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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

Table 2 – Analysis of randomized and population based trials on irradiation of internal mammary lymph nodes in patients with breast cancer.

Study	MA.20	French study	EORTC 22922/10925	British-Columbia	Danish BCCG
Patients (with irradiation of IMLN[a])	1832 (916)	1334 (667)	4004 (2002)	2413 (989)	3089 (1492)
Patients with involved axillary LN[b] (%)	1655 (90.3%)	1000 (75%)	2224 (56%)	529[c] (53%)	1492 (100%)
Patients with internal-central localization of BC	356[d]	327[d]	1247[d]	338	477[d]
Estimated number of patients with involved IMLN[a] in irradiated group (per 100 women)	71.8 (7.8)	46.6 (7.0)	118.4 (5.9)	56.7[e] (10.7)	125.5 (8.4)
Improvement in overall survival (NP[f])	1.0%[g] (7.8)	3.3%[g] (2.12)	1.6%[g] (3.69)	3%[e,h] (3.6)	3.7%[i] (2.3)
Improvement in disease-free survival (NP[f])	–	–	3.0%[g] (1.97)	2%[e,h] (5.4)	
Improvement in distant metastatic-free survival (NP[f])	5.0%[g] (1.6)	–	3.0%[g] (1.97)	2%[e,h] (5.4)	
Patients without lymph flow to internal mammary region (%)	702 (76.7%)	498 (74.7%)	1441 (72.3%)	381[e] (72.1%)	1163 (77.9%)

[a] IMLN – internal mammary lymph nodes.
[b] LN – lymph nodes.
[c] Number of patients with involved axillary lymph nodes in the group of patients with irradiated internal mammary lymph nodes.
[d] Estimated number (calculated as 32% of the whole group) of patients with central/internal localization of breast cancer in group with irradiated internal mammary lymph nodes.
[e] In group of 529 women with involved axillary lymph nodes.
[f] NP – number of patients with metastatic internal mammary lymph nodes that must be irradiated in order to achieve 1% increase of survival rate.
[g] 10 year survival rate.
[h] 5 year survival rate.
[i] 8 year survival.

is unknown so we presumed that 32% of patients had BC in internal/central quadrants.

In the French randomized study,[5] results of which were published in 2013, 667 of 1334 patients received IMLN irradiation. Axillary LN metastatic involvement was diagnosed in 75% of all cases. All 167 women with irradiated IMLN and negative axillary nodes had internal/central BC localization. We assumed that among ladies with positive axillary LN 160 had internal/central and 340 external localization of primary tumour.

Danish prospective population based study was undertaken in 3089 women with operable BC and macrometastases to one or more axillary LN.[4] In this trial, 1492 women with BC of the right breast underwent irradiation of IMLN. As localization of primary lesions were not reported in the abstract form, we again presumed that 32% of patients had BC in internal/central quadrants. In the remaining 1597 women with left sided BC IMLN radiotherapy was performed without inclusion of IMLN.

Observation study carried out by specialists of the British Columbia Group included 2413 patients.[8] However, the efficacy of IMLN irradiation was analyzed in 1308 patients with positive axillary LN, 529 of them underwent irradiation of IMLN. In this study we know that 338 ladies had internal/central localization of primary breast lesion.

3. Results and discussion

According to data published by Poortmans et al.,[3] irradiation of IMLN was performed in 2002 patients who were included in the EORTC 22922/10925 trial. Our calculations show that morphological signs of IMLN invasion could be revealed in 24 of 888 women with internal/central localization of BC and without involvement of axillary LN. It is possible to propose that around 47.9 ladies with internal/central BC and positive axillary LN had additional involvement of IMLN. It can be assumed that 122.1 (16%) of 763 patients with external BC and positive axillary LN had lymph flow to IMLN. This means that about 46.5 (38.1%) women from this group could have positive IMLN. Finally, we can propose that 118.4 of 2002 patients with irradiated IMLN had metastases in IMLN. In this case, estimated risk of IMLN metastatic involvement in irradiated patients was 5.9%. Considering a positive effect of RT in experimental group, which caused 1.6%, 3% and 3% increase of overall, disease-free and distant metastatic-free 10 year survival, we can assume, that irradiation of every 3–4 (3.69) patients with involved IMLN can help to avoid one death over a period of 10 years. Moreover, it is possible to propose, that inclusion of IMLN in irradiated volume in every 2 (1.97) women with involved IMLN prevents one case of BC relapse, including one distant relapse. If we

agreed with the postulate that irradiation of IMLN must be performed only in women with lymph flow from primary tumour to the IM region, then 72.3% of women, included in the trial, must receive standard RT without irradiation of IMLN. On the other hand, in the remaining 556 (27/7%) patients the probability of IMLN metastatic involvement can reach 21.2% (118 cases). It means that if randomization would be performed in this group we can expect 5.8% and 10.8% improvement in overall and relapse-free survival of women with irradiated IMLN.

In prospective randomized trial MA20 only 88 of 916 patients with irradiated IMLN had negative axillary LN.[6] In this trial benefits after IMLN irradiation in 10 year overall, disease-free and distant metastatic-free survival accounted to 1.0%, 5.0% and 3.9%, respectively. According to our calculations this result was achieved after irradiation of 71.8 women with involved IMLN (estimated invasion risk 7.8%). Thus, according to the above mentioned assumptions and study results after 10 year follow up, irradiation of every 7–8 (7.8) patients with involved IMLN enables to prevent 1 death, about 5 relapses including 3–4 relapses with generalization of BC. Use of lymphoscintigraphy results for determination candidates for IMLN irradiation would help to avoid RT to the internal mammary region in 76.7% of patients, included in the trial. After randomization in a group consisting of 23.3% remaining women, gain of experimental RT in terms of 10 year overall and disease-free survival could reach 4.3% and 21.4%, respectively.

Analysis of French study[5] demonstrated low (6.99%) calculated risk of IMLN invasion in patients included in the experimental group. This means that irradiation of 46.6 patients with involved IMLN provided 3.3% increase of 10 year overall survival. Thereby, irradiation of every 2.12 women with positive IMLN within the next 10 years enables to prevent 1 death. According to the scenario where lymphoscintigraphy is used for selection of patients for IMLN irradiation, we must expect a decrease of radiotherapy volume in 74.7% of patients. This can reduce increased rates of contralateral BC occurrence detected after IMLN irradiation in another French study.[7]

Moreover, it can be proposed that irradiation of INLN in remaining 25.3% patients with scintigraphic signs of lymph flow from primary tumour to IMLN can significantly (13%) improve 10 year overall survival rates.

Prospective Danish trial[4] demonstrated significant increase in overall survival of patients with irradiated IMLN. After long-term follow-up gain in 8 year overall and distant metastatic-free survival reached 3.7% and 2.3%, respectively. Authors concluded that radiotherapy to IMLN "does contribute to the effect of adjuvant radiotherapy in early BC". We calculated that about 125.5 women (8.4%) included in the Danish trial were presented with IMLN involvement. This makes it possible to assume that in order to prevent one death we need to irradiate 2–3 (2.3) patients with metastatic IMLN. Irradiation of 3–4 ladies with involved IMLN prevents one distant relapse (3.7) and one death from BC (3.4). If lymphoscintigraphy would drive decision concerning irradiation of IMLN in Danish trial population then around 77.9% women would escape radiotherapy to IMLN and in remained 22.1% cases benefits of IMLN irradiation in terms of overall and distant metastatic-free survival would reach 16.8% and 10.3%.

Retrospective analysis of IMLN radiotherapy results in patients, included in the "British Columbia Retrospective study",[8] did not confirm significant positive influence of IMLN irradiation on five year overall survival rate. However, our calculations showed that even in this study RT to IMLN in every 3–4 (3.6) patients with involved IMLN enabled to save the life of one woman within the first 5 years of follow-up. In addition, it is possible to propose that in every 5–6 women with irradiated IMLN radiotherapy would prevent one BC relapse. Moreover; if randomization would be performed in the group of patients with lymph flow from primary lesion to IMLN, irradiation of these nodes can be associated with 10.8% improvement in overall survival.

As already mentioned above, the decision to include the IMLN in the target volume is mainly based on two clinical factors: localization of primary tumour and status of axillary LN. Presented analysis demonstrated that this algorithm is not very effective. Calculations showed that probability of IMLN metastatic invasion in all evaluated randomized and large observation studies did not exceed 10%. In this case it was quite difficult to determine opportunities of radiotherapy in treatment of patients with metastases in IMLN. Unfortunately, radiological examinations has low accuracy in detecting IMLN invasion by BC, which can be explained by their poor ability to detect lesions that are less than 6–7 mm in diameter.[15] In this regard, biopsy of IMLN must be considered as the main tool for selection of patients for radiotherapy to internal mammary region. However, if morphological verification of IMLN status is not possible, lymphoscintigraphy can be used as an effective method, which helps to select patients for irradiation of IMLN. First of all, these are women with visualized sentinel LN in the internal mammary region and metastases in axillary LN. In this case, IMLN invasion risk reaches 38.1% and irradiation of IMLN can increase 10 year overall survival by 5–16%. Advantages of IMLN irradiation are less evident in patients with negative axillary LN and visualized sentinel LN in the internal mammary region. In these women, the risk of IMLN metastatic involvement does not exceed 8% and possible improvement in overall survival after irradiation of IMLN is not more than 1–3%.

4. Conclusions

1. Presented analysis demonstrated that after intra- (peri-)tumoral injection of 99mTc-nanocolloids visualization of lymph flow from primary breast cancer can affect the decision whether to perform irradiation of IMLN or not.
2. In patients with BC results of lymphoscintigraphy help to avoid unnecessary irradiation of IMLN in 72–78% cases, in remained 22–28% women irradiation of IMLN can significantly increase 5 and 10 year overall and disease-free survival.

Conflict of interest

None declared.

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None declared.

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