

The sentinel node biopsy is not contraindicated in multifocal breast carcinoma

La biopsia del linfonodo sentinella non è controindicata nel carcinoma multifocale della mammella

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Summary

Aim. Following the availability of the results of validation studies, the sentinel lymph node biopsy (SLNB) has replaced routine axillary dissection (AD) as the new standard of care in early unifocal breast cancers. Multifocal (MF) and multicentric (MC) tumours have been considered as a contraindication for this technique due to the possible incidence of a higher false-negative rate. In this retrospective study we try to demonstrate the usefulness of SLNB in MF/MC breast carcinoma. **Patients and Methods.** Eight hundreds and fifty-eight patients with breast carcinoma underwent a conservative surgery and sentinel node excision. Ninety-four out of 858 patients had histological diagnosis of multifocal breast carcinoma; out of these patients, 22 had SLN localization by both radio-colloid and blue dye, and 72 had localiza-

Riassunto

Scopo. Con la disponibilità degli studi di validazione, la biopsia del linfonodo sentinella (LS) ha sostituito completamente la pratica dello svuotamento ascellare imponendosi come unico standard di cura per i tumori unifocali della mammella diagnosticati precocemente. In questo studio retrospettivo cerchiamo di dimostrare l'utilità della biopsia del LS nel carcinoma mammario multifocale/multicentrico. **Pazienti e metodi.** 858 pazienti affetti da carcinoma mammario si sono sottoposti ad intervento conservativo ed exeresi del LS. Degli 858 pazienti, 94 hanno mostrato una diagnosi istologica di carcinoma mammario multifocale: in 22 è stato ricercato il LS mediante radiotraccianti e blue dye, mentre nei restanti 72 il LS è stato ricercato per mezzo del solo radiotracciante. **Risultati.** Con la sola tecnica radioisotopica il LS è

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tion by radio-colloid only. **Results.** Using radioisotope technique SLN was identified in 90/94 cases (95.7%). Using radioisotope technique and blue dye the SLN was identified in all 94 cases. SLNs were positive for metastases in 53 of the 94 cases (56.4%), in 39 cases (41%) were negative. The axillary dissection was performed in all 53 patients with positive SLNs: in 22 patients (41.5%) the SLN was the only site of axillary metastasis. None of the patients within this group experienced axillary recurrence at follow-up (median 54 months, ranging from 19 to 110 months). **Conclusions.** The high accuracy of SLNB in MF and MC breast cancer demonstrates, according to the results of other series published in the literature, that both MF and MC tumours do not represent a contraindication for SLNB anymore. *Eur. J. Oncol.*, 16 (2), 105-110, 2011

Key words: sentinel lymph node, multifocal breast cancer, multicentric breast cancer, axillary dissection

Introduction

The pathologic status of the axillary lymph nodes remains the most important prognostic indicator for patients with breast cancer and a major determinant of adjuvant treatment. Sentinel lymph node biopsy (SLNB) has a widely accepted evaluation and staging procedure for the axilla in patients with breast cancer, and this is mainly due to the minimal morbidity and the high degree of histology accuracy it provides. In order to ensure and maintain the high accuracy and low false-negative rate of the SLNB procedure, several selection criteria and relative contraindications for the procedure have been reported, together with few safety issues. These contraindications include multifocal or multicentric disease. The presence of multifocal invasive breast cancer was considered as a relative contraindication for the SLNB, since suspicions that the multiple tumours might involve more than one dominant lymphatic trunk draining to the regional axillary lymph nodes are present. Multiple lymphatic trunks might drain to

stato individuato in 90 dei 94 casi (95.7%). Usando entrambe le tecniche con marcatore radioattivo e blue dye il LS è stato individuato in tutti i 94 casi. I linfonodi individuati sono risultati positivi per metastasi in 53 dei 94 casi (56.4%), mentre nei restanti 39 casi (41%) questi sono risultati negativi. Lo svuotamento ascellare è stato effettuato in tutti i 53 pazienti con LS positivo e in 22 di essi il LS è risultato essere il solo sito di metastasi ascellare (41.5%). Al follow-up, in nessuno dei pazienti all'interno di questo gruppo si è evidenziata recidiva ai linfonodi ascellari (mediana 54 mesi, con un intervallo compreso tra 19 e 110 mesi). **Conclusioni.** L'elevata accuratezza dello studio del linfonodo sentinella nel tumore della mammella dimostra che sia i tumori multifocali che i multicentrici non rappresentano comunque una controindicazione alla biopsia del LS. *Eur. J. Oncol.*, 16 (2), 105-110, 2011

Parole chiave: linfonodo sentinella, cancro mammario multifocale, cancro mammario multicentrico, svuotamento cavo ascellare

different sentinel lymph node(s) and may be overlooked. However, with the use of lymphatic mapping and the increased experience in SLNB, there is now increasing evidence-based support of the theory that the lymphatic of the mammary gland drain through a few common afferent lymphatic trunks to specific axillary sentinel lymph nodes, regardless of the tumour location (1, 2). Ferrari et al (3) demonstrated that the tracer when injected in different quadrants of the breast, migrated in the upper outer quadrant were converged into a unique lymphatic channel which terminated in one or more SLN(s). Evidence obtained in the past few years about the functional anatomy of the lymphatic drainage of the breast supports the theory that all quadrants of the breast drain into same lymph node(s). Kim and colleagues reported five patients with multicentric breast cancer who had undergone a sentinel node mapping and biopsy procedure. Clinically each patient had carcinoma in two different quadrants of the breast. One tumour was mapped with technetium-labeled sulfur colloid and the other tumour was

mapped with isosulfan blue dye. In each case at least one node in the axilla was identified that was both hot and blue (4). This study is a retrospective analysis of the success rate, accuracy, and negative predictive value of SLN localization in multifocal or multicentric breast cancer patients using isosulfan blue vital dye and radio-colloid techniques.

Patients and methods

Between February 1999 and December 2008, 858 patients with breast carcinoma underwent a conservative surgery and sentinel node excision. Ninety-four out of 858 patients had histological diagnosis of multifocal breast carcinoma: all patients were women (age range, 29-77 y; mean age, 52.44 y). Out of these 94 patients, 22 had SLN localization by both radio-colloid and blue dye, and 72 had localization by radio-colloid only. A detailed report of both methods used to identify the SLN is entirely described in a previous trial performed by the Authors (5). In short, on the day before surgery, the radioactive tracer was injected peri-tumour by nuclear medicine physician if cancer was palpable. Ultrasound or mammographic localization was used for not palpable lesions. Colloidal particles of human albumin (Nanocoll, Sorin Biomedica, Saluggia, Italy) labelled with 300 mCi of ^{99m}Tc were used as radioactive tracer. A two-projection lymphoscintigram was used to identify any "hot spot" in the draining basin and skin marks were placed in order to facilitate axillary incision.

In the operating room, 2 ml of blue dye (Patent Blue V, Laboratoire Guerbert, Aulnay-sous-Bois, France) was injected in sub-dermal area, exactly above tumour location, and 5 minutes after the axillary incision near the hot spot was performed. Careful and bloodless dissection was performed to identify the blue lymphatic channels leading to the blue SLN. Additionally, a gamma probe (Neoprobe, Ethicon Endosurgery Inc, Cincinnati USA) was used to identify the hot SLNB. All hot and blue nodes were excised. Following removal of each node, the gamma probe was placed back into the wound to identify additional sentinel nodes. Suspicious palpable nodes detected during the procedure were also excised. All removed nodes were sent for definitive histologic evaluation.

Complete axillary dissection was performed whereas sentinel nodes contained metastases. Before 2003 histological examination of sentinel node was made on a few sections of the specimen such as lymph nodes of a typical axillary dissection; starting from March 2003 the number of sections was increased so that it was possible a complete examination of the whole sentinel node to detect micrometastases. Here is described the technique used at our Institution. First of all the SLN is sliced at 2 mm intervals perpendicular to long axis. One routine Haematoxylin-Eosin (H&E) stained section is examined; if negative, serial level slices are performed through each block (two sections for each level, with a spacing of 50 μm between the following levels). One segment for each level is stained with H&E and one is for an additional immuno-histochemical analysis with keratins to compare cluster of histologically suspected cells. This approach offers a good sensitivity for detection of micrometastases and isolated tumoral cells with reasonable costs.

Results

Out of the 94 patients with multifocal breast tumour, pT1a was present in 1 (1.06%) patient, pT1b in 11 (11.70%) patients, pT1c in 39 (41.48%) patients, pT2 in 43 (45.74%) patients. All patients were women (age range 29-77 y; mean age 52.44) (Table 1). Using radioisotope technique SLN was identified in 90/94 cases (95.7%). Using radioisotope technique and blue dye the SLN was identified in all 94 cases (100% identification rate). The mean number of SLNs detected was 1.8. The incidence of the number of sentinel nodes detected per patient was reported as follows: 1 sentinel node in 48 out of 94 pts (51.1%), 2 sentinel nodes in 26 out of 94 pts (27.6%), 3 sentinel nodes in 10 out of 94 pts (10.6%), and 4 or more sentinel nodes in 12 out of 94

Table 1 - Characteristics of the patients

pT	Multifocal breast cancer
1a	1 (1.06%)
1b	11 (11.7%)
1c	39 (41.5%)
2	43 (45.7%)

Table 2 - Characteristics of sentinel node

Sentinel node	Multifocal breast cancer
N0	39 (41%)
N ⁺	53 (56%)
Micrometastases	13 (12%)
Isolated tumoral cells	2 (2%)

Table 3 - Characteristics of axillary dissection in sentinel node positive

Axillary dissection	Multifocal breast cancer
N0	22 (41.5%)
N ⁺	31 (58.5%)
> 3N ⁺	6 (11%)
< 3N ⁺	25 (47%)

pts. (12.7%), respectively. SLNs were positive for metastases in 53 of the 94 cases (56.4%), including 13 cases of micrometastases and isolated tumoral cells in 2 cases; in 39 cases (41%) SLNs were negative (Table 2). The axillary dissection was performed in all 53 patients with SLNs positive: in 22 patients (41.5%) the SLN was the only site of axillary metastasis, sixty patients (11%) had a second positive lymph node and twenty-five patients (47%) had

more than three positive lymph nodes (Table 3). None of the patients within this group experienced axillary recurrence at follow-up (median 54 months and range 19 to 110 months).

Discussion

No uniformly accepted definition of multicentricity and multifocality in breast carcinoma is available; however, the most widely accepted definitions for multicentric was two or more carcinomas arising in separate quadrants of the breast separated by normal intervening breast tissue: the term multifocal breast cancer usually refers to the presence of separate foci of carcinoma in the same quadrant of the breast (6, 7). The incidence of multicentricity reported varies from 15% to 47% of mastectomy specimens (7, 8). MF/MC breast cancer has been reported in 9% to 75% of cases depending on the different examination methods employed (9). Recent large multicentre studies demonstrated that SLN could be used in clinically node-negative MF/MC breast cancer with identification rates and false-negative rates comparable with those in unifocal breast cancer. As shown in Table 4, despite of high variability among different studies, all retrospective series and some

Table 4 - Studies of Sentinel node biopsy in multifocal/multicentric breast cancer

Studies	Number of patients	Identification Rate	Sensitivity	Accuracy	False Negative Rate
Hill, 1999 (10)	60	91.7%	NR	NR	1.6%
Mertz, 1999 (11)	16	85%	100%	100%	0%
Schrenk, 2001 (12)	19	100%	100%	100%	0%
Jin Kim, 2002 (4)	5	100%	100%	100%	0%
Ozmen, 2002 (13)	21	85.7%	60%	77.8%	33.3%
Layeeque, 2003 (14)	40	100%	100%	100%	0%
Tousimis, 2003 (15)	70	96%	92%	96%	8%
Kumar, 2003 (16)	59	93.5%	100%	100%	0%
Goyal, 2004 (17)	75	94.7%	91.2%	95.8%	8.8%
Bergkvist, 2005 (18)	56	NR	85.7%	78.9%	21%
Gentilini, 2006 (19)	42	100%	95.2%	97.6%	4.8%
Knauer, 2006 (20)	142	91.5%	96%	97.3%	4%
Ferrari, 2006 (3)	31	100%	92.8%	96.8%	7.1%
D'Eredità, 2007 (21)	30	100%	93.7%	96.6%	6.7%
Holwitt, 2008 (22)	93	100%	93%	96.8%	7%
Fearmont, 2009 (23)	23	100%	NR	NR	15%
Solà, 2009 (24)	174	93.8%	NR	NR	NR
Bezu, 2009 (25)	43	100%	100%	100%	0%
Lo, 2009 (26)	23	100%	100%	100%	0%

NR = not relevant

Table 5 - Studies of incidence of sentinel node metastasis in multifocal/multicentric breast cancer

Studies	Number of patients	Incidence of sentinel node metastasis
Tousmis, 2003 (15)	70	38/70 (54%)
Kumar, 2003 (16)	48	19/48 (39.5%)
Goyal, 2004 (17)	75	31/71 (43.6%)
Ferrari, 2006 (3)	31	13/41 (41.9%)
Solà, 2009 (24)	174	50/74 (29%)
Lo, 2009 (26)	23	7/23 (30%)
Present series	94	53/94 (56%)

multicentric trials report high accuracy and low false negative rates. The overall identification rates range from 85.7% to 100%. The overall false-negative rates range from 0% to 33%; the accuracy rates range from 79% to 100%; the sensitivity rates range from 85.7% to 100%. In recent series, post 2006, the identification rates range from 91.5% to 100%; the accuracy rate range from 96.6% to 100%; the sensitivity rates range from 92.8% to 100% and the false negative rates range from 4% to 15%. In our series the identification rate was 100%. The incidence of sentinel node metastasis, as shown in Table 5, range from 29% to 54%, in our series was 56%. The incidence of axillary recurrence is 0% in our series with a median follow-up of 54 months; also Holwitt (22) and Gentilini (19) with a median follow-up respectively of 57 months and 24 months reported the incidence of axillary recurrence of 0% (Table 5).

Conclusions

Our data and literature review demonstrates that sentinel node biopsy in multicentric and multifocal clinically node-negative breast cancer is feasible, with high sensitivity and specificity and low false-negative rates with no axillary recurrence.

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