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Original research article

Lymph flow guided irradiation of regional lymph nodes in patients with cervical cancer: Preliminary analysis of scintigraphic data

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ABSTRACT

Purpose: To evaluate patterns of lymph flow from primary lesions in patients with cervical cancer and to determine how useful for radiotherapy planning this information can be.
Materials and methods: SPECT–CT visualization of sentinel (SLN) lymph nodes (LNs) was performed in 36 primary patients with IB-IIB cervical cancer. The acquisition started 120–240 min after 4 peritumoral injections of 99mTc-radiocolloids (150–300 MBq in 0.4–1 ml). We determined localization of LN with uptake of radiocolloids, type of lymph flow (mono-, bi-lateral) and lymph flow patterns (supraureteral paracervical, infraureteral paracervical and directly to para-aortic LNs).
Results: SLNs were visualized in 31 of 36 women. Bilateral lymph-flow was detected in 22 (71%), monolateral – in the other 9 (29%) cases. The distribution of SLNs was as follows: external iliac – 64.5%, internal iliac – 54.8%, obturator – 32.2%, common iliac – 35.5% and pre-sacral 3.2%. Para-aortic LNs were visualized in 5 (16.1%) patients. The supraureteral paracervical pattern of lymph flow was identified in 22, infraureteral paracervical – in 4 and their combination – in the other 5 women.
Conclusion: Visualization of an individual pattern of lymph flow from primary cervical cancer can be considered as a promising tool for optimization of the volume of irradiated regional LNs.

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1. Background

Chemoradiotherapy is the primary treatment method of patients with cervical cancer staged IB2-IVA where the irradiation of pelvic lymph nodes (LNs) is considered as an integral component of modern radiotherapy programs. Some authors propose that combination of pelvic irradiation with radiotherapy to para-aortic LNs can improve treatment efficacy in patients with IB-IIIB cervical cancer.[1,2] However, other studies have shown that irradiation of para-aortic LNs do not improve the recurrence-free and overall survival.[3,4] Moreover, it almost doubles the treatment toxicity. Introduction of state-of-the-art intensity modulated radiation therapy (IMRT) significantly decreased the volume of the irradiated normal tissues and reduced the frequency and severity of side effects.[5] At the same time, the implementation of IMRT technique in clinical practice requires precise anatomical localization of target LNs which has a significant influence on the treatment efficacy and safety.[6]

A sentinel lymph node (SLN) concept occurred and was developed in the late 20th century. According to that concept, lymphatic spread evolves in a sequential order and SLN is the first node that received lymph-flow from the tumor. The accumulated clinical experience confirms that the SLN is indeed the first node to be involved during regional metastatic spread.[7–9] The idea of "lymph flow guided radiotherapy" represents logical continuation and development of SLN hypothesis which proposed that regional dissemination occurs in sequential fashion. The corner stone of this concept is visualization of individual patterns of lymph flow from the primary tumor and subsequent irradiation of those lymph nodes that received lymph fluid from the primary cancer.[10,11] Currently, there are several reports that analyze a possible role of SLNs visualization for radiotherapy planning in patients with breast, prostate and head and neck cancer.[12–14]

In this study we analyzed our experience of the visualization of individual patterns of lymph flow from the cervical cancer and evaluation topography of SLNs. We also considered possible utilization of the obtained data for the optimization of treatment fields that are used for irradiation of regional LNs in women with cervical cancer.

2. Materials and methods

This prospective single center study was approved by the Institutional Ethical Committee. The informed consents were obtained from all patients before SPECT–CT examination. The study was performed in a group of 36 cervical cancer patients aged from 45 to 77 (mean 63; 55–71). A clinical and instrumental examination was conducted at the N.N. Petrov Cancer Research Institute from March 2016 to June 2017. All women had IB-IIB (cT1b-T2bN0M0) cervical cancer with histological confirmation of the diagnosis. Whole body PET–CT was not routinely used for staging of cervical cancer and was substituted by a chest and abdomen CT. In all cases MRI and US examinations of pelvic and para-aortic LNs did not reveal signs of metastatic LN involvement.

The visualization of SLNs was performed by hybrid single photon emission computed tomography/computed tomography (SPECT/CT) imaging. The acquisition started 120–240 min after the peritumoural injection of 0.4–1.0 ml (150–300 MBq) of ^{99m}Tc -radiocolloids with the particle diameter of 100–1000 nm ("Senti-Scint", "Technephit"). Radiocolloids were injected superficially under the visual control in 4 points just around to the primary lesion in equal aliquots at the 12-, 3-, 6- and 9 o'clock positions.

The acquisition was performed by a high resolution hybrid camera (Symbia T16, Siemens, Germany) using a low-energy high-resolution collimator. The study was performed with a patient in a supine position. The study started with a single photon emission computed tomography (SPECT) with the following parameters: 128 × 128 matrix, scan step of 3°, exposure time of 16 s, and each detector rotation angle of 180°. The upper bound of the scanning region was located at the level of the twelve thoracic vertebrae (Th12), the lower one was 1–2 cm below the femoral heads. After completion of the SPECT study (without changing the patient position on the table), the helical computed tomography (CT) was performed with the exposure of 80–100 mAs, 120 kV with rotation time of 0.5 s, scan time of 15 s, a pitch of 1 mm, slice thickness of 5 mm with reconstruction interval of 1.5 mm.

The post-processing fusion of SPECT and CT images was performed on the Siemens Syngo Workstation: for scintigraphic data an iterative reconstruction technique was used (8 iterations and 16 subsets), with and without the attenuation correction. The total time of a single SPECT–CT study was 16–20 min.

Hybrid images were evaluated by two experts (a radiation oncologist and a radiologist) with over 10 years' experience. They analyzed the number of visualized SLNs and their anatomical location. All lymph nodes that accumulated radiocolloids were regarded as SLN. They were assigned to 6 nodal groups against their anatomic location in relation to blood vessels. These groups were defined as follows (Fig. 1):

1. Obturator nodes that were localized within a triangle between external and internal iliac vessels.
2. Internal iliac nodes were next to the internal iliac vessels and their branches.
3. External iliac nodes corresponded to the nodes around the external iliac vessels from bifurcation of common iliac vessels to femoral artery.
4. Pre-sacral nodes localized anterior to and in close vicinity to the sacrum.
5. Common iliac nodes were defined as all LNs that were within 10 mm around the common iliac vessels from bifurcation of the aorta to the division of the common iliac vessels.
6. Para-aortic LNs determined as LNs adjacent to the aorta or inferior vena cava from the Th12-L1 to the inferior border of L4 vertebrae (the level of aorta bifurcation).

In addition, one of 3 main patterns (Fig. 2) of lymph flow from the uterine cervix was determined in every woman[15]:

1. Supraureteral paracervical route with lymphatic flow from cervical lymphatic plexus along the uterine artery to the

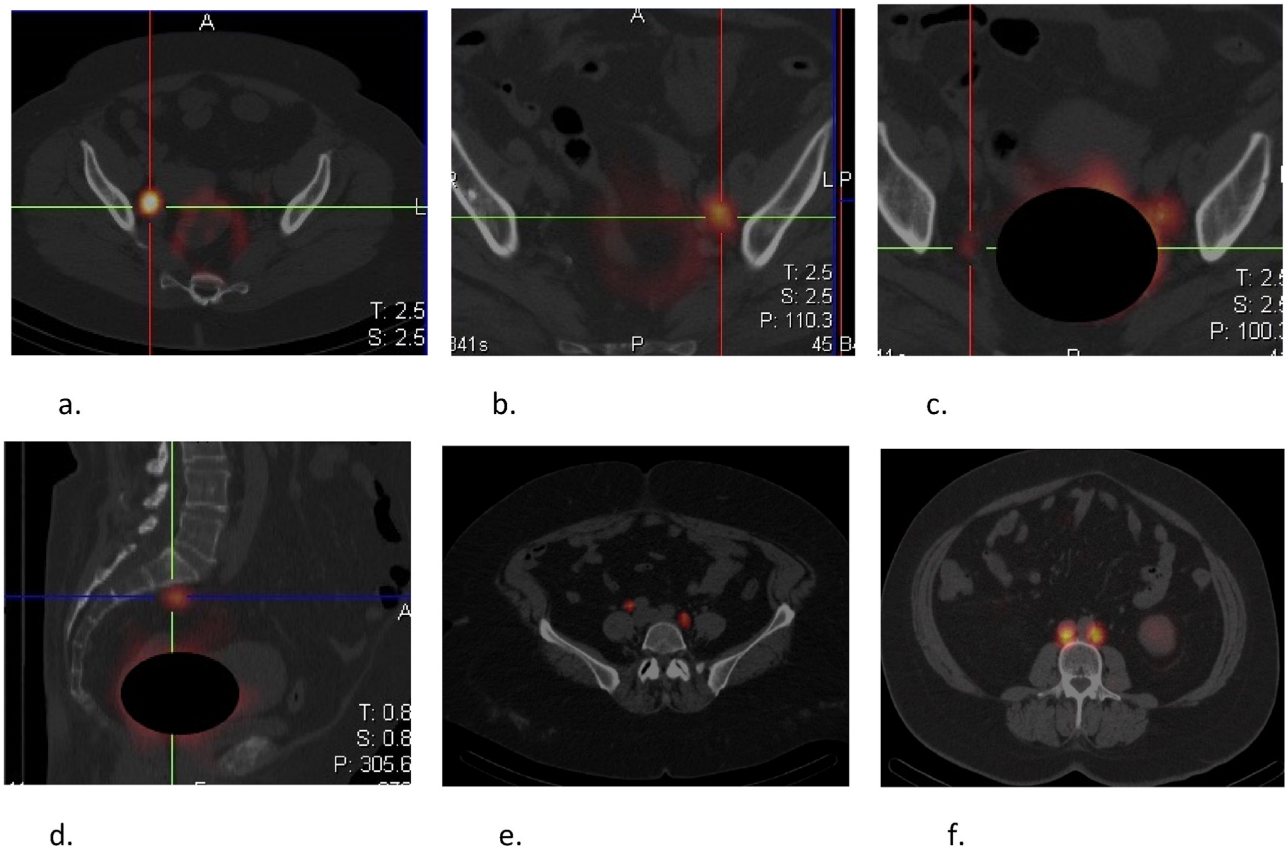

Fig. 1 – Sentinel lymph nodes with uptake of 99mTc-radiocolloids: (a) obturator, (b) external iliac, (c) internal iliac, (d) presacral, (e) common iliac, (f) para-aortic.

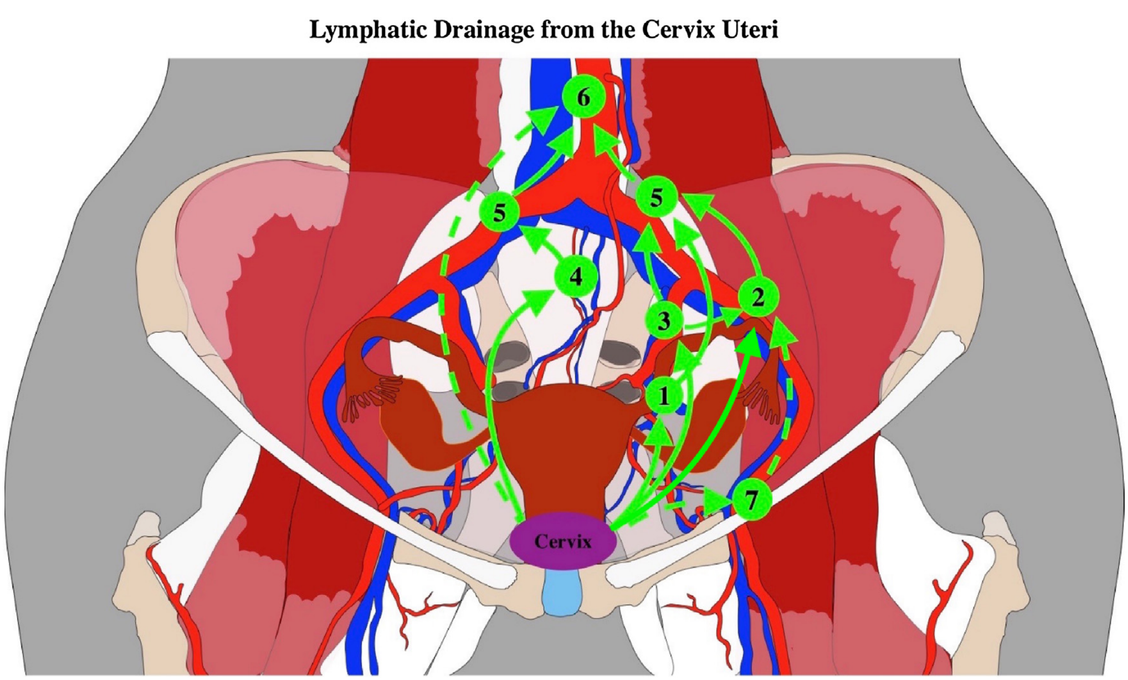

Fig. 2 – Lymph flow patterns and topography of the regional lymph nodes in patients with cervical cancer: 1. obturator, 2. external iliac, 3. internal iliac, 4. presacral, 5. common iliac, 6. para-aortic, 7. inguinal; solid lines – main routes of lymph flow from the cervix; dotted lines – possible routes that we were not able to visualize in our patients.

external iliac and obturator LNs and subsequently running to the common iliac and para-aortal LNs.
2. Infraureteral paracervical route with lymph flow to the internal iliac or/and pre-sacral LNs and then draining to the common iliac and para-aortic LNs.
3. The third pathway is characterized by direct draining from primary tumor to the para-aortic LNs.

Finally, all patients underwent radical surgical treatment with subsequent postoperative radiotherapy in patients with deep stromal involvement, tumor diameter of more than 4 cm or lymphovascular invasion. According to an institutional protocol, SLN biopsy precedes a complete bilateral pelvic lymphadenectomy without routine para-aortic LN dissection.

Postoperative external beam irradiation of pelvic lymph nodes was performed without taking into account results of SPECT–CT examination. Radiation portals were arranged to cover the common iliac, presacral, internal and external iliac LNs.[6]

At the end of the study, we discussed how SPECT–CT information about distribution of SLNs can be used for individual optimization of clinical target volumes for irradiation of regional LNs in women with cervical cancer.

3. Results

In this cohort of 36 women with cervical cancer (30–77 years old), SPECT–CT examination successfully visualized sentinel lymph nodes in 31 (86%) patients. The uptake of radiocolloids was mentioned in 81 SLNs. The number of detected LNs varied between 1 and 6; in average 2.6 SLNs per patient. The unilateral pattern of lymph flow was found in 9 (29%), bilateral – in 22 (71%) observations (Fig. 3).

The histological examination of the excised LNs determined node invasion by cervical cancer in 4 cases (11.1%). In 3 women metastases were localized only in SLN, in one woman with lymph flow block and non-visualized SLNs, metastases were revealed in four pelvic LNs. In other 3 women with non-visualized SLN the histological examination did not reveal pelvic metastases. The distribution of pelvic LNs according to the groups is represented in Fig. 4. The external iliac LNs accumulated radiocolloids in 20 patients (64.5%), internal iliac LNs – in 17 (54.8%), obturator LNs – in 10 (32.2%) and pre-sacral LNs – in one (3.2%) woman. Common iliac LNs were visualized in 11 (35.5%) cases and in all but 2 observations were associated with the visualization of SLNs in the obturator, external and/or internal iliac groups. Para-aortic LNs were detected in 5 (16.1%) women and in all cases were associated with tracer uptake in the pelvic LNs. Probably, LNs of the para-aortic region can be considered as the second echelon nodes.

In 31 cases, we were able to determine patterns of lymph flow from cervical cancer: supraureteral paracervical route was identified in 22, infraureteral paracervical – in 4 and their combination – in other 5 patients. We did not see any case of direct lymph flow from primary tumor to the para-aortic LNs.

4. Discussion

The irradiation of pelvic LNs is an obligatory component of concurrent chemoradiotherapy program both in patients with stage IB-IIA and IIB-IV cervical cancer. According to consensus guidelines, the LNs clinical target volume should include the entire anatomical pelvic LNs distribution: external, internal and common iliac LNs, obturator and pre-sacral LNs.[6]

The evaluation of metastatic LN distribution in patients with cervical cancer demonstrated that the most frequently affected nodes were the obturator and/or external iliac LNs (27–91% cases), less frequently – internal iliac LNs (14–16% cases), while the pre-sacral LNs were very rarely affected (1–5% cases).[16–18] The sentinel concept postulates that a SLN is the first node or group of nodes that a cancer cell drains and invades in during the metastatic process. The visualization of SLNs can help to determine the individual patterns of lymph flow from the tumor and to identify LNs with the highest risk of metastatic involvement. Meta-analysis of 47 prospective studies (4130 patients) demonstrated that in early stage cervical cancer patients without metastases in SLNs the estimated risk of occult metastatic lesions in regional LN is only 0.08%.[8] Our experience illustrated that in most of the evaluated women with cervical cancer the SLNs were detected in the obturator (32.2%), external (64.5%), internal (54.8%) and common (35.5%) iliac groups of the pelvic region. These data correspond to the "classical" view on topography of regional LNs with the elevated risk of involvement by cervical cancer which must be covered by standard radiotherapy fields.[6] Obtained results are consistent with the literature data. Diaz et al.,[19] indicates that in most cases SLNs are detected in the external iliac (35%), internal iliac (30%) and obturator (20%) subgroups. According to Marnitz et al.,[20] most SLNs (71%) are located between external and internal iliac vessels which the authors called an "interiliac region". Salvo et al.[21] also show that the most frequent locations can be found in the obturator and internal iliac LN (41.9%) and external iliac LN (31.6%). At the same time authors mentioned that SLNs were very rarely (0.6%) located in the pre-sacral region. In the literature analysis performed by Marnitz et al.[20] the percent of SLNs visualized in the pre-sacral region varied between 0.8% and 4.6% in the largest series. Kasuya et al.[16] proposed that taking into account low probability of metastatic invasion of the pre-sacral LNs, the latter can be excluded from the irradiation volume at least in some patients with cervical cancer. Such reduction of clinical target volume can lead to lower toxicity of the radiotherapy program. In our patients the lymph flow to the pre-sacral nodes was noticed in 3.2% cases. Probably, in the remaining 30 patients pre-sacral LNs can be excluded from the irradiation volume.

According to our findings, SLNs were visualized unilaterally in 29% of our patients. In previously reported studies, the rate of unilateral location of SLNs varied between 28% and 46%.[20,8] In this regard, Altgassen et al.[18] mentioned that the pelvic basin must be regarded as a unit and "if one SLN was detected, bilateral LN dissection could be omitted". On the other hand, Marnitz et al. (2006) proposed a "systematic complete lymphadenectomy" on the side where no SLNs were detected. For safety reasons, we are not proposing unilateral LNs irradiation in women with unilateral location of SLNs.

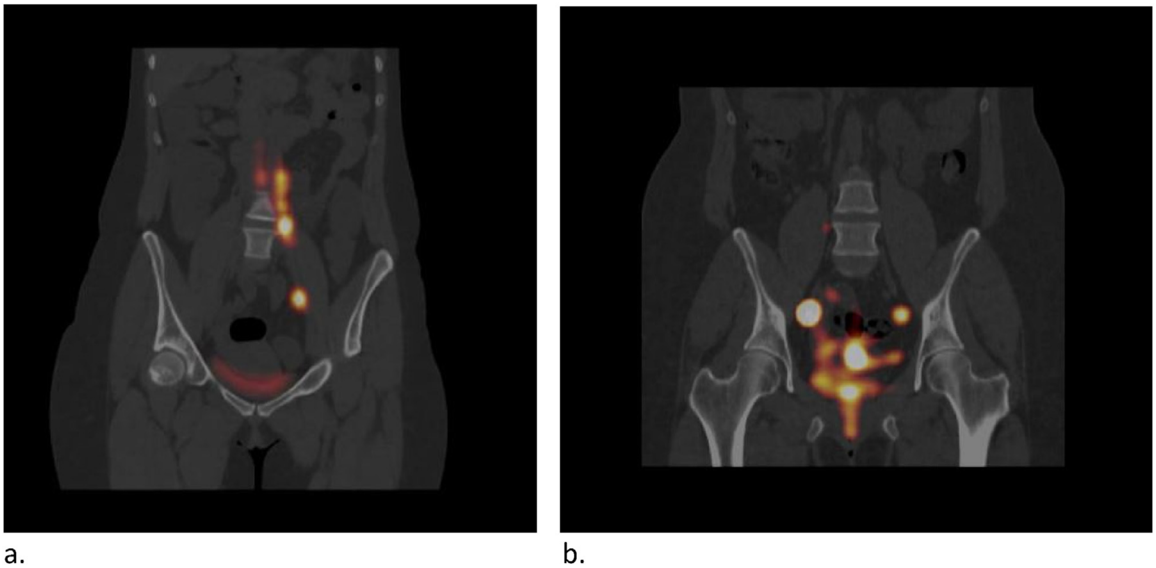

Fig. 3 – Bilateral and unilateral patterns of lymph flow from the cervical cancer: (a) unilateral lymph flow pattern with 99mTc-radiocolloids uptake in the left external iliac, common iliac and para-aortic lymph nodes. (b) Bilateral lymph flow with 99mTc-radiocolloids uptake in the left and right obturator lymph nodes.

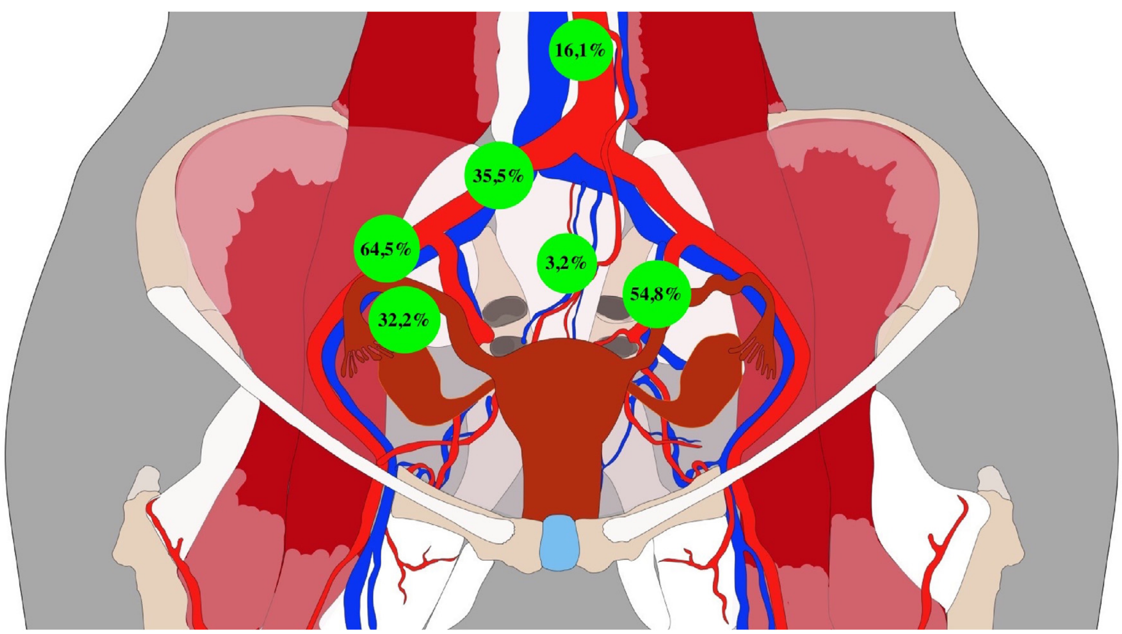

Fig. 4 – Topography of visualized lymph nodes in patients with cervical cancer: obturator – in 10 (32.2%), external iliac – in 20 (64.5%), internal iliac – in 17 (54.8%), presacral – in 1 (3.2%), common iliac – in 11 (35.5%), para-aortic – in 5 (16.1%) cases.

As mentioned earlier, the prophylactic irradiation of the para-aortic LNs is a subject of long lasting debates. At the end of the 20th century, RTOG randomized trial demonstrated that prophylactic irradiation of pelvic and para-aortic LNs significantly improves the overall survival and decreases the rate of distant metastases.[1] On the other hand, EORTC trial did not demonstrate any advantage of para-aortic LNs irradiation but showed a significant increase of toxicity in patients who had undergone the extended field radiotherapy.[4] More recently, Yap et al.[3] evaluated the role of prophylactic para-aortic LNs irradiation in patients with cervical cancer who had undergone chemoradiotherapy. The authors concluded that "the addition of para-aortic LNs irradiation to pelvic radiotherapy seems to offer little benefit to patients with locally advanced cervical cancer". At the same time Liang et al.[2] compared results of chemoradiotherapy with pelvic and para-aortic LN irradiation that was prospectively performed in 31 cervical cancer patients with historical control group that was represented by 47 women with cervical cancer. Analyses of treatment results demonstrated that the extended field radiotherapy covers pelvic and para-aortic LNs associated with significant improvement in overall, disease free and distant metastatic free survival: 87% vs. 62%, 82% vs. 54% and 79% vs. 57%, respectively. The acute myelotoxicity was mentioned in 27.8% of treated patients and was determined by the authors as the major limitation.

In our point of view, it is reasonable to propose that at least a small group of women with cervical cancer without instrumental signs of LNs involvement can benefit from prophylactic para-aortic LNs irradiation. At the same time, in many of these patients radiotherapy to the para-aortic region would cause additional toxicity only.

It is possible to propose that the lymph flow to the para-aortic LNs must precede their metastatic involvement. It means that women with radiocolloids uptake in the para-aortic LNs can be the best candidates for prophylactic irradiation of this region. At the same time, non-visualization of the para-aortic SLNs can be used as an additional argument against radiotherapy to the para-aortic nodes in patients with early cervical cancer. Analysis of the literature indicates that during the SLN procedure para-aortic LNs can be visualized in 3–10% cases. According to our data radiocolloids uptake in the para-aortic LNs was determined in 16.1%. This can be explained by high sensitivity of the SPECT–CT technique and substantial delay (2–4 h) from tracer injection to the acquisition start.

The presented data have several limitations. The low number of the evaluated patients with few cases of LN node invasion prevents from making a convincing conclusion on the risk of metastatic invasion of non-visualized pelvic LNs, particularly nodes that are located cranially from visualized SLNs. Unfortunately, a histological examination of para-aortic nodes was not performed even in women with visualized LNs in the para-aortic region, and we were not able to assess any correlation between the probability of metastatic involvement of para-aortic LNs and their visualization with radiocolloids during the SLN procedure. In addition, as we did not perform dynamic acquisition, it is possible to propose that at least some of the visualized para-aortic LNs can be the second echelon nodes. In the same time, according to widely accepted definition after pericervical/peritumoural injection of radiocolloids all hot LNs are considered as SLNs.[18,20,22] We accept this concept in our study.

In conclusion, SPECT–CT examinations with radiocolloids demonstrated a substantial variability in the location of SLNs in women with cervical cancer. The visualization of individual patterns of lymph flow from primary tumor can be considered as a promising tool for optimizating the volume of irradiated regional LNs.

Conflict of interest

None declared.

Financial disclosure

None declared.

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