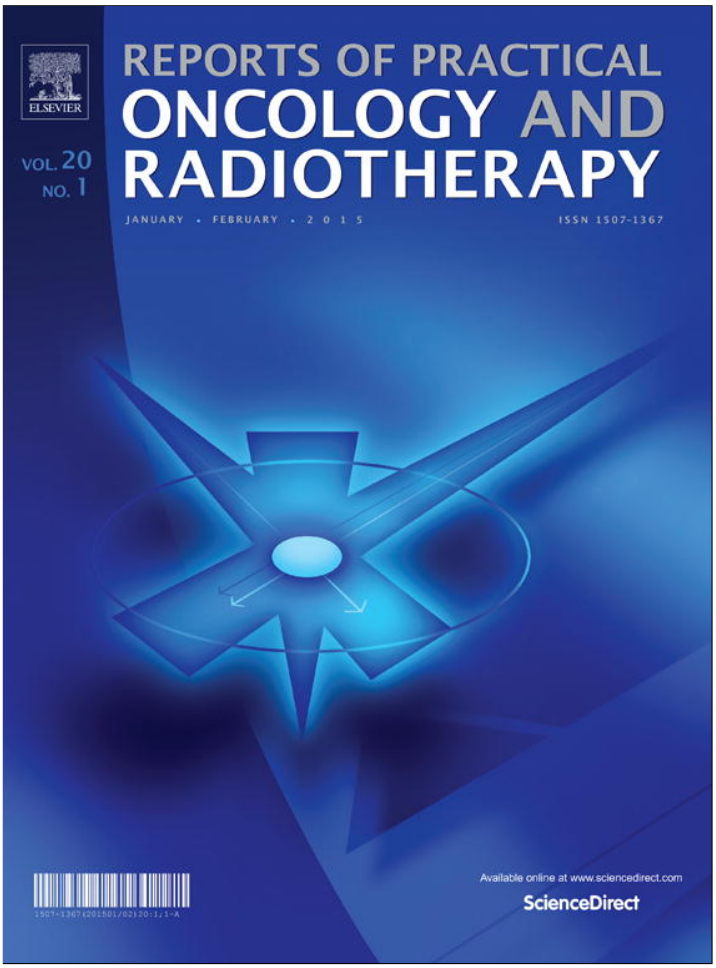

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Original research article

Comparison of two treatment strategies for irradiation of regional lymph nodes in patients with breast cancer: Lymph flow guided portals versus standard radiation fields

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ABSTRACT

Aim and Background: Radiotherapy being an essential part of breast cancer treatment, we evaluate various radiotherapy strategies in patients with breast cancer.

Materials and methods: Lymph node (LN) scintigraphy was performed in 172 primary patients with BC. LN visualization started 30–360 min after intratumoral injection of 75–150 MBq of 99mTc-nanocolloids.

Our standard recommendation for postoperative radiotherapy in patients with LN invasion by BC were as follows: for patients with external localization of tumour – breast + axillary (Ax) + sub-supraclavicular (SSCL) regions; with internal localization – all above + internal mammary nodes (IM). Proposed strategy of lymph flow guided radiotherapy is based on the assumption that only regions that contain 'hot' LNs must be included in a treatment volume.

Results: Among 110 patients with external localization of BC, Ax LNs were visualized in all cases and in 62 patients it was the only region with 'hot' LN. Twenty-three patients (20.9%) had drainage to Ax + SSCL, 12 (10.9%) – Ax + IM, 13 (11.8%) – Ax + SSCL + IM regions. After the visualization of lymph flow patterns, standard treatment volume was changed in 87/110 cases (79.1%): in 56.4%, reduced, in 22.7%, enlarged or changed.

In 62 patients with tumours in internal quadrants, we revealed the following patterns of lymph-flow: only to the Ax region in 23 (37.1%); Ax + IM, 13 (21%); Ax + SSCL, 15 (24.2%); Ax + IM + ISSCL, 11 (17.7%) cases. After lymph-flow visualization, the standard irradiation volume was reduced in 53/62 (85.5%) cases.

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Conclusion: Visualization of an individual lymph flow pattern from BC can be used for the optimization of standard fields used for irradiation of regional LNs.

1. Background

Radiotherapy is an essential part of breast cancer treatment, it provides 70–75% decrease of risks of locoregional relapses.[1,2] Up till now, the decision about the volume and topography of a radiation field is made considering the probability of lymph nodes (LN) invasion. In particular, in cases of metastatic involvement of axillary lymph nodes and external localization of breast cancer, it is recommended to irradiate the rest of axillary and sub-supraclavicular LNs, while in the cases of central or internal localization of breast cancer irradiation of internal mammary LNs can be discussed.[3,4] Unfortunately, the question about the volume of internal mammary irradiation has not been settled yet. Some groups[5] recommend using wide radiation fields that include the area of internal mammary LNs (IMLNs) on both sides of the sternum. Other investigators underline the monolateral character of IMLN involvement and advocate "narrow fields" which cover only IMLNs located on the side of the tumour. Approaches to the question about the length of an IMLN radiation field can be different as well. According to a generally accepted technique, the upper border of the field includes LNs of the I intercostal space, while the lower border ends on the IV rib.[6] On the other hand, Veronesi et al.[7] mentioned, that in the cases of tumours localized in the upper quadrants of the breast, only IMLNs located in the I–III intercostal spaces are at an increased risk of invasion when the lower quadrants are affected by breast cancer – high risk LNs are distributed between the III and V intercostal spaces.

One of the ways to resolve these contradictions is to determine lymph flow from a tumour in every patient's case; this will definitely allow to optimize the volume of regional radiotherapy and adapt it to the needs of a specific patient.[8,9] In this study, we tried to compare the topography of standard radiation fields with treatment portals arranged according to individual properties of lymph flow from each breast lesion determined by a scintigraphic visualization.

2. Materials and methods

The study population consists of 172 consecutive patients (*32–63 years old*) with breast cancers that were diagnosed and treated in the N.N. Petrov Institute of Oncology between 2008 and 2011. In all the cases, included in the analysis, breast cancer was confirmed by aspiration and/or excision biopsy before or during operation. Scintigraphic visualization of lymph flow from breast cancer (SVILF) was performed in all cases and preceded surgical intervention, including the excision biopsy. Patients who had had previous operations on the breast were excluded from the analysis. Breast-conserving surgery was performed in 131 women included in this study, the remaining 41 patients underwent mastectomy. Breast surgery was accompanied by sentinel lymph node biopsy or limited (less than 6 nodes) lymph node dissection in 149 cases and in another 23 women – by standard axillary lymph node dissection (7–22 lymph nodes). According to histological examinations, 26.7% (46 cases) of 172 operated patients had metastases in the removed axillary lymph nodes.

In patients with histological signs of LN involvement by breast cancer, the extent and topography of standard fields designed for postoperative radiotherapy are highly determined by primary tumour localization. In patients with breast cancer located in the external quadrants, treatment volume usually included axillary and sub-supraclavicular LNs, in cases of internal localization of the tumour, radiation portals covered IMLNs lying in the I–IV intercostal spaces on one or both sides of the sternum. For the purpose of this study, to compare a standard and lymph-flow guided strategy of regional lymph node irradiation, we evaluated all 172 patients that underwent SVILF as candidates for regional radiotherapy.

SVILF was performed as a series of static images obtained 30–60 and 240–360 min after intratumoral injection of 75–150 MBq (0.1–1 ml) of 99mTc-nanocolloids (NCs) with the size of the particles less or equal to 80 nm. NCs were prepared according to the standard protocol, recommended by manufacture. After preparation of 75–150 MBq of NCs in the volume of 0.1–1.0 ml, they were injected directly into the tumour. Static images were detected with an interval of 5–10 min over first 30 min after injection of radiocolloids until image of the sentinel LNs appeared. Delayed scans were performed 240–360 min after infection in order to document the final distribution of the tracer in the sentinel and second echelon LNs. All nodes visualized on early and delayed images were considered as target (regional) to the breast lesion. This approach helped us to design radiation portals in accordance with individual lymph flow patterns and stipulated irradiation of the regions with LNs actively accumulating NCs.

When sentinel LNs were revealed in the internal mammary region, their localization with regard to standard anatomical landmarks was specified by a gamma camera. Moreover, with the help of specialized radioactive pointer, the projection of 'hot' LNs was marked on the skin of the front chest wall. This simplified further use of scintigraphic information for the design of radiation fields.

At the last stage, we carried out a comparative analysis of radiation portals, designed according to our standard strategy driven by localization of the primary tumour and a strategy which was based on scintigraphic data presenting individual lymph flow from every breast cancer.

Table 1 – Distribution of scintigraphic lymph flow patterns in patients with breast cancer localized in external or internal quadrant of the breast.

Lymph flow pattern	Number of patients in relation with breast cancer localization	
	External quadrants	Internal quadrants
Only axillary LN	62 (56.4%)	23 (37.1%)
Axillary + sub-supraclavicular LN	23 (20.9%)	15 (24.2%)
Axillary + internal mammary LN	12 (10.9%)	13 (21%)
Axillary + sub-supraclavicular + internal mammary LN	13 (11.8%)	11 (17.7%)
Overall	110 (100%)	62 (100%)

3. Results

According to our routine practice in patients with a central and internal localization of breast cancer, standard radiation fields cover internal mammary, axillary and sub-supraclavicular LNs. This strategy is supported by many international groups.[3,4,9] At the same time, results of SVIL (Table 1), which was performed in 62 patients with an internal or central localization of breast cancer, demonstrated that an individual topography of 'hot' LNs corresponded to standard radiation fields only in 11 (17.7%) cases. Accumulation of radiocolloids in axillary, internal mammary and sub-supraclavicular LNs was detected in all 11 cases. In 23 (37.1%) patients lymph flow was restricted only by axillary LNs, this permitted a significant reduction of standard radiation volume. In 13 cases, (21%) SVILF visualized internal mammary and axillary LNs, in other 15 cases (24.2%), axillary and sub-supraclavicular LNs. In all those patients, SVILF data prompted us to decrease the extent of treatment portals in comparison with topography of standard radiation fields. Moreover, radiotherapy strategy based on SVILF helped to exclude IMLNs from the irradiation volume in 38 (61.3%) cases and allowed significant reduction of irradiation volume in 85.5% of patients with an internal and central localization of breast cancer. This allowed us to decrease substantially the level of radiation burden of coronary vessels, myocardium and other normal tissues.

Second group consisted of 110 patients with an external localization of breast cancer. Standard volume of regional radiotherapy for such patients includes axillary, subclavicular and supraclavicular LNs. According to scintigraphic data (Table 1), lymph flow to axillary LNs was determined in all 110 cases with an external localization of breast cancer. Moreover, in 62 (56.4%) patients, the accumulation of radiocolloids was noticed only in LNs of the axillary area, this permitted the reduction of standard radiation fields which were limited to the remained breast tissue and axillary LNs. In 48 (43.6%) patients, results of SVILF demonstrated NC transport to LNs, located in 2 or 3 various anatomic areas. In 23 (20.9%) cases, we observed an outflow of radiocolloids in LNs of the axillary and sub-supraclavicular areas. Only in these cases did standard radiation volumes correspond to an individual topography of lymph flow from breast cancer. Significant difference between the localization of standard radiation fields and the localization of regional LNs with an active tracer uptake was determined in 25 (22.7%) other patients. In particular, in 12 (10.9%) patients, SVILS visualized LNs in the axillary and internal mammary regions, in 13 (11.8%), in the internal mammary, axillary and sub-supraclavicular regions. Lymph flow to IMLNs is considered uncommon for lesions located in the external breast quadrants. According to our data, this lymph flow pattern can be determined in every fourth woman with an external localization of breast cancer. Besides, in 13 (11.8%) cases the visualization of IMLNs can be viewed as a reason to increase radiation volume, in 12 (10.9%) other cases the volume of planned radiotherapy was changed significantly – it was reduced due to the exclusion of the sub-supraclavicular LNs from radiation portals and increased due to proposed irradiation of IMLNs. Thus, the information obtained with SVILF can help to reduce the extent of treatment portals used for irradiation of regional LNs in a half of patients with breast cancer located in the external quadrants. In a quarter of these patients, the volume corresponded to the topography of standard radiation fields; in the other quarter of cases, it should include IMLNs.

Topography of radiation portals used for treatment of IMLNs was evaluated in a group consisting of 49 patients that had active accumulation of radiocolloids in the internal mammary region. It is notable, that more than a half of the mentioned patients (25 women) had an external localization of breast lesions. Moreover, our results did not confirm the well known statement that the localization of tumour in the upper and lower quadrants of the breast determines intercostal topography of IMLNs. In particular, in 5 of 13 (38.4%) patients with tumours localized in the lower quadrants of the breast, internal mammary sentinel LNs were visualized in the I–II intercostal spaces. On the other hand, in 20 of 36 (55.5%) patients with lesions occupying the upper quadrants, radiocolloids were absorbed in LNs located in the III–V intercostal spaces.

In 45 of 49 (91.8%) patients, internal mammary sentinel LNs were visualized only on the side of the primary tumour. This allowed to reduce radiation portals to IMLNs located only on the side of affected breast. At the same time in 4 (8.2%) cases lymph flow visualization revealed tracer uptake in LNs located on the both sides of the sternum, leading to the use of wide bilateral radiation fields.

4. Discussion

Radiotherapy is an integral part of cancer treatment for most patients. According to data of evidence based medicine 83% of patients need radiotherapy on a certain stage of treatment.[10] However, an optimal topography of treatment portals used for irradiation of regional LNs has not been determined yet.[11] There are no doubts that radiotherapy can significantly improve loco-regional control in different categories of patients with breast cancer.[2–4,10] For example, in women

with morphological signs of axillary LN involvement, irradiation helps to reduce the probability of loco-regional relapses by 50%, and in those with 4 or more LNs invaded, it is reduced three- to fourfold.[2,12,13] On the other hand, it is well known that radiotherapy can cause a number of serious negative consequences. According to Swedish trials |13|, irradiation of the left breast with/without internal mammary LNs resulted in almost a double increase of deaths caused by cardiovascular diseases. According to literature data, 7–60% of patients with breast cancer suffer from pulmonitis and lung fibrosis related to radiotherapy of the sub-supraclavicular region, 15% have lymphedema, 36–50% suffer from pain and sensory loss caused by radiotherapy of the axillary region.[10,14]

Sub-supraclavicular LNs are considered as one of the main targets for the regional radiation therapy of breast cancer.[5] In some categories of patients, particularly in patients with axillary LN invasion, the necessity of radiotherapy for sub-supraclavicular LNs is doubtless, because without irradiation the risk of relapses in this area reaches 11–20% and in the case of extensive involvement, it exceeds 25–30%.[15] On the other hand, in a large category of patients with breast cancer, the probability of sub-supraclavicular relapse does not exceed 4–7%,[16,17] which means that more than 90% of those patients do not actually need irradiation of this region.

SVILF results show that lymph flow to LN of the sub-supraclavicular area is observed only in one third (35.6%) of patients with breast cancer, regardless of the localization of primary tumour. On the one hand, it is important to note, that the results obtained corresponded quite accurately to the above mentioned literature data with 30% probability of sub-supraclavicular LN invasion in the case of extensive involvement of axillary LNs.[15] On the other hand, it should be stressed, that the determination of individual lymph flow patterns make it possible to discuss the necessity of sub-supraclavicular irradiation in 62% of evaluated patients.

Views on indications for irradiation of IMLNs remain varied. Many authors underlie that the risk of internal mammary involvement is increased in patients with axillary metastases and in accordance with literature data it varies between 20–30% and can be as high as 70%.[9,18] Other groups have mentioned moderate probability of relapse in IMLNs.[16,19] For example, Donegan[16] describe only 1 case of clinical manifestation of a regional relapse in a group of 20 unirradiated patients with morphologically proved metastases in internal mammary lymph nodes. On the other hand, lower rates of relapse free and overall survival were mentioned in women with a central and internal localization of breast cancer[20,21] and they reach a statistical significance in studies with high number of recruited patients.[3,4,17] Special attention should be drawn to Yao's et al. data[22] that demonstrated significant impairment of relapse-free and overall survival in patients with lymph flow to internal mammary LNs, which was more evident in a group with metastatic invasion of the axillary LNs, i.e. in cases with the highest probability of cancer invasion. In the last group, the overall and relapse-free survivals were 71% and 69%, in contrast with 91% and 84% in women without lymph flow to IMLNs. Therefore, the presence of scintigraphic signs of lymph flow in the internal mammary region in patients with axillary LNs increase the probability of unfavourable outcome almost 3 times. Irradiation of internal mammary LNs in this category of patients can significantly improve treatment results as proved by Veronesi et al.[7] Recent results of retrospective and prospective trials confirm an important value of internal mammary lymph node irradiation in women with tumours in the central and inner quadrants: significant improvement in a long term cancer-specific and overall survival was reached in 2–16% of those patients.[3,4]

SVILF results show quite a high frequency of lymph flow in the internal mammary region, which amounts to 22.7% of patients with an external localization of breast cancer and 37.6% in women with lesions located in the internal and central regions of breast. We believe that these are the patients who are at higher risk of IMLN invasion by the tumour and need to receive postoperative irradiation. Therefore, it can be proposed that the decision about an optimal topography of radiation fields in patients with breast cancer can be based on results of SVILF, regardless of whether the primary tumour is located in the internal or external quadrants of the breast. It is interesting that results of extended mastectomy do not confirm a positive connection between the localization of breast cancer and frequency of metastases in IMLNs, which can be 13.3–35.3% in the case of lesions located in the external quadrants and 19.5–32.6% in patients with a central or internal localization of tumour.[19,23] Question about the length and width of radiation fields to be used for irradiation of IMLNs is of special importance. From one point of view, small radiation fields which include IMLNs of the I–IV intercostal spaces on the side of breast cancer can significantly minimize unfavourable consequences of radiotherapy concerning damage of the myocardium and coronary vessels. On the other hand, it is noted, that wide (both sides of the sternum) radiation fields spreading from I to IV intercostal spaces can significantly improve rates of 5-year relapse-free survival.[24] SVILF results help to reach a consensus in this group as well.[8,10,25] In 8.9% of these patients, IMLNs are visualized on both sides of the sternum. Probably, the use of wide double-sided radiation fields is justified in this category of patients. At the same time, in 91.8% of women with scintigraphic signs of lymph flow to internal mammary region the visualized LNs were localized only on the site of primary tumour. It can be concluded that a "narrow one sided" treatment field is sufficient in this category of patients.

Conflict of interest

None declared.

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