

Axillary treatment of patients with breast cancer and micrometastatic disease in the sentinel lymph node

Our experience



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Axillary treatment of patients with breast cancer and micrometastatic disease in the sentinel lymph node. Our experience.

AIM: Since the introduction of the sentinel lymph node biopsy (SLNB) in patients with breast cancer, micrometastases are detected frequently in the sln.

PATIENTS AND METHODS: Between July 2005 and June 2016, 1244 patients were submitted to surgery for breast cancer. 431 patients cT1-2 N0 underwent to sentinel lymph node (SLN) and micrometastases were found in 68 of 431 screen-detected patients. Nearly all patients with both micro and macrometastases had axillary lymph node dissection (ALND).

RESULTS: The SLN was negative in 69% of patients (296 of 431), 121 patients (28%) instead turned positive for lymph node metastases and in 14 patients (3%) were identified isolated tumor cells (ITC). SLN micrometastases were detected in 15,7% of patients (68 of 431). All patients with micrometastases underwent a completion ALND. In 85% of cases, therefore, the sentinel node with micrometastases was the only site of nodal disease. Neither loco-regional recurrences or distant metastases occurred in any of the Patients with sln micrometastases.

DISCUSSION: There is considerable interest in foregoing axillary dissection (AD) when the sentinel node (SN) is positive in early breast cancer, particularly when axillary involvement is minimal (micrometastases or isolated tumor cells). Several trials are addressing the problem. In breast cancer patients survival is not affected by the presence of micrometastatic lymph node involvement.

CONCLUSION: In our experience we always underwent to ALND all patients with micrometastases. In the light of the results we observed our attitude no longer provides for the axillary lymphadenectomy.

KEY WORDS: Axillary dissection ,Breast cancer, Sentinel Lymph Node Biopsy

Introduction

Axillary lymph node status at the time of diagnosis remains one of the most important prognostic indicators for women with breast cancer. The presence of lymphogenic

metastases and number of lymph nodes involved significantly contribute to adjuvant systemic treatment decision; in fact they are associated with an increased probability of recurrence and mortality. The goal of axillary lymph node dissection is to provide accurate staging information and local control of disease. However, the procedure has many potential complications, including lymphedema, persistent seroma, shoulder disfunction and paresthesias. Nowadays, sentinel lymph node biopsy (SLNB) provides information on the axillary node status with lower morbidity than complete axillary lymph node dissection (ALND). Therefore,

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according to the results of several international randomized trials SLNB is considered the standard of care for patients with early breast cancer and negative axillary nodes. The complexity of breast tumor biology has changed cancer treatments, consequently the choice of administering systemic therapy is influenced by a variety of clinical and pathology-related factors, with lymph node tumor status influencing but not necessarily dictating the use of chemotherapy. These evolving concepts have called into question the need for ALND, especially for limited sentinel lymph node involvement. Published data suggest that the absence of metastatic tumor cells in the sentinel lymph node accurately predicts the absence of metastases in the remaining axillary nodes in 95-100% of cases. Actually, SLNB may be more sensitive to detect metastases than axillary node dissection. Compared with analysis with hematoxylin and eosin (H&E) only in axillary lymph node dissection specimens, the use of step sectioning and immunohistochemistry in the sentinel lymph node results in a more accurate histopathologic examination and is associated with a higher detection rate of small metastases (micrometastases and isolated tumor cells). In the 7th edition of the AJCC staging system the concept of "micrometastases" (N1mi) has been introduced in the official staging criteria: micrometastasis is defined as a metastases measuring from 0.2mm to not more than 2.0mm. However, the prognostic significance of micrometastases in the sentinel node is currently unclear and creates a new dilemma in the clinical management of patients with breast cancer¹.

Micrometastases or sub-micrometastases can be detected by standard histopathological method sometimes associated with immunohistochemistry in lymph nodes, bone marrow and blood. The consequence of these small size involvement may be prognostic and therapeutic. Two factors are necessary to assess this kind of involvement: the rate of involvement of non-sentinel lymph node after axillary lymph node dissection and significative difference of survivals. The rate of involvement of non-sentinel lymph node in case of micrometastases or sub-micrometastases is different from the rate of involvement in case of no lymph node metastases (7 to 8%) or in case of macrometases (30 to 50%). Micrometastase is an important factor to determine the rate of involvement of non-sentinel lymph node, the overall or disease free survival and to assess the need of radiotherapy and chemotherapy. In conclusion, micrometastases and sub-micrometastases have a clinical impact even if complementary axillary lymph node dissection is still discussed².

Patients and Methods

Between July 2005 and June 2016, a total of 431 SLNB procedures were performed. Inclusion criteria for the

present study were as follows: (1) presence or not presence of palpable breast cancer, (2) tumor size clinically ≤ 3 cm in diameter, and (3) absence of clinically palpable suspicious axillary lymph nodes. All patients were underwent to biopsy and MRI before the surgery. Written informed consent was obtained from all them. Lymphoscintigraphy was performed preoperatively to identify lymphatic flow to axillary and/or parasternal lymph nodes. Micrometastases are defined on the basis of a size of >0.2 mm to ≤ 2 mm in diameter according to the 2003 International Union Against Cancer (UICC) classification. Therefore, isolated tumor cells or tumor cell clusters measuring <0.2 mm in diameter did not meet the definition of micrometastases. Patients with submicrometastases (UICC, ≤ 2 mm) were considered node negative for this investigation. Patients with SLN macrometastases and micrometastasis immediately underwent ALND level I, II and III. After breast-conserving surgery, patients received adjuvant radiotherapy. Adjuvant therapy consisted of hormone treatment and/or chemotherapy.

Results

Between July 2005 and June 2016, 1244 patients were submitted to surgery for breast cancer. 431 of these underwent to sentinel lymph node biopsy (SLNB) in case of early stage breast cancer (cT1-2 N0). On average they were found 2 lymph nodes per patient. The SLN were tumor-free in 296 (69%) and positive in 121 patients (28%). In 14 patients (3%) were identified isolated tumor cells (ITC). In positive patients, we identified in 53 cases (44%) partial or massive metastases and in 68 cases (56%) micrometastases. In patients with partial or massive metastases in about half of cases (53%) we did not find other metastatic lymph nodes. In patients with micrometastases, only 15% have identified other positive lymph nodes, with an average of 1.7 to 29 lymph nodes removed. In 85% of cases then the sentinel node with micrometastases was the only site of nodal disease. In 5% of cases we identified the lymph node positive near sentinel while the sentinel node was negative. Immunohistochemistry was used when there were difficulties in the BLS study with the only hematoxylin-eosin. In these cases we found micrometastases in 14% of cases observed. In 2 patients (0,5%) the sentinel node has not been identified. We never made the BLS when the patient underwent to chemotherapy. All patients with SLN micrometastases (n = 68) underwent formal completion level I, II and III ALND.

The characteristics of the patients with micrometastases undergoing SLNB are expressed in Tab I. No local, axillary, or distant recurrences were observed during a median follow-up of 72 months.

TABLE I - Patient and tumor characteristics

Parameters	Characteristics	%
Age	41-82 range 61.7 medium age	
Tumor size (cm)	0.9 – 2.5 1.6 medium size	
T stage	N.	
T1a	5	7%
T1b	14	21%
T1c	38	56%
T2	11	16%
T3	0	0%
T4	0	0%
Histology	Ductal 49 Lobular 14 Other 5	72% 21% 7%
Histological grading	G1 4 G2 36 G3 28	6% 53% 41%
Surgery	Mastectomy 3 Quadrantectomy 63 Other 2	5% 92% 3%
Recurrence of disease	Local recurrence 0 Regional recurrence 0 Distant metastases 0	0% 0% 0%

Discussion

The sentinel lymph node (SLN) biopsy has emerged as the standard staging method in evaluating the axillary lymph node status in early-stage breast cancer patients and has replaced level I, II and III axillary lymph node dissection (ALND) in many institutions. Many studies have proved the accuracy and the high negative predictive value of the SLN procedure³. There is considerable interest in foregoing axillary dissection (AD) when the sentinel node (SN) is positive in early breast cancer, particularly when axillary involvement is minimal (micrometastases or isolated tumor cells). In fact, clinical practice has run ahead of the evidence, since recent population-based data indicate that AD is 'under-used' in breast cancer patients when the SN is positive. Several trials are addressing the problem (IBCSG 23-01, ASCOG Z0011, EORTC AMAROS) (4). Only Z0011 has published interim results, finding, after a median follow-up of 6.3 years, no differences in locoregional recurrence or regional recurrence between patients, with a positive SN, who received AD vs. no further axillary treatment. In this retrospective study evaluated patients with micrometastases or isolated tumor cells in the SN who

received no further axillary treatment. The authors found high five-year survival and low cumulative incidence of axillary recurrence, supporting the findings of Z0011 and justifying the increasingly common practice of foregoing AD in women with minimal SN involvement. It is important to sound a note of caution however: if axillary dissection is not always necessary in women with a positive axilla, it seems important to be able to reliably identify the patients at high risk of developing overt axillary disease who should receive elective AD. Ancillary analyses of the IBCSG 23-01 and AMAROS trials, still in follow-up, may be able to do this.

Between January 2000 and January 2003, 1411 patients with a cT1-2N0 invasive breast carcinoma underwent surgery in 7 hospitals in the Netherlands. Sentinel lymph node biopsy was done in all patients⁵. Based on lymph node status, patients were divided into 4 groups: pN0 (n = 922), pN1micro (n = 103), pN1a (n = 285), and pN1b (n = 101). Median follow-up was 6.4 years. At the end of follow-up, 1121 women were still alive (79.4%), 184 had died (13.0%), and 106 were lost to follow-up (7.5%). Breast cancer recurred in 244 patients: distant metastasis (n = 165), locoregional relapse (n = 83), and contralateral breast cancer (n = 44). Following adjustment for possible confounding characteristics and for adjuvant systemic treatment, overall survival (OS) remained comparable for pN0 and pN1micro and was significantly worse for pN1a and pN1b (hazard ratio [HR] 1.18; 95% confidence interval [95% CI] 0.58–2.39, HR 2.47; 95% CI 1.69–3.63, HR 4.36; 95% CI 2.70–7.04, respectively). Disease-free survival (DFS) was similar too in the pN0 and pN1micro group, and worse for pN1a and pN1b (HR 0.96; 95% CI 0.56–1.67 vs HR 1.64; 95% CI 1.19–2.27, HR 2.95; CI 1.98–4.42). The distant metastases rate also did not differ significantly between the pN0 and pN1micro group and was worse for pN1a and pN1b (HR 1.22; 95% CI 0.60–2.49, HR 2.26; 95% CI 1.49–3.40, HR 3.49; CI 2.12–5.77). In breast cancer patients survival is not affected by the presence of micrometastatic lymph node involvement.

Between November 2000 and December 2006, SLN biopsy was successfully performed in 1178 patients with invasive breast carcinoma⁶. Only patients with macrometastasis (>2 mm) underwent ALND, while patients with negative SLN or micrometastases did not undergo further treatment of the axilla, by either surgery or radiotherapy. Regarding adjuvant therapy decision, patients with SLN-micrometastases (pN1) were considered as node-positive patients. Of 1,178 patients, 59 (5%) had micrometastases. Of those with micrometastases, 14 (24%) underwent ALND because the intraoperative study of the SLN yielded a positive result. With a median follow-up of 60 months (range, 8–94), none of the patients with SLN micrometastases in whom ALND was omitted developed an axillary recurrence, while one patient in whom ALND was performed developed infraclavicular lymph node recurrence. One patient, who declined postoperative

breast irradiation, developed breast recurrence and distant metastasis. Breast cancer patients with SLN micrometastases in whom ALND was omitted had a very low locoregional failure rate. This study supports the theory that ALND might be avoided in these patients, providing that adjuvant systemic treatment equal to treatment provided to treat node-positive disease is administered. However, longer follow-up and results of additional prospective studies are needed.

From 1996 to 2005, breast cancer patients were enrolled in an Institutional Review Board-approved, multicenter study⁷. SLNs were examined at multiple levels by hematoxylin and eosin; most (85%) hematoxylin and eosin-negative SLNs were also examined by cytokeratin immunohistochemistry. Data from 1,259 patients with invasive breast cancer and in whom an SLN was found were reviewed for this analysis. Of the 1,259 patients, 893 (71%) had negative SLNs, 25 (2%) had ITCs, 57 (5%) had MIC, and 284 (23%) had positive SLNs. None of the 13 patients with ITCs who underwent an ALND had additional positive nodes, compared with 27% (11 of 41) of patients with MIC. At a mean follow-up of 4.9 years, the distant recurrence rates for SLN-negative, ITC, MIC, and SLN-positive groups were 6%, 8%, 14%, and 21%, respectively. The presence of MIC in the SLN was associated with a significantly shorter disease-free interval than was SLN negativity ($p < 0.02$ by Cox regression model). This prospective breast cancer study found that sentinel node MIC, but not ITCs, were associated with additional positive nodes and with distant recurrence. These data suggest that ALND may be unnecessary in patients with ITCs. But ALND and more aggressive adjuvant therapy should be considered in patients with SLN micrometastases.

In pN1mi patients, treated with mastectomy without adjuvant radiotherapy, current data are insufficient to support the omission of ALND⁸.

Completion axillary lympho node dissection performed as a standard procedure after a positive sentinel node biopsy in breast cancer patients results, in almost 40-70% of cases, in no additional positive nodes. A nomogram has been developed at Memorial Sloan Kettering Cancer Center (MSKCC) to predict the likelihood of non-sentinel node metastases of a positive sentinel node biopsy⁹.

Conclusions

The use of axillary dissection in patients with micrometastases is still actually controversial, however, for some authors it is an indication to follow. The surgical removal of subclinical nodal disease is associated with a benefit in terms of survival minimum, but still greater than zero, while for others the adjuvant systemic therapy and/or radiation would be opportune to treat these patients adequately. Micrometastases probably don't interfere with the

prognosis and management of breast cancer. In the absence of guidelines for level 1 with respect to the treatment of patients with micrometastases in the SLN, each case requires careful study on the tumor and the patient-related factors in the context of a multidisciplinary team. The identification of micrometastases remains highly dependent on the analytical technique used, and there exists the potential to stage the disease and to determine the suitable treatment¹⁰.

While several retrospective studies show that patients with micrometastases and isolated tumor cells in their sentinel node had a significantly worse disease-free and overall survival compared to node-negative patients, other studies could not confirm this observation.

Our experience, and that of many other influential Authors, who have not kept local or regional recurrence, or worsening of prognosis, leads us to believe the axillary lymphadenectomy is not necessary in cases of micrometastases in sentinel lymph nodes. The omission of ALND in patients with either micrometastasis involvement or ICT of SLN has been spreading in the international scientific community; however it is recognized that there is a significative risk even in a minority proportions of patients; for such a reason, at the same time, the search is aiming to detect those factors which are useful in predicting the presence of disease in NSLN and identifying at risk population¹¹.

Riassunto

Lo stato dei linfonodi ascellari al momento della diagnosi rimane uno dei più importanti indicatori prognostici per le donne affette da cancro al seno. La presenza di metastasi linfatiche ed il numero di linfonodi coinvolti contribuiscono significativamente alla decisione del trattamento adiuvante sistemico. In realtà essi sono associati ad un aumento della probabilità di recidiva e di mortalità. L'obiettivo della dissezione dei linfonodi ascellari è quello di fornire informazioni accurate sulla stadiazione e il controllo locale della malattia. Tuttavia la procedura può determinare complicanze come linfedema, sieroma persistente, disturbi funzionali alla spalla e parestesie. Nella 7° edizione del sistema di stadiazione AJCC il concetto di "micrometastasi" (N1mi) è stato introdotto nei criteri ufficiali: micrometastasi è definita come una metastasi di misura da 0.2mm a non più di 2,0 millimetri. Tuttavia, il significato prognostico di micrometastasi nel linfonodo sentinella è attualmente poco chiaro e crea un nuovo dilemma nella gestione clinica dei pazienti con cancro al seno.

Abbiamo voluto analizzare i risultati della nostra esperienza e confrontarli con quelli della letteratura ed abbiamo osservato che su 431 pazienti, afferenti agli stadi I e II (cT1-2 N0) e sottoposti, dal 2005 al 2016, a biopsia del linfonodo sentinella abbiamo osservato la negatività del linfonodo in 296 casi (69%) e la presenza di

metastasi linfonodali in 121 pazienti (28%). In 14 pazienti (3%) sono state identificate cellule tumorali isolate (ITC). Nei pazienti positivi sono stati identificati in 53 casi (44%) metastasi parziali o massive e in 68 casi (56%) micrometastasi. Nei pazienti con micrometastasi solo nel 15% abbiamo identificato altri linfonodi positivi, con una media di 1,7 su 29 rimossi. Nell'85% dei casi quindi il linfonodo sentinella con micrometastasi era l'unica sede di malattia linfonodale. Mentre diversi studi retrospettivi dimostrano che i pazienti con micrometastasi nel linfonodo sentinella hanno una prognosi significativamente peggiore e minore sopravvivenza globale rispetto ai pazienti con linfonodi negativi, altri studi non hanno confermato questa osservazione. Le micrometastasi probabilmente non interferiscono con la prognosi e la gestione delle pazienti affette da cancro al seno. In assenza di linee guida di livello 1 ogni caso richiede un attento studio sul tumore e dei fattori correlati al paziente nel contesto di un team multidisciplinare. La nostra esperienza, insieme a quella di molti altri A.A., che non hanno osservato recidiva locale o regionale, o peggioramento della prognosi, ci porta a credere che la linfadenectomia ascellare non è necessaria nei casi di micrometastasi nei linfonodi sentinella.

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