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Why do we need irradiation of internal mammary lymph nodes in patients with breast cancer: Analysis of lymph flow and radiotherapy studies

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ABSTRACT

Aim: Using clinical data and results of lymphoscintigraphy to calculate probability of internal mammary lymph node (IMLN) invasion by breast cancer (BC). To evaluate clinical value of lymphoscintigraphy as the guide for irradiation of IMLN.

Methods: Using the data of eight published studies that analyzed lymph flow from primary BC (4541pts) after intra-peri-tumoral injection of nanosized 99mTc-colloids we determined probability of lymph-flow from internal-central and external BC to IMLN. In 7 studies (4359pts) axillary staging was accompanied by IMLN biopsy (911pts) that helped us to estimate probability of IMLN metastatic invasion in relation to the status of axillary LN. Finally, we estimated probability of IMLN invasion by BC in five randomized and observation studies that analyzed effect of IMLN irradiation on overall survival (OS). We calculated possible gain in survival if they would be treated according to lymph-flow guided radiotherapy to IMLN.

Results: Lymph-flow from internal/central BC to IMLN was mentioned in 35% from external lesions – in 16% cases. In women with negative axillary LN metastases in IMLN were revealed in 7.8%pts, in the case of positive axillary nodes average risk of IMLN invasion increased to 38.1%. Calculated probability of IMLN metastatic invasion in pts included in evaluated trials did not exceed 10%. If lymphoscintigraphy would drive decision about irradiation of IMLN than 72–78% of pts included in these studies would escape radiotherapy to IMLN. In the remaining 21–28%pts with lymph-flow to IMLN their irradiation probably would increase gain in OS from 1.0–3.3% to 4.3–16.8%.

Conclusion: Lymphoscintigraphy can be used to optimize the strategy of IMLN irradiation.

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1. Background

Indications for irradiation of regional lymph nodes (LN) in patients with breast cancer (BC) were determined after several randomized trials and fundamental meta-analysis carried out by a group of EBCTCG experts.[1,2] At the same time, approaches for radiotherapy to internal mammary lymph nodes (IMLN) remained controversial. Several large randomized and observation studies were organized to determine clinical value of radiotherapy to IMLN. In all of these studies experimental groups consisted of patients with internal/central localization of primary tumour and/or metastatic involvement of axillary LN. Obtained results indicated that in these patients with BC irradiation of IMLN can substantially (1–3%) reduce frequency of local and distant recurrences with borderline improvement in 5–10 year disease-free survival.[3–8] Small but reproducible improvement in overall survival that was mentioned in most studies pointed out that in some patients with BC irradiation of IMLN can evidently improve treatment efficacy. At the same time, it is clear that routinely used clinical factors (tumour localization, regional lymph node status) are not very powerful in discriminating those women who would benefit from IMLN irradiation and those who would not.

It seems logical to propose that lymph flow from BC to IMLN must be considered as an obligatory condition for developing IMLN metastatic lesions. If this is the case than visualization of lymph flow from the tumour can be a promising discriminator between women with elevated and low risk of IMLN involvement by BC.[9,10] Thus, it is possible to assume that scintigraphic visualization of lymph flow from BC in combination with the clinical risk factors can be used as basic instruments to decide whether IMLN should be irradiated or not. In the presented study, we tried to evaluate the possible benefit which can be achieved by irradiation of visualized sentinel LN localized in the internal mammary region.

2. Materials and methods

Recently, lymphoscintigraphy has been widely used for visualization of lymph flow from BC and identification of sentinel LN in axillary and internal mammary regions.[11–13] Hindie et al.[11] carried out meta-analysis of six prospective studies in which visualization of IM sentinel LN was combined with biopsy. Lymphoscintigraphy data of 3876 BC patients was thoroughly studied. Later study by Postma et al.[12] investigated results of IMLN biopsy performed in other 483 patients. When we combined both data sets, the whole group used in our analysis consisted of 4359 women. Lymph flow from primary lesion to IMLN was revealed in 911 of 4359 (20.9%) evaluated patients. Biopsy revealed metastatic involvement of IMLN in 156 (17.1%) cases. Metastastatic invasion of axillary LN significantly correlated with malignant involvement of IMLN: in women with negative axillary LN metastases in IM sentinel LN were revealed in 7.8% cases, in patients with positive axillary nodes risk of IM sentinel LN invasion by BC increased to 38.1%.

Localization of primary tumour significantly correlated with probability of lymph flow to IMLN. In order to calculate the probability of lymph flow from primary lesions, localized in various breast quadrants, to IMLN we used data of Hindie et al.[11] together with results of two later studies.[12,13] Thus, analysis of lymphoscintigraphy data carried out in 4541 BC patients showed that the probability of IMLN visualization after intratumoral injection of 99Tc-nanocolloids in women with external localization of primary tumour accounted for 16%, in cases of internal/central BC localization it increased to 35%.

Table 1 – Calculated probability of internal mammary lymph node metastatic involvement in various clinical groups participating in analyzed (randomized and observation) studies.

Localization of primary tumour	Metastases in axillary LN	Probability of IMLN metastatic invasion (%)
Internal/central	Yes	13.3
Internal/central	No	2.7
External	Yes	6.1
External	No	1.2

Obtained figures help us to estimate an average probability of IMLN involvement (Table 1) in standard clinical groups who were used for analysis in randomized and observation trials.[3–8] As in descriptions of some studies we did not find figures that characterized patient distribution according to localization of primary lesion in the breast, we used average rate extracted from two large population based trials.[8,14] In accordance with these studies, we assumed that, on average, 32% of women with BC had internal/central and remaining 68% – external localization of primary tumour.

At the next step in each of the three randomized and two population based trials included in the analysis we calculated the probable number of patients with IMLN metastases. This estimation was based on probabilities of IMLN invasion in various clinical groups (Table 1) included in every trial. Finally we combined information about improvement in metastatic-free, disease-free and overall survival with estimated number of patients with IMLN involvement in each trial. With the help of this data, we evaluated the efficacy of radiotherapy to metastatic IMLN, in particular according to scenarios where a decision about irradiation of IMLN is based on results of lymphoscintigraphy (Table 2).

Randomized EORTC 22922/10925 study[3] included 4004 patients; 2002 women underwent irradiation of IMLN. It is known that 44% (1780 patients) of women included in the study had no signs of axillary LN invasion. This helps us to assume that all the mentioned patients had internal/central localization of primary lesions. Axillary involvement was diagnosed in the remaining 56% (2224 patients). Exact number of patients with internal/central and external localization of primary tumour in this group of patients is not known. We proposed that 32% of these women had BC of internal/central localization.

Results of the second prospective randomized study MA.20 were published recently.[6] It is known that majority (85%) of patients included in the protocol had involved axillary LN and in 91% of cases they received chemotherapy. Distribution of patients according to localization of primary lesions