.

radiotherapy

Patients treated with breast-conserving surgery (quadrantectomy) received adjuvant radiotherapy either from an external source or through an electron intraoperative therapy (ELIOT).

When internal mammary nodes metastases were detected, RT was administered on the IMC. Treatment was planned with a three-dimensional planning system and technical parameters of irradiation were individually adjusted in order to encompass the target with adequate margins. The IMC was contoured by the identification of the internal mammary vessels, from the first intercostal space to the top of the fourth rib. The exclusion of the lower spaces allowed sparing myocardium.

The internal mammary nodes were treated with a separate anterior angled electron and photon beam field, with limited inclination of 10–15° in order to minimize the under dosage at the junction (cold triangle) with the tangential breast field. The prescribed dose was 50 Gy in 2 Gy fractions over a period of 5 weeks, delivered by mixing electrons and Mega Volt photons.

Dose volume histograms were produced quantifying the volume of homolateral irradiated lung and heart. The mean volume of heart in left-sided breast receiving >30 Gy was <5% and the mean volume of ipsilateral lung receiving >20 Gy was <20%. In patients in whom these constraints could not be reached, the intensity modulated radiotherapy technique was applied, enabling to further reduce the heart and lung doses to <1% and 15%, respectively [20].

statistical methods

Associations between IMC lymph nodes status and other clinicopathological features were tested using the chi-square test or the Fisher's exact test. Clinicopathologic features statistically significant on univariate analysis were tested using a multivariate logistic model and odds ratios with 95% confidence intervals were calculated.

Disease-free survival was calculated from date of surgery to any local, regional, distant relapse or death from breast cancer, whichever occurred first, or to last visit date in case of no events. It was computed in a competing risk framework and compared across different subgroups by means of the Gray test. Overall survival was defined as the time interval from date of surgery to death from any cause or to last date of follow-up and it was compared across different subgroups by means of the log-rank test.

All analyses were carried out with the SAS software (SAS Institute, Cary, NC). All tests were two-sided.

results

Out of the 663 cases of all series, there were 233 cases (35.1%) with positive axillary nodes, while the internal mammary nodes were involved in 68 cases (10.3%). Altogether there were 250 patients with regional node involvement. In 182 cases, axillary nodes only were involved, in 51 cases both nodal stations were involved and in 17 cases internal mammary nodes only were positive. Out of all cases with regional node metastases in 27.2% (68 out of 250) the internal mammary nodes were involved.

Internal mammary metastases were equally distributed between the second (39 out of 409 explored) and the third (28 out of 244 explored) intercostal spaces. The first space was explored in seven cases (one positive) and the fourth space was explored in seven cases without any metastatic node.

The rate of involvement was more frequent (12.7%) in women of ≤50 years than in women older than 50 years (7.3%) and was greatly conditioned by the size of primary carcinoma: in tumors of ≤10 mm in maximum diameter the internal mammary nodes were rarely involved (1.9%), in cases between 11 and 20 mm the involvement raised to 9.3% while larger tumors showed a higher rate of internal mammary node metastases (16.0%). Two parameters were important to determine the risk of internal mammary invasion: presence of peritumoral vascular invasion (22.8%) and presence of axillary metastases (21.9%) (Table 1). Grading, estrogen, progesterone receptors and proliferative rate had no influence on the internal mammary involvement. Histological type was not significantly important, although lobular carcinoma showed less internal mammary metastases than the ductal and tumors with well-differentiated histology seldom showed metastases (5.7%).

Correlating the positivity of the IMC with the characteristics of the primary carcinomas in the multivariate analysis, it appeared that the three factors influencing the IMC involvement are, in order of importance: (i) the presence of histological peritumoral vascular invasion in the primary carcinoma, (ii) the presence of axillary node metastases and (iii) the size of the primary tumor.

When considering patients with negative axilla, the only pathologic feature influencing the presence of metastases in the IMC was the peritumoral vascular invasion status (Table 2).

Out of the 254 radioguided cases, 28 (11.0%) showed metastatic involvement. Out of the other 409 cases, for which the internal mammary biopsy was not radioguided because no hot nodes were present, 40 showed positive nodes (9.8%). It appeared therefore that no advantages were found in terms of identification of involved internal mammary nodes, with the use of a radiotracer. Patients were accurately followed up with annual mammography, chest X-ay ultrasound scan of the breast and the liver. The median follow-up time was 46 months (range 5–112). Events are described in Table 3. Overall survival according to IMC status is described in Figure 1, while overall survival according to axillary and IMC combined status is described in Figure 2.

Patients without regional node metastases enjoyed a very good overall survival, 97% at 5 years, while cases with regional node involvement, axillary and/or internal mammary,

Table 2. Patients' characteristics and stratification for internal mammary chain (IMC) lymph nodes status in patients with negative axillary lymph nodes

	Classification	Total, *n* (%)	IMC+, *n* (row%)	Univariate *P* value[a]	Multivariate odds ratio and 95% CI[b]
All patients		430	17 (4.0)		
Age (years)	<35	26 (6.0)	2 (7.7)		
	35–50	186 (43.3)	7 (3.8)		
	≥51	218 (50.7)	8 (3.7)	0.600	–
Laterality	Right	221 (51.4)	7 (3.2)	0.399	–
	Left	209 (48.6)	10 (4.8)		
Size of tumor (cm)	≤1	88 (20.5)	0 (0.0)	0.001	NS
	1.1–2	234 (54.6)	9 (3.8)		
	>2	107 (24.9)	8 (7.5)		
Tumor location	Inner quadrants	353 (82.1)	15 (4.3)	0.427	–
	Areola region	8 (1.9)	0 (0.0)		
	Supraareolar or underareolar region	64 (14.9)	2 (3.1)		
	Outer quadrants	5 (1.2)	0 (0.0)		
Histotype	Ductal	348 (80.9)	14 (4.0)	0.649[c]	–
	Lobular	35 (8.2)	2 (5.7)		
	Mixed	10 (2.3)	0 (0.0)		
	Other	37 (8.6)	1 (2.7)		
Estrogen receptors	Negative	78 (18.1)	4 (5.1)	0.525	–
	Positive	352 (81.9)	13 (3.7)		
Progesterone receptors	Negative	115 (26.7)	6 (5.2)	0.410	–
	Positive	315 (73.3)	11 (3.5)		
Grading	G1	101 (23.9)	4 (4.0)	0.356	–
	G2	161 (38.1)	4 (2.5)		
	G3	161 (38.1)	9 (5.6)		
Ki-67 (%)	<20	216 (50.5)	5 (2.3)	0.076	NS
	≥20	212 (49.5)	12 (5.7)		
Vascular invasion	Present	61 (14.2)	10 (16.4)	<0.001	8.9 (3.2–24.9)
	Absent	369 (85.8)	7 (1.9)		

[a]Univariate analysis: associations between IMC lymph nodes status and other clinicopathologic features are tested using the chi-square test or the Fisher's exact test.

[b]Multivariate analysis: clinicopathologic features statistically significant on univariate analysis are tested using a multivariate logistic model, with size of tumor and Ki-67 considered as continuous variables; CI, confidence interval; NS, non significant.

[c]Only ductal and lobular histotypes are compared.

Table 3. Description of first events and stratification for internal mammary chain (IMC) lymph nodes status

Description of first events	All patients ($N = 663$)		IMC+ ($N = 68$)		IMC− ($N = 595$)	
	n	%	*n*	%	*n*	%
Deaths (any cause)	24	3.6	4	5.9	20	3.4
Local or regional	25	4.5	5	7.4	20	4.2
Distant	35	5.3	3	4.4	32	5.4
Bone	12	1.8	1	1.5	11	1.8
Liver	9	1.4	0	0.0	9	1.5
Lung	4	0.6	0	0.0	4	0.7
Other or multiple sites	10	1.5	2	2.9	8	1.3
Local and distant	1	0.2	0	0.0	1	0.2
Second ipsilateral tumor	5	0.8	0	0.0	5	0.8
Contralateral breast tumor	7	1.1	3	4.4	4	0.7
Other primary tumor	7	1.1	2	2.9	5	0.8

showed a 5-year survival ~92%. The survival of patients with internal mammary involvement only was similar to the survival of patients with axillary involvement only (Table 4). The survival of all patients with axillary metastases was compared with the survival of all patients with internal mammary node metastases: the curves show that the survival

was very similar in the two subgroups (Figure 3), confirming our previous results [2, 21] which showed that the prognostic power of internal mammary node involvement is similar to that of axillary involvement.

discussion

The lymphatic flow which originates in the breast is directed through the lymphatic ducts to the axillary nodes and to the internal mammary nodes. The two primary lymphnodal stations are considerably different, the axillary one being composed by an average number of 25 lymph nodes, while the IMC contains an average of four to five lymph nodes. The latter nodes are situated in the parasternal region posterior to the first, second, third and fourth intercostals spaces and are generally of smaller size than the axillary nodes [22]. Also functionally the two nodal stations are different. In the axilla, the lymph flows upward from the lower portion of the axillary and the spread of cancer cells from a breast carcinoma involves initially the lower lymph nodes of the first level, then the intermediate ones of the second level and finally the lymph nodes of the third level situated in the subclavicular space, defined also as the apex of the axilla. This regularity of the axillary lymphatic spread is an important premise to the sentinel node biopsy methodology. The situation is different as regards the internal mammary nodes. Here, the lymphatic flow from the mammary gland reaches the internal mammary nodes through tiny lymphatic vessels of each intercostal space. The lymph coming from the upper portion of the breast flows to the internal mammary nodes at the level of the first and second intercostal space while the lymph originated in the lower part of the mammary gland reaches the internal mammary nodes at the third and fourth space. The sentinel node concept does not apply therefore to this nodal station as there is not a node which predicts whether the other lymph nodes are involved or not involved, which is the basis for the 'sentinel' node concept.

This observation clearly explains why we did not find differences in terms of nodal positivity among cases in which the internal mammary biopsy was guided by the gamma probe and among patients who had a not-radioguided internal mammary biopsy, which was only on the basis of the anatomical site of the primary carcinoma: second intercostal space

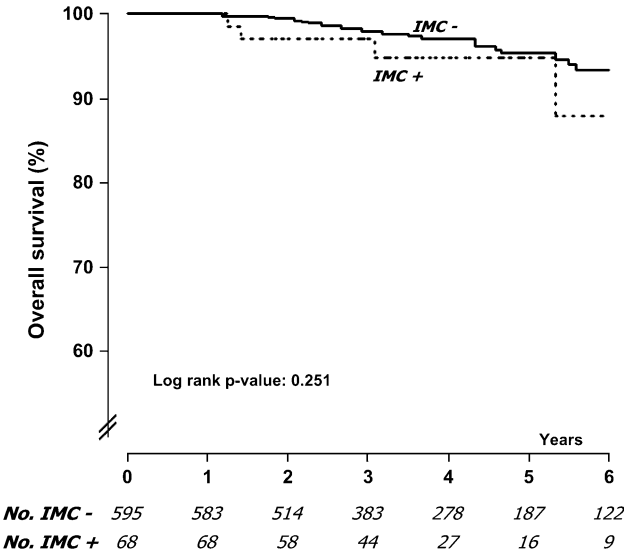

Figure 1. Overall survival stratified according to internal mammary chain (IMC) status.

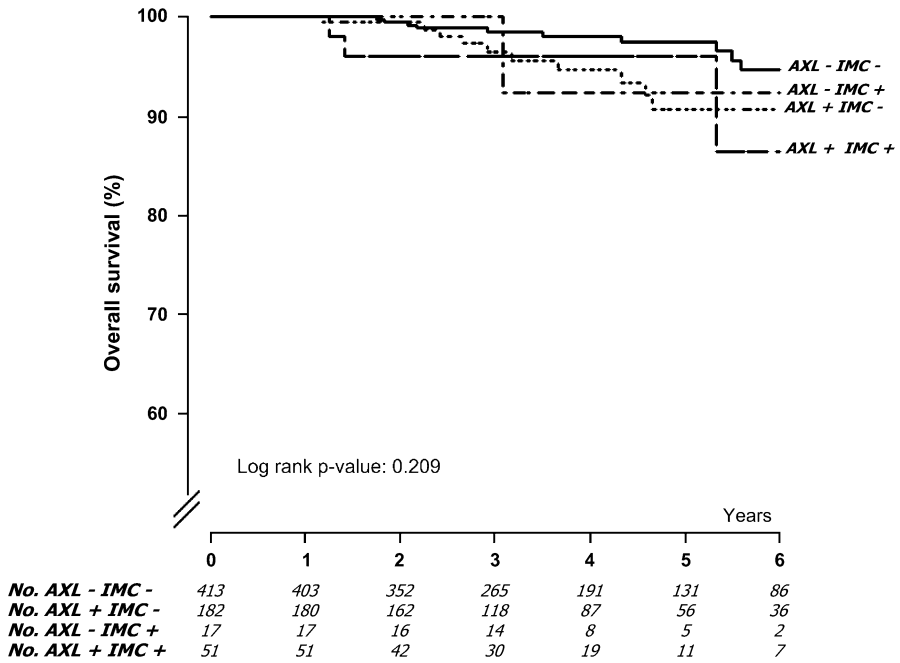

Figure 2. Overall survival stratified according to axillary and CMI status.

Table 4. Univariate analysis: survival stratified according to internal mammary chain (IMC) lymph nodes status and clinicopathologic features associated to IMC status

	Classification	Number at risk	Disease-free survival[a]		Overall survival	
			No. of events (5-year survival %)	*P* value[a]	No. of events (5-year survival %)	*P* value[b]
All patients		663	64 (83)		24 (95)	
Age (years)	<35	48	3 (82)	0.333	3 (87)	0.259
	35–50	314	31 (82)		8 (97)	
	≥51	301	27 (87)		13 (95)	
Size of tumor (cm)	≤2	454	29 (90)	<0.001	10 (97)	<0.001
	>2	206	35 (69)		14 (90)	
Axillary status	Negative	430	27 (92)	0.002	11 (97)	0.046
	Positive	233	37 (80)		13 (92)	
IMC status	Negative	595	55 (85)	0.401	20 (95)	0.251
	Positive	68	9 (78)		4 (95)	
Combined status	AXL−/IMC−	413	22 (91)	<0.001	10 (97)	0.209
	AXL+/IMC−	182	33 (73)		10 (91)	
	AXL−/IMC+	17	5 (67)		1 (92)	
	AXL+/IMC+	51	4 (84)		3 (96)	
Ki-67 (%)	<20	325	17 (91)	<0.001	5 (98)	0.002
	≥20	336	47 (77)		19 (92)	
Vascular invasion	Absent	483	35 (69)	0.001	13 (97)	0.021
	Present	180	29 (89)		11 (91)	

[a]Events: any local, regional or distant relapse (61 events) or deaths from breast cancer without previous relapse (three events). Differences in survival between strata are tested using the Gray test in a competing risk framework.
[b]Differences in survival between strata are tested using the log-rank test.

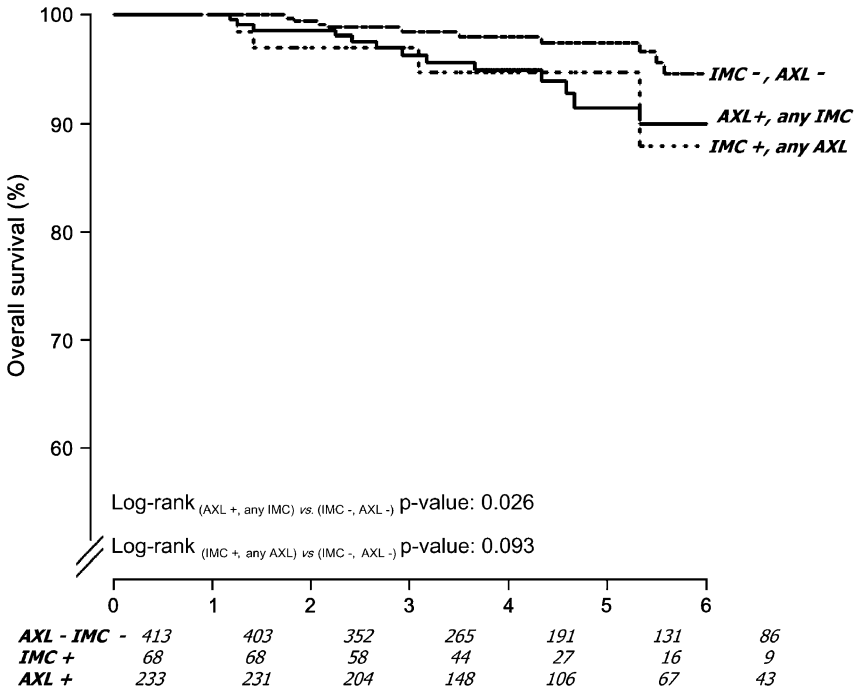

Figure 3. Overall survival in regional negative patients and axillary or internal mammary positive patients.

explored in tumors of the upper inner quadrants and third intercostal space explored in tumors of the lower inner quadrants.

As regards the visualization of internal mammary nodes by the lymphoscintigraphy, our rate of identification (254 of 623, 40.8%) is much higher than in most series. Generally, with the common lymphoscintigraphic methods used to identify the axillary sentinel nodes, the rates of positive cases at the internal mammary nodes are very low, ranging from 4%–8% [4, 9, 10] to 17%–18% [11–13]. The high rate in our cases is due to the fact that in the majority of our cases (428), the injection of the

radiotracer was carried out either in the peritumoral region or in a deep position close to the pectoralis major fascia. In fact in a previous study [23], we showed that a good visualization of internal mammary nodes is possible only when the radiotracer injection is carried out in a deep space close to the muscular fascia.

In spite of the fact that the spread from a breast carcinoma is directed to two different lymphatic station, breast surgeons have been interested mainly in one of the two stations (the axillary one), ignoring to great extent the other one. This attitude could have been explained in the past when the regional nodes were removed mainly for therapeutic reasons, as a randomized trial conducted in the 60s showed no advantages in survival with the dissection of the internal mammary nodes [3, 24].

However, their impact on prognosis was clear so that in the present view of the 'staging' role of surgery the exploration of internal mammary nodes becomes important. In an analysis of 1035 cases of the 60s and 70s treated with internal mammary node exploration, it appeared that prognosis was greatly worsened when there was an implication of the internal mammary nodes [2].

In the present series, 27% of regional node metastases were at the internal mammary nodes. How to make use of this information? The first is to assess the prognosis. The prognosis is worsened by the internal mammary node involvement and there is a 'stage migration'. The patients with internal mammary node metastases and no axillary involvement who would be considered stage I with excellent prognosis, become stage II, with a more serious outcome and a need for appropriate adjuvant systemic treatments. The second issue regards the local regional treatment to be applied when an internal mammary node metastasis is discovered. The therapeutic policy should be consistent with the policy currently in force as regards axillary nodes, which if involved are either surgically removed or treated with radiotherapy. For the sake of consistency also the internal mammary nodes should deserve the same management. As the complete surgical dissection of the internal mammary nodes is not easy, radiotherapy is a logical option. Moreover, it is likely that radiotherapy on the internal mammary nodes is more effective than surgical dissection, because radiotherapy encompasses a wider area of tissues to be sterilized. In particular, radiotherapy may prevent pleural metastatization by destroying cancer foci involving superficially the pleura [17].

Considering this risk, in many centers, the treatment of the IMC with radiotherapy to all patients with tumor in the inner quadrants of the breast has become a routine [25]. We believe that this policy may represent an overtreatment, while a more targeted approach, with radiotherapy limited to patients with internal mammary nodes metastases appear a logical and rational solution.

The high survival rates of patients with internal mammary metastases may appear rather surprising, considering that for many decades the internal mammary involvement was considered an ominous prognostic sign. In the 60s, the great surgeon C. D. Haagensen, who investigated the internal mammary involvement in a large series of case, declared that whenever metastases were present at the internal mammary nodes the patient had to be considered ineligible and incurable. The comparison between our previous series, when patients with positive internal mammary nodes did not receive radiotherapy [26, 27], and the present series, where they had internal mammary node radiotherapy, shows considerable survival differences. It appears that the internal mammary nodes involvement is not a detrimental prognostic factor as it appeared 30 years ago and is reasonable to believe that the good results of today might in part be due to the selective radiotherapy to IMCs. To demonstrate that radiotherapy on IMC is beneficial, a randomized study comparing patients with positive internal mammary nodes receiving or not receiving radiotherapy on the parasternal region is strongly needed.

conclusions

A complete mapping of regional node involvement in breast cancer cases cannot ignore the internal mammary node chain. We are surprised to see the sophistication of the search for micrometastases and isolated tumor cells in the axillary sentinel node with innumerable histological sections, and the use of immunohistochemistry and PCR to improve minimally the prognostic evaluation of the case, while the internal mammary nodes are completely ignored by the great majority of the surgeons and pathologists. We believe that this inconsistency should be corrected and the internal mammary nodes chain regularly explored. The surgical technique is simple, without important complications and requires no more than 10- to 15-min prolongation of the surgical session. The main indication refers to the patients with a breast carcinoma located in the medial portion of the breast. As the positivity of internal mammary nodes is rather high in cases with axillary metastases, the exploration of the IMC in those cases should be seriously considered. The therapeutic value of IMC radiotherapy, according to the results of our study, seems to be considerable, but a final correct judgment may be obtained by a controlled randomized trial.

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