LYMPH NODE – MAJOR IMPORTANCE PREDICTIVE FACTOR IN BREAST CANCER

SUMMARY: Information about the lymph node status is an important prognostic factor, influencing breast cancer staging and treatment options. The primary tumor drains along a lymph trajectory in a first regional lymphatic node, called sentinel node (SN), which captures the disseminated tumor cells. Breast’s lymph drainage is complex; together with the main axillary drainage pathway there are also secondary pathways, with significant practical importance in case of breast cancer. The study material was represented by 35 female patients, aged between 31 and 74 years, with palpable breast malignant tumor. We analyzed primary tumor size and location, and injected radiopharmaceutical (RP) substances. The RP substances used were $^{99m}$Tc–Hepatate and $^{99m}$Tc–Nanocoll, in doses of 15-30 MBq, by intradermal or peritumoral injection. The scintigraphic detection of the SN was possible in 34 cases (97.14%), with the following locations: axillary SN – 28 cases (82.36%); internal mammary SN – 4 cases (11.76%); infraclavicular SN – 1 case (2.94%); both axillary and internal mammary SN – 1 case (2.94%). All the four breast quadrants drain mostly towards the axillary SN. Tumors located medially and centrally drain towards the internal mammary and infraclavicular SN. In case of intradermal RP injecting we detected the SN after 15-20 minutes when using $^{99m}$Tc-Nanocoll, respectively after 45 minutes with $^{99m}$Tc-Hepatate, independently of primary tumor size ($T<2.0$ cm or $2.0 \text{ cm} < T < 5.0$ cm) and location. On the study lot, the most frequent location of the SN was those located in axilla (Supported by CNMP 4.1-058/2007).

Key Words: sentinel lymph node, breast cancer, radiopharmaceutical substances

NODULUL SANTINELĂ - FACTOR PREDICTIV MAJOR ÎN CANCERUL DE SÂN

Rezumat: Statusul limfonodului santinelă este un factor de prognostic important în stadializarea neoplasmului de sân și opțiunile terapeutice. Tumora primară drenază de-a lungul traiectului limfatic în primul limfonodul regional, numit nodul santinelă, care captează celulele tumorale diseminate. Drenajul limfatic al sânului este complex; împreună cu drenajul limfatic axilar sunt căi secundare cu importanță practică în neoplasmul de sân. În studiul au fost incluse 35 de femei cu vârsta între 31-74 ani cu tumori maligne palpabile. Am analizat dimensiunile și localizarea tumorii și am injectat substanțe radiofarmaceutice (RF). Substanțele RF utilizate au fost $^{99m}$Tc-Hepatate și $^{99m}$Tc-Nanocoll, în doze de 15-30 MBq injectate intradermic și peritumoral. Detectarea scintigrafică a nodului santinelă a fost posibilă în 34 cazuri (97,14%) cu următoarele localizări: axilară - 28 cazuri (82,36%), mamară internă - 4 cazuri (11,76%), infraclaviculară - 1 caz (2,94%), axilară și mamară internă - 1 caz (2,94%). Cele patru cadrate ale sânului drenază frecvent în nodulul santinelă axilar. Tumori de localizare centrală și medială drenază în limfonodul mamar intern și infraclaviculari. În cazul injectării intradermice s-a detectat nodulul santinelă după 15-20 de minute utilizând $^{99m}$Tc-Nanocoll, respectiv 45 de minute cu $^{99m}$Tc-Hepatate, independent de dimensiunea și localizarea tumorii primare ($T<2.0$ cm sau $99m$Tc-Hepatate 2-5cm). În studiul analizat localizarea frecventă a nodului santinelă a fost în axilă.

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INTRODUCTION

Breast cancer is a serious disease, with severe prognosis, affecting a large number of people of increasingly younger age. The survival rate at 5 years for all stages has a mean of up to 85%. Localized breast cancer has a 5 years survival rate of 96%, diminishing to 75% in case of regional dissemination and to 20% in case of distant metastasis (KESHTGAR et al, 1999). It is well known that patients with positive axillary lymph nodes present a high probability to develop distant metastasis, node, which captures disseminated tumoral cells (VIALE et al, 2005; HUANG et al, 2007).

Detection and biopsy of the axillary lymph nodes is a standard procedure of the oncologic protocol. It is well known that the breast has complex lymph drainage; besides the main axillary pathway there are also secondary pathways, of practical importance in case of skin invasive cancer:
- internal thoracic pathway (internal mammary);
- supraclavicular pathway, anterior to the clavicle;
- pathway towards the opposite side.

Sentinel node biopsy developed as a method of mammary carcinoma staging. Lack of metastatic invasion of the sentinel node avoids dissection of axillary lymph nodes, increasing patients’ quality of life (VERONESI et al, 2006; BLIDARU et al, 2006).

Sentinel node detection in breast cancer is theoretically based on the premises that the lymph drainage is specific and predictable, and that malignant cells spread sequentially: local, regional and distance metastasis. The primary tumor drains along a lymphatic trajectory in a first regional lymph node, called sentinel

between the cutaneous vessels of the two mammary regions there is a communication on the median line. This is one of the main pathways of extension from one mammary region to another of a breast cancer that invaded the skin. The lymphatic trunks themselves cross the median line to extend from the skin of a mammary region to the contralateral axillary region. These are mainly the retro-pectoral trunks (BASTIAN, 1995).

MATERIAL AND METHOD

The study was done in the Nuclear Medicine Laboratory, in the Plastic and Reconstructive Clinic of the Emergency County Clinical Hospital Timisoara and the University of Medicine and Pharmacy “Victor Babes” Timisoara.
The study lot was constituted by 35 female patients, aged between 31 and 74 years, that presented the eligibility criteria for sentinel node detection in case of breast cancer:

- positive diagnosis following clinical examination, imaging studies and anatomopathology;
- palpable malignant breast tumor.

We excluded from the study the patients with multifocal breast cancer, palpable axillary lymph nodes, previous surgery of the affected breast, pregnant and post-partum patients.

Three individual variables were analyzed:

- Primary tumor location
- Primary tumor size
- Injected radiopharmaceutical substance

The method consists of intradermal, peritumoral or intratumoral injection of radiopharmaceutical substance, followed by detection at skin surface of the gamma radiation emission of the sentinel node.

Most often, the radiopharmaceutical substance was injected intradermally; in subjects with large breasts and deep located tumor we preferred peri- or intratumoral injection.

The intradermal injection is justified by the fact that breast’s embryologic origin is ectodermal. Lymph ducts from breast skin and parenchyma merge in the subareolar lymphatic plexus, from where the lymph is drained towards the axilla through one or two main lymphatic trunks (GRANT et al, 1959; HALSELL et al, 1965; KETT et al, 1970; BORGSTEIN et al, 1998).

The intradermal injection consists of a unique dose of 15-30 MBq in 0.2-0.5 ml solution $^{99m}$Tc-Hepatate / $^{99m}$Tc-Nanocoll, at the level of tumor’s skin projection, the subject being placed in dorsal decubitus and with the ipsilateral upper limb in extreme abduction. Radiopharmaceutical substance aspiration in the syringe is preceded by aspiration of 0.2 ml air, to avoid contamination after injection and to favor colloid dispersion into the subcutaneous tissue. After radiotracer injection the puncture site is covered with a small impermeable plaster and the patient is invited to rub it for a few minutes.

In case of primary tumors $T>5.0$ cm, the radiotracer is injected peritumoral, in 4 injection points (1 ml solution/point) (KESHTGAR et al, 1999).

The radiotracers used were colloids – HEPATATE and NANOCOLL – radioactively labeled with $^{99m}$Tc. $^{99m}$Tc is constantly provided by a molybdenum generator from the Nuclear Medicine Laboratory.

In 10 cases patients were injected with $^{99m}$Tc-Hepatate, respectively with $^{99m}$Tc-Nanocoll in 25 cases.

The radiotracer particles that reach the interstitial level cross the endothelium of the lymph capillary to the first lymph node, where they are captured.

<table>
<thead>
<tr>
<th>PRIMARY TUMOR LOCATION</th>
<th>NR. SUBJECTS</th>
<th>PERCENTAGE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATERAL – EXTERNAL QUADRANTS</td>
<td>18</td>
<td>51.43</td>
</tr>
<tr>
<td>CENTRAL - PERIAREOLAR</td>
<td>5</td>
<td>14.28</td>
</tr>
<tr>
<td>MEDIAL – INTERNAL QUADRANTS</td>
<td>12</td>
<td>34.29</td>
</tr>
<tr>
<td>TOTAL</td>
<td>35</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Table 1. Distribution of clinical cases according to primary tumor location.

<table>
<thead>
<tr>
<th>PRIMARY TUMOR SIZE</th>
<th>NR. SUBJECTS</th>
<th>PERCENTAGE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T&lt;2.0$ cm</td>
<td>11</td>
<td>31.43</td>
</tr>
<tr>
<td>$2.0 cm &lt; T &lt; 5.0$ cm</td>
<td>16</td>
<td>45.71</td>
</tr>
<tr>
<td>$T &gt; 5.0$ cm</td>
<td>8</td>
<td>22.86</td>
</tr>
<tr>
<td>TOTAL</td>
<td>35</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Table 2. Distribution of clinical cases according to primary tumor size.
Scintigraphic data acquisition, the result of gamma radiation emission from the sentinel node, was done with a planar gamma camera with the following parameters: 
- Collimator Low Energy High Resolution (LEHR),
- Matrix: 256 x 256 pixel,
- Energetic window: 140 keV for $^{99m}$Tc,
- Dynamic acquisition from oblique-anterior position with a duration of 20 minutes (40 frames x 30s),
- Static acquisition from oblique-anterior and lateral position with duration of 5 minutes, at 20 minutes, 45 minutes and 2.3 hours after injection.

The scintigraphic image of the sentinel node appears as a focal zone with intense hyper fixation.

After preoperative lymphoscintigraphic detection of the sentinel node, it is identified and excised intraoperatively, followed by anatomopathology examination that establishes the diagnosis of certitude of metastases in the lymph node.

RESULTS

After intradermal or peritumoral injection of the radiopharmaceutical substance ($^{99m}$Tc-Hepatate / $^{99m}$Tc-Nanocoll) and after dynamic (20 minutes – 40 frames x 30 s) and static (5 minutes – at 20 minutes, 45 minutes and 2 hours from injection) acquisition, we obtained the scintigraphic detection of the sentinel node in 34 cases (97.14%).

The location of the sentinel node was as follows:
- Axillary lymph nodes – 28 cases (82.36%),
- Internal mammary lymph nodes – 4 cases (11.76%),
- Infraclavicular lymph nodes – 1 case (2.94%),
- Axillary and internal thoracic (internal mammary) – 1 case (2.94%).

The drainage towards the axillary lymph node is done from all the four quadrants.

In cases where the sentinel node was found at the level of the internal thoracic (internal mammary) lymph duct (11.76 cases), the primary tumor was located periareolar (1 case) and in the medial quadrants (3 cases).

The lymph drainage towards the infraclavicular lymph nodes was encountered in a single case (2.94%), in which the primary tumor ($T > 5.0$ cm) was located in the superior-medial quadrant.

The primary tumor ($T > 5.0$ cm) with two lymph drainage trajectories, with simultaneous visualization of two sentinel nodes, axillary and internal thoracic (internal mammary) (2.94%) was located in the inferior-medial quadrant.

In case of intradermal injection of the radiopharmaceutical substance we noticed the quick visualization of the sentinel node, at 15-20 minutes when
using $^{99m}$Tc-Nanocoll and at 45 minutes with $^{99m}$Tc-Hepatate, independently from the sizes ($T<2.0$ cm or $2.0 \text{ cm}<T<5.0$ cm) or location (lateral, central or medial) of the primary tumor.

In case of peritumoral injection, visualization of the sentinel node was done by late static acquisitions (during 5 minutes, at 2 or 3 hours after injection).

**DISCUSSIONS**

The oncologic protocol requires preoperative scintigraphic visualization of the sentinel node, surgical identification and excision, followed by anatomopathological examination, sentinel node status being a major predictive factor in breast cancer.

Although breast lymph drainage is mainly axillary, there are also secondary pathways, of considerable practical significance for breast cancer; there is a possibility for the sentinel node to be located on the internal thoracic (internal mammary) or supraclavicular pathway, or at contralateral level.

Breast's lymph ducts spread along the whole gland, achieving both deep and superficial drainage. There are separate lymph vessels for each lobe or lactifer duct. The lymphatic vessels communicate with the periareolar lymphatic plexus and are associated in this area with the venous plexus. The connections of direct deep lymph ducts perforate the deep fascia towards the underlying muscles. Primary lymphatic outflow crosses the superior-lateral quadrant along the pectoralis major muscle, towards the deep pectoral lymph nodes. Other lymph vessels communicate directly with the subscapular nodes. Thus, the lymph flows towards the central axillary group, then the apical axillary group and then towards the supraclavicular nodes. The internal thoracic (internal mammary) perforators are accompanied by medial lymphatic ducts draining into the parasternal nodes. The whole breast lymph network is tributary to these medial lymph nodes (BOSTWICK, 1983).

In the present study we succeeded the scintigraphic detection of the sentinel node in 34 out of 35 cases (97.14%), results similar to those obtained by other authors:

- BORGSTEIN (1998) – 89%
- VERONESI et al (1997) – 98%

The most frequent location of the sentinel node at the level of axillary lymph nodes was sustained and demonstrated by numerous authors. Sentinel node biopsy developed into a method of staging for the mammary carcinoma (VERONESI et al, 1997; BORGSTEIN, 1998; DIXON, 1998; KUEHN et al, 2004; VIALLE et al, 2005; HUANG et al, 2007).

In 1995, UREN et al made a study on 34 subjects with breast cancer and, using colloid small particles (3-12 nm), demonstrated multiple pathways of breast’s lymph drainage:

- Towards the axillary lymph nodes exclusively in 58% cases;
- Towards axillary and internal thoracic lymph nodes in 19.4 cases;
- Towards axillary, internal thoracic and infraclavicular lymph nodes in 13% cases;
- Towards the axillary and infraclavicular lymph nodes in 3.2% cases;
- Towards internal mammary lymph nodes in 6.4% cases.

In case of intradermal administration of colloid small particles, the lymph drainage is fast, requiring early data acquisition. The smaller the diameter of the colloid particles, the larger number of visualized lymph nodes.

**Fig.3** - Lymphoscintigraphic image, showing a unique focal area with intense collecting, located in the left axilla - increased probability of sentinel lymph node (SN).

The scintigraphic study was performed after intradermal injection of 0.8 mCi/0.5 mL of $^{99m}$Tc-Nanocoll, dynamic acquisition (20 minutes – 40 frames x 30 s) and static acquisition (5 min / 500000 counts), from left oblique-anterior position, using a planar gamma-camera with the following parameters: LEHR Collimator, matrix 256 x 256 pixel; energetic window – 140 KeV for $^{99m}$Tc
Larger colloid particles migrate slowly, requiring late acquisition of data.

The characteristics of the ideal colloid for visualization of the sentinel node are:

- Particles between 80-200 nm,
- Marked with $^{99m}$Tc,
- Stable during storage and in the blood flow,
- Quickly carried through lymph drainage pathways,
- Captured by the sentinel node.

After scintigraphic detection of the sentinel node, it is identified and excised intraoperatively, and then undergoes anatomicopathological examination. Biopsy of sentinel lymph node in breast cancer allows evaluation of its status, leading to axillary staging of the disease, minimally invasive surgical procedures, diminishing of postoperative morbidity and improvement in the quality of patients’ life.

**CONCLUSIONS**

The primary tumor drains along a lymph trajectory, into a first regional lymph node, called sentinel node, which captures disseminated tumoral cells.

Drainage towards the axillary lymph node is done from all the four quadrants.

Most frequent location of sentinel node in breast cancer is axillary – 82.36%, the lymph drainage being mostly towards the axillary lymph nodes.

There are also other locations of the sentinel node, due to the secondary pathways of drainage with practical importance in breast cancer: internal thoracic lymph nodes (11.76%), infraclavicular lymph nodes (2.94%), axillary and internal thoracic lymph nodes (2.94%).

The drainage towards the sentinel nodes from the internal thoracic and infraclavicular level was done by tumors having a medial or central location. Data acquisition has to be done with a large dimension detector or using multiple incidences, in order to detect these less frequent locations of the sentinel node.

In case of intradermal injection of the radiopharmaceutical substance, the sentinel node is detected quickly when using $^{99m}$Tc-Nanocoll (at 15-20 minutes), and later with $^{99m}$Tc-Hepatate (at 45 minutes), independently of primary tumor size ($T<2.0\ cm$ or $2.0\ cm<T<5.0\ cm$) and location (lateral, central or medial).

**REFERENCES**

REFERENCES (continued)