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Sentinel lymph node biopsy in epithelial malignant tumors

KEYWORDS: Sentinel Lymph Node Biopsy; Carcinoma; Surgery

The curative surgery of the epithelial malignant tumors is consisted of surgery of the primary tumor as well as lymph nodes in the regional lymphatic basin.

The role of lymph node dissection in locoregional treatment of patients with epithelial malignant tumors is still controversial.

Is a dissection of lymph nodes more therapeutical or diagnostic procedure?

Lymph node dissection enables removal of metastatic lymph nodes as potentially sites of new metastatic spread. Therefore it has a therapeutical and prognostic role. Also, lymph node dissection provides the most precise information on stage of the disease as well as decision on further therapeutic approach.

The extent of lymph node dissection - Where should we stop?

The extent is based on our actual knowledge of spreading of every type of carcinoma to the lymph nodes: breast cancer, thyroid cancer, skin melanoma, cervical cancer, gastric and rectal carcinoma, etc. It is still a matter of numerous actual controversies. Randomized clinical trials must provide the answers to these questions.

The optimal time for lymph node dissection

Initial, with the operation for primary tumor, when it has therapeutical, prognostic and staging importance.

Delayed, as loco-regional relapse in lymph nodes, when it also has therapeutic and curative importance.

The surgical removal of lymph nodes followed by histopathological analysis, using standard as well as techniques of immunochemistry, is the only way to confirm or exclude the presence or absence of lymph nodes metastases.

The clinical examination, ultrasonography, computerized tomography, nuclear magnetic resonance, and positron emission tomography are not able to provide a safe diagnosis of lymph nodes metastases.

Sentinel lymph node (SLN) concept

Sentinel lymph node was defined as the first draining lymph node for epithelial malignant tumors. Ramon Canabas, a South American surgeon, introduced the concept of sentinel lymph node (SLN) for predicting the regional lymphatic node status in penile carcinoma in 1977 (1). Nevertheless, Gould and his colleagues from the Washington Hospital Center have published their work and first introduced (sentinel node(in tumors of a parotid gland in 1951 (2). The concept of SLN in the management of melanoma especially those affecting the trunk where the lymphatic drainage could be ambiguous, using a blue-dye (isosulphan blue) injected around melanoma or the biopsy scar, is atribuded to Morton and his colleagues back in 1992 (3). In the early nineties, SLN concept was applied to breast cancer using a blue dye and later using a radioactive colloid to localize the sentinel node (4, 5). Recent published literature seems to support the fact that a combination of blue dye and radioisotope gives better results than either substance on its own. (6). Kelemen and co-workers have published the first results on SLN lymphadenoctomy in thyroid carcinomas in 17 patients in 1998 (7).

Is dissection of lymph nodes not involved by metastases useless and may it jeopardize patient's health?

Techniques of sentinel lymph node mapping

* The use of a vital blue dye (Metilen Blau, Isosulphan Blue, Patent Blue V, etc.) by intratumoral or peritumoral injection.

* The use of radioactive colloid (Tc 99) with preoperative and intraoperative (gamma probe) scintigraphy (8).

* Techniques of histological and immunochemical confirming, including PCR for detection of malignant cells without formed metastatic tissue in lymph nodes (9).

In which way is it possible to obtain the best results - a combination of vital dye and lymphoscintigraphy?

In the current literature the average rate of SLN identification is 91% (66%-100%) and when identified, the SLN accurately predicts the disease status of the neck in most patients (80%-100%) (10). The study from Roman group of SLN in thyroid malignancy showed the identification rates 66%, 50% and 83% for preoperative lymphoscintigraphy, vital dye and gamma probe scanning, respectively, as well as 100% using a combination of all three methods (11).

Where is the problem?

"Skip metastases", another draining nodes (internal mammary in breast cancer, skin melanoma of the trunk, mediastinal SLN in thyroid cancer, D2-3 levels in gastric carcinoma, etc).

In which way these problems may be solved?

Postoperative lymphoscintigraphy one day after surgery could be an answer to this question.

Current studies on SLN

The concept of SLN is the most commonly used for skin melanoma and breast cancer. After the first clinical trial for stage I skin melanoma, made by Donald Morton back in 1992 (3), numerous studies were investigated the feasibility and accuracy of SLN mapping in almost all epithelial malignant tumors.

There are few undergoing studies that should be mentioned at this time:

1. Intraoperative lymphatic mapping by the sentinel node technique in clinical stage I melanoma patients. WHO Melanoma Programme, 1997; Study Chairman: N. Cascinelli

2. A study investigating the diagnosis and treatment of early lymph node involvement in patients with primary cutaneous melanoma by sentinel lymph node biopsy with or without completion lymphadenectomy and molecular markers. NCRI/MSG SLNB in Melanoma Feasibility Study, 2001; Tim Eisen, Mo Keshtgar, David Ross, Christobel Saunders

3. After mapping of the axilla: Radiotherapy or Surgery AMAROS. EORTC 10981, 2001, Randomised Phase III (No of patients 3485), EORTC BCG

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What can be enhanced after the SLN concept?

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Sentinel node biopsy in the breast cancer: Possibility of the avoidance of axillary node dissection

KEYWORDS: Breast Neoplasms; Sentinel Lymph Node Biopsy

INTRODUCTION

Surgical treatment of early breast cancer includes the removal of the primary tumor and the removal of axillary lymph nodes, which drain the lymph from the tumor site.

Apart from the removal of the whole breast and dissection of the lymph nodes, the early breast cancer treatment, according to Halsted and Meyer method, became more extensive and culminated with hyper-radical interventions of Urban in the middle of 20th century. Their aim was to eradicate the malignant tissue and in this way to eliminate the possibility of disease spreading into the body (1,2). In the meantime, the significance of lymph nodes involvement for disease staging and prognosis was recognized, influencing also the extent of further systemic treatment and radiotherapy.

Completely different surgical approach to the disease, in the early eighties, was introduced by Veronesi, with the idea of conserving the breast and removal only the quadrant of the breast where the tumor is situated. Since noninvasive diagnostic procedures could neither confirm nor deny the lymph nodes involvement, axillary dissection remained the "gold standard" of these operations, and they have always been performed together with conserving operations. The term "sentinel node" (SN) (guard node), indicating the first lymph node which drains the tumor region, was introduced by Donald Morton (3).

Concept of the sentinel node biopsy (4) is dated in 1977, when Cabanas (4,5) performed the first operation of this type in the penile cancer. The largest number of studies in this field was conducted on malignant melanoma. Sentinel nodes were also studied on thyroid gland tumors, vulvar and uterine cervix cancer, and on gastrointestinal and colorectal tumors.

In 1994, Gulliano introduced SN biopsy and lymphatic mapping (determination of lymph paths) in the breast cancer (4). Considering significant analogy with the malignant melanoma (predictability of the lymph drainage), the concept has become easily applicable and widely accepted. Numerous large

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projects are trying to prove the hypothesis that high quality and simple disease staging can be provided by histological analysis of SN biopsy.

The expected percentage of patients with the involved axillary nodes is about 30%-40%, which means that two thirds of patients undergo axillary dissection because of negative lymph nodes (2). On the basis of histopathological processing of the fast frozen preparation of SN, one could predict with statistical significance whether remaining lymph nodes contain metastases or not. When metastases are not present in SN, dissection of remaining axillary nodes and all potential complications related to axillary dissection could be avoided in precisely defined conditions. Consequently, the quality of life would be improved (6,7).

MATERIAL AND METHODS

Sentinel node biopsy has been performed since February 1999 at the Clinic for Surgical Oncology of the Institute of Oncology Sremska Kamenica. Until the preparation of this manuscript, 124 interventions were performed. Patients included in the analysis had tumors sized from T1 to T2a. Ultrasound and/or mammographic visualization of the tumor are assumed. Axillary nodes were not palpable in any of the patients. The patients with the earlier breast operation, multicentric tumors and presence of carcinomatous mastitis, and pregnant patients, were excluded from analysis. After sentinel node biopsy, radical breast surgery (conservative or mastectomy) and lymph node dissection of level I and II was performed in all cases.

Marking and identification of the sentinel nodes

Marking of sentinel nodes exclusively with stain was used in the first 50 patients, with intraoperative visual identification. In 73 patients combined SN marking technique was used (stain + radiotracer); intraoperative identification was done visually and with manual gamma counter (Gammed IV-Capintec).

Figure 1. Stained SN immediately before extirpation

Figure 2. Extirpated stained lymph node

We used original stain Patentblau V-Byk Gulden (2 ml). Radiotracer was Antimony sulfide (Sb2S3), marked with Tc 99 m, and of 0.3 mCy (9.6 MBq) activity. Application method of both contrasts was identical. Application depth depended on the primary breast tumor localization, and it was subdermal, subcutaneous, or peritumoral in deeply positioned tumors.

Radiotracer application time preoperatively was 16 hours, while the stain was applied immediately before operation (10-15 min). Preoperative scintigraphy was performed in 15 patients with stable gamma camera (Orbite 75-Siemens). X ray was done minimum 2.5 hours after the application of radiotracer.

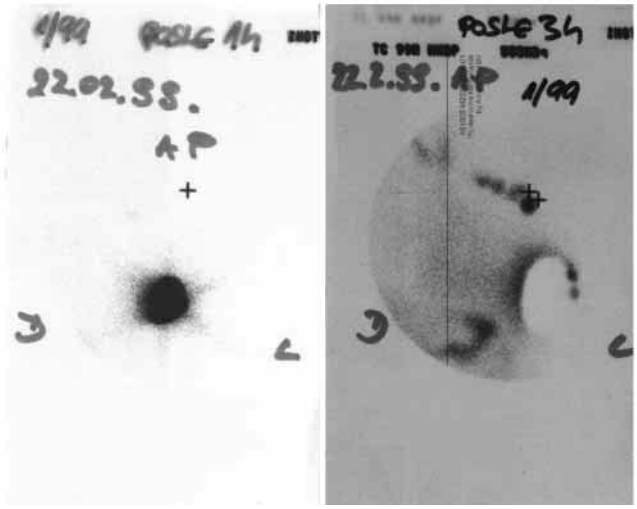

Figure 3. Scintigraphy images 1h and 3 h after application of Tc 99mm-antimony sulfide. SN marked with ++ on the right image

Histopathological SN analysis in the first 100 patients was performed from definitive paraffin preparations with classical hematoxilin-eozin (HE) staining. In 22 patients, starting from January 2002, extempore SN analysis was introduced on fast frozen preparations with compulsory use of immunohistochemical analysis (EMA) in case of the absence of metastases on HE preparations. Other dissected axillary nodes were analyzed from definitive paraffin preparations. All treated patients were divided in three subgroups and separately analyzed.

Subgroup A: In 50 patients SN marking was performed only with stain and visual intraoperative identification, and the remaining lymph nodes were analyzed on paraffin preparations.

Subgroup B: In 50 patients combined SN marking was performed (with stain and radiotracer), while SN histopathological analysis and the other lymph nodes were analyzed on the paraffin preparations.

Subgroup C: In 22 patients SN marking was done as in subgroup B, but histopathological SN analysis was done on fast frozen preparations with immunohistochemical treatment in case of the absence of metastases on HE stained preparations. All other axillary nodes were treated with standard paraffin preparations.

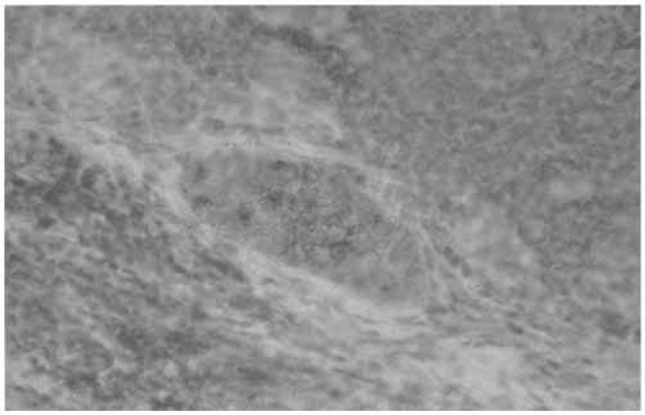

Figure 4. Micrometastasis detected in SN on extempore immunohistochemical examination (EMA)

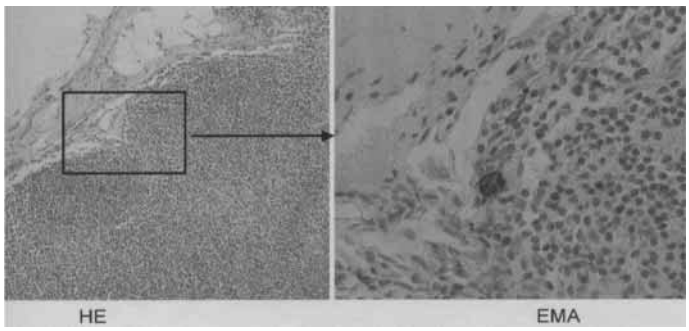

Figure 5. Immunohistochemically (EMA) detected micrometastasis from SN paraffin preparation

RESULTS

Table 1 shows that SN marking exclusively with stain (Patentblau V-Byk Gulden) and with their exclusively visual intraoperative identification, false-negative result appeared in 3 patients (6%), i.e. in 3 cases histopathological SN analysis was negative (without metastases), while metastases were found in other axillary lymph nodes. This influenced the sensitivity to decrease to 80%, predictable negative finding was reduced to 81%, and the total accuracy to 89.29%.

False-negative finding was not noticed in subgroup B (SN marking performed with both contrasts, and identification was visual and with use of manual gamma counter) which reflected the value of other findings. In subgroup C (where extempore histopathological analysis of SN on fast frozen preparations was done), there were no false-negative findings, and the sensitivity, specificity, predictable positive finding, predictable negative finding, and the total accuracy were 100%.

Table 1. Sensitivity, specificity and total accuracy of the test

	Subgroup A	Subgroup B	Subgroup C
Sensitivity	80%	100%	100%
Specificity	100%	100%	100%
False-negative finding	6%	100%	100%
Predictable positive finding	100%	100%	100%
Predictable negative finding	81%	100%	100%
Total accuracy	82.29%	100%	100%

DISCUSSION

Obtained SN biopsy results were mutually compared to determine the optimal method of their marking and optimal method of their histopathological treatment. SN marking and its precise identification, as well as histopathological analysis, are essential components, without which the complete procedure cannot be carried out. So, neither statistical data would be representative, nor they could be clinically used.

Our results showed that in SN marking combined techniques (staining used together with radiotracer) should be used, what a number of authors also confirmed (8-10). The application of preoperative scintigraphy with stable gamma camera is also important (10-12) because it enables preliminary insight into the lymphatic mapping and helps intraoperative identification of sentinel nodes with manual gamma camera.

Scintigraphy should be performed at least 2 to 2.5 hours after the application of radioisotope, since its adequate accumulation in SN cannot be expected earlier.

Preoperative time of stain contrast application is also an important factor. It may vary depending on position of the primary tumor in the breast. Practically, in case of all our patients the application time intervals for preoperative staining were between 10 and 20 minutes. Apart from making possible to stain the SN, the stain contrast can also stain lymph paths, which during preparation may serve as a direction to stained sentinel nodes.

Isolated stain marking technique has several objections. The most important one is the appearance of false-negative results, what was 6% on our sample. This value corresponds to the average value of false-negative results when isolated staining technique is applied. Also, it is possible not to stain axillary nodes. In the first place, drainage into internal mammary plexus disables SN biopsy, except when biopsy is routinely searched for in both localizations (in axilla and parasternally). Delay of operation with inadequate SN staining may cause difficulties in its identification.

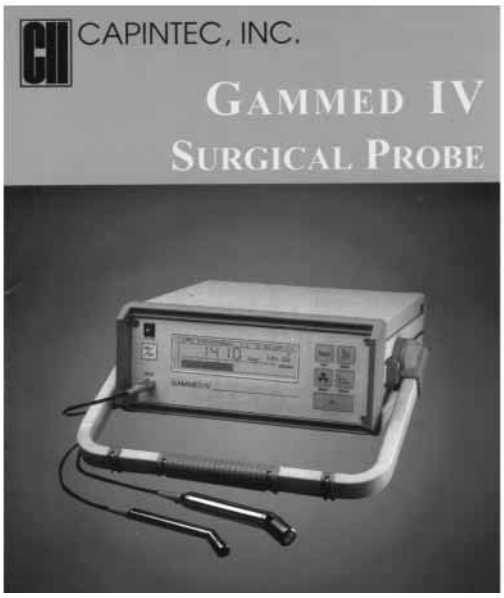

Figure 6. Intraoperative manual gamma camera GAMMED

Figure 7. Preoperative determination of the place of the greatest activity - Intraoperative SN localization with manual gamma camera

Introduction of radioisotope Tc 99m antimony sulfide combined with stained contrast for SN marking brought, in case of our sample, to the improvement of method sensitivity from 80% to 100%, false-negative SN dropped from 6% to 0%, and predictable negative level increased from 81% to 100%. However, series is not big enough to allow speaking of absolute supremacy of combined identification method, but trend in this direction is very clear. Other authors also confirmed the above stated (9,13-15). Activity (9.6 MBq) of applied radiotracer is absolutely sufficient for apparatus used during intraoperative identification (GAMMED IV), giving the sufficient sensitivity (16). As many authors report, our findings also indicate that operation should be performed within 24 hours after the application of radioisotope. The use of the manual gamma camera-counter enables the precise SN localization in the axillary region and, with scintigraphic images made preoperatively, easily identifies SN in the internal mammary plexus or other localization (13). Biopsy of the mammary chain (IMC) was not performed. In the patients with the strongest activity in this region, this fact was only stated, and the node with the strongest activity was extirpated, regardless its staining, since the aim of the study was to detect the predictability of histopathological finding of axillary lymph node involvement. In future, it would be very interesting to do

the biopsy of IMC nodes as well, in order to determine the need for parasternal irradiation (14), especially when primary tumor is localized in medial quadrant. Combination of drainage to both axillary nodes and IMC nodes was noticed in this study, what corresponds to data from literature.

Histopathological analysis is a third link required for the success of this method of SN biopsy. Precision of laboratory treatment, preparation cutting in search for metastatic deposits both in SN and other axillary nodes are essential for adequacy of this method. The percentage of micrometastases found in subgroup C (50%), which is substantially higher than literature data (17), alarmingly indicates that they can easily be overlooked and in that way compromise the complete procedure (18). Apart from a pathologist's experience in SN analysis on fast frozen preparation, the use of immunohistochemical methods of staining (18) is obligatory (in our case EMA-epithelial membrane antigen). Although some authors claim that dissection of other axillary nodes can be avoided in tumors under 1 cm in diameter and with SN metastases, our opinion is that the dissection of other lymph nodes is justified whenever micrometastases in SN are present (10). Histopathological treatment of preparations, complete with analysis on fast frozen preparations, cannot be performed under 40 minutes, what corresponds to literature data (19), but if it results in avoiding of axillary dissection, then it is absolutely justified.

Widespread use of SN biopsy in the breast cancer shows that it is easy for application. But since its introduction into the clinical practice, many authors are of the opinion that insufficient training leads to the occurrence of the false-negative results, especially in the first 30 operations (15). When surgeon is completely trained in this technique, the sensitivity of 98% and 100% can be expected, with the false-negative result maximum of 3% (20). Minimal predictive negative level should be 97% (21). It means that, on the basis of the absence of metastases in SN, we may claim that other axillary nodes do not contain metastases.

Combination of stained contrasts and radiotracers, and the obligatory use of intraoperative manual gamma camera-counter (14) should be used in marking and identification of SN. Preoperative scintigraphy with stable gamma camera, although not of key importance, is of help in the lymphatic mapping (11).

Experience of pathologists in extempore analysis of fast frozen SN preparations with the use of immunohistochemical staining is equally important as the experience of surgeon is.

CONCLUSION

This researching, and many others, indicates that in certain patients (especially T1a and T1b), under precise criteria, when SN metastases are not present, axillary dissection in the breast cancer (10, 22) and all its consequences (lymphoedeama, numbness, pain, limited movement in the shoulder joint) could be avoided.

We should remember that nowadays at least 50% of women undergo axillary nodes dissection within the breast cancer operative treatment because of histopathologically negative nodes.

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The sentinel lymph node in gastric cancer

KEYWORDS: Stomach Neoplasms; Sentinel Lymph Node Biopsy

On the basis of studying physiology of the stomach lymph drainage system, as well as follow-up of metastases' incidence, Japanese Research Association for the Stomach Cancer (JRSGC), has given recommendations on the systematic lymph nodes dissection D2, which has been established as a standard in the surgical treatment. According to the tumor localization and the disease stage, recommendations have been given which group of the lymph nodes should be removed during the surgical intervention. The lymph nodes' mapping by the vital colors is considered a significant method for intraoperative planning of dissection level and it was introduced at our Institute as a routine method in the clinical practice 5 years ago. Recently, the lymph nodes' sentinel biopsy has been intensively tested with aim to decrease intervention radicalness and morbidity. Significance of this method in the stomach cancer has been still tested. Former experience indicates that the complex stomach lymph drainage is significantly decreased using this method.

The sentinel node hypothesis states that the histopathological status of the first node on the lymphatic drainage pathway from a primary tumor reflects the tumor status of the entire lymphatic drainage basin. Within this hypothesis is the assumption that the surgeon can correctly and consistently identify this node (1). The anatomical definition of the sentinel node as the lymph node closest to the primary lesion does not take into consideration the physiology of lymph drainage: the node closest to the primary tumor is the first one to be involved only when it receives direct drainage from the injecting site.

Only a few studies have investigated the lymphatic flow system of gastrointestinal cancers from the point of view of the sentinel node (SN) concept. The validity of the sentinel node hypothesis is still controversial for gastrointestinal cancers including gastric cancer (2). It is important to determine the value of this procedure in an accurate staging and in minimally invasive approach to gastric cancers (3).

As Siewert and Sendler state, while the lymphatic flow on the surface of the body can be defined easily, the lymphatic drainage of the stomach is much more complicated (4). Namely, following rotation of the stomach during embryonic development, the lymphatic flow is not directed in a simple fashion. It is questionable whether a specific area of the stomach will drain into one lymph node echelon only (4). It is one of the essential obstacles for SLN biopsy (SLNB) in gastric cancer. Furthermore, skip metastasis seems to be quite common in cancer of the stomach (4).

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Most of authors use the dye method instead of the radionuclide method to detect the sentinel node. Ichikura et al. used indocyanine green injected endoscopically into the gastric submucosa adjacent to the tumor (5). Some of the authors used isosulfan blue dye, as Tsioulias (6). Miwa used patent blue dye (7).

The perigastric nodes close to the primary tumor are generally the SNs and the use of the radionuclide method implies interference by the gamma rays emitted from the primary tumor located very close to these lymphatic metastases.

The dye is usually injected around the tumor and was soon bound to albumin and carried specifically through the lymphatic vessels. The green-stained nodes are removed.

Moreover in the blue dye technique the time of injection of blue dye needs a careful monitoring, because there is a short window of time during which selective identification of the SN is possible. That is why Kitigawa et al. affirm that a combination of intraoperative endoscopic injection of blue dye and gamma probe inspection is helpful for localizing sentinel nodes in gastric cancer (8). To confirm the complete resection of sentinel nodes a survey of the abdominal cavity by a gamma-detecting probe is essential (3).

Then gastrectomy with extended lymphadenectomy was performed. Both SNs and non SNs are subjected to histological examination with hematoxylin-eosin.

In research of Kitagawa, using radio-guided method, SNs were identified in 138 of 145 patients (95.2%). The SN was positive in 22 of 24 patients with lymph node metastasis. The incidence of metastasis in the SNs was significantly higher than that in the non-SNs. The diagnostic accuracy according to SN status was 98.6%. Kitagawa underlined that radio-guided SN mapping is an accurate diagnostic procedure for detecting lymph node metastasis in patients with early-stage gastric cancer (2).

Hiratsuka reports that the success rate of SN detection is as high as 99%, with only one false negative (2).

A good basis for discussing the possibility of using the sentinel node mapping in patients with gastric cancers was done by Tsuburaya et al. (9). Namely, in order to examine the biology of sentinel lymph node of stomach cancer, they investigated solitary lymph node metastases that were hypothesized to represent sentinel lymph node. Out of 4620 patients with primary gastric cancers, 1271 cases with a localized tumor were selected and the localization of the solitary metastases in relation to the primary tumors were studied. They found that out of 130 tumors with a single basin metastasis, only 71% of the tumors in the upper third, 75% of the middle and 80% of the lower involved the node basins in the close vicinity (9). In the anterior wall and the greater curvature the rates of adjacent metastasis were more than 90%, while in the posterior wall and the lesser curvature they were 76% and 43%, respectively. Metastases of the remaining cases were identified at more distant basins (9).

According to Kitagawa, radical lymphadenectomy is the standard surgical approach even for early-stage gastric cancer with a relatively low incidence of lymph node metastasis because of the limited sensitivity of diagnostic imaging to detect micrometastases in regional lymph nodes (3).

In T1 gastric cancer (depth of cancer invasion limited in the mucosal or submucosal layer) the incidence of nodal involvement is reported to be as low as 2% to 18%, and in the T2 gastric cancer (cancer invading the muscular or subserosal layer) the incidence is about 50%.

Therefore Hiratsuka et al. consider that if D2 lymphadenectomy is larger than necessary in a considerably high proportion of T1 and T2 gastric cancer patients, than sentinel node concept is reliable indicator that could predict the absence of lymph node metastases with high accuracy, thus eliminating major operations (proximal, distal or total gastrectomy) and the lymphadenectomy (2).

Miwa stated in his research that extensive lymphadenectomy (D2) in 295 patients with early gastric cancer resulted in a significantly lower 10-year recurrence rate than limited lymph node dissection (D1) in 97 patients (7).

Among node-positive patients, the recurrence rate following D2 was significantly lower than that after D1. Among node-negative patients, there was no difference in recurrence rate between two groups. Miwa therefore suggests that we should always dissect the lymphatic basins even in cases with no sentinel node metastasis. In addition, patients with sentinel nodes containing metastasis should be treated with the D2 procedure (7).

Aikou et al. also stated that wide and complicated lymphatic stream from a gastric tumor contributed to the relatively high (23%) incidence of micrometastases and the frequent occurrence of skip metastasis (10).

A similar view was reported by Kosaka et al. Namely. According to their survey, not every sentinel node is located in the perigastric region near the primary tumor and that, if the preoperative examination indicates submucosal invasion, then a systematic regional lymph node dissection should therefore be carried out (11). Kosaka reports skip metastases in 15% of 51% patients with gastric cancer (11).

Finally, according to Maruyama opinion, the ability to identify a tumor free SN might enable the surgeon to avoid the morbidity associated with radical lymphadenectomy in patients with gastric cancer (12). But he concludes that it is too early to apply sentinel node biopsy for reducing the extent of lymphadenectomy for gastric cancer because of the complicated anatomy of lymphatic streams from the stomach, and because of the frequent skip metastasis and micrometastasis (12).

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The sentinel lymph node concept in thyroid carcinoma - Preliminary results

KEYWORDS: Thyroid Neoplasms; Sentinel Lymph Node Biopsy

Sentinel lymph node was defined as the first lymph node that the tumor would drain to, within the regional lymphatic basin of that tumor. The concept of sentinel lymph node (SLN) being predictive of the status of the regional lymphatic basin is commonly attributed to Ramon Canabas, a South American surgeon, following his pioneering work on the lymphatic drainage in carcinoma of the penis in 100 patients back in 1977 (1). Gould and his colleagues from the Washington Hospital Center published their work and first introduced (sentinel node(in tumors of a parotid gland in 1951 (2). In 1992, Morton and his colleagues introduced the concept of SLN in to the management of melanoma especially those affecting the trunk where the lymphatic drainage could be ambiguous, using a blue-dye (isosulphan blue) injected around melanoma or the biopsy scar (3). In the early nineties, SLN concept was applied to breast cancer using a blue dye and later using a radioactive colloid to localize the sentinel node (4,5). Recent published literature seems to support the fact that a combination of blue dye and radioisotope gives better results than either substance on its own. (6). In 1998, Kelemen and coworkers have published the first results on SLN lymphadenoctomy in thyroid carcinomas in 17 patients (7).

Different methods have been used for lymphatic mapping. First it was the application of vital color and later the concept lymphoscintigraphy and gamma probe was established. The vital dye and radiocolloid are applied intratumorally. Lymphoscintigraphy is performing preoperatively, while additional gamma probe and injection of vital dye are performed intraoperatively. After thyroidectomy marked sentinel lymph nodes are dissected and sent to frozen section and subsequent definitive histopathology.

The ideal radiotracer should have particles small enough to enter the lymphatics. All radiotracers that have been used are tagged to Technetium 99 with half-life time of 6 h, which enables the radioactive source to decay rapidly after injection (8). The optimal dose of radioactivity is still not established and ranges from 22 to 37 MBq per injection (9,10). Different vital dye was used in different studies - Metilen Blau, Patent Blue V, Isosulphan blue dye, in doses of 0.1 to 0.8 ml (mean 0.5 ml) per injection (7, 11,12).

From 2001 to 2002, we performed SLN biopsy in 14 patients with thyroid

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tumors. There were 5 cases of papillary thyroid carcinoma (one in thyroglossal duct cyst), 1 Hurthlle cell carcinoma, 7 follicular adenomas and 1 Hashimoto thyroiditis. All except one (Patent Blue V) were stained with Metilen Blau dye (mean 0.5ml/per injection). SLN identification rate was 72% (the staining failed in one case of follicular adenoma, 1/14). In all cases of malignancy and follicular lesions on frozen section histopathology, after frozen section of SLN, the dissection of central and/or lateral (jugular) lymph nodes were performed. All SLN were examined both by frozen section and HE definitive histopathology. SLN were located in cervico-central basins in 12 of 14 cases. In 1 case of follicular adenoma SLNs were first found in jugular basin ("skip") and in a case of papillary carcinoma in the thyroglossal duct cyst; SLNs were found in the level of carotid artery bifurcation bilaterally. We found no false-positive or negative results on HE definitive examination.

The impact of lymph node metastases in differentiated thyroid carcinoma is still controversial. Most of the relevant studies have shown no impact on long-term outcome (13,13). Presence of cervical lymph node metastases increases the regional relapse risk (14, 15).

The management of cervical lymph nodes varies from “berry picking“ to modified radical neck dissection. There is no argument of the necessity of neck dissection in cases of clinically enlarged lymph nodes. There is a significant disproportion in percentage of pre- and intraoperatively enlarged lymph nodes (27-45%) and histologically confirmed micro-metastases (80%-90%) in papillary thyroid carcinoma. Explanation for this could be in elective lymph node examination performed by experienced surgeons (16-21). The frequency of true lymphatic metastases from follicular thyroid carcinoma to regional lymph nodes is extremely unusual, being less than 1% (22).

Between 15% and 75% of all medullary thyroid carcinoma (MTC) cases have spread to the lymph nodes at the time of diagnosis. For this reason, Clark advocates a formal modified radical neck dissection for any lesion greater than 2 cm on the side in which it is located with a central node dissection on the contralateral side (23).

Keleman and coworkers published that in 2 of 17 cases colored SLN were retrosternal and so invisible intraoperatively using only blue dye (7). The group of Japanese authors claims that concordance between the SLN findings and regional lymph node status on definitive histopathology was 90.5%. Two of 22 patients had negative SLN and positive non-SLN nodes. The overall reliability of the method was 86.3% (11). Arch-Ferrer analyzed the accuracy of HE and immunohistochemistry staining and found 60% and 100% accuracy, respectively (24). Pelizzo reported 75.9% located SLN using only Patent Blue V dye. He found no false negative results after examination of both SLN and NSLN node (12). The group from Salzburg failed to detect SLN in cases with follicular carcinoma of the thyroid using both preoperative lymphoscintgraphy and intraoperative hand-held gamma probe (10). The group form University of Rome "La Sapienza" used the combination of all three methods of lymphatic mapping in papillary thyroid carcinoma, and showed 100% accuracy all together. Considering one method alone, identification rates were 66%, 50% and 83% for preoperative lymphoscintigraphy, vital dye and gamma probe scanning respectively (9).

In the current literature the average rate of SLN identification is 91% (66-100%) and when identified, the SLN accurately predicts the disease status of the neck in most patients (80%-100%). Limitations of SLN biopsy on thyroid cancer include staining of parathyroid glands, draining to medistinum "shine through" effect (25). The SLN biopsy for thyroid carcinoma is good and feasible technique for estimating the cervical lymph node status. It is now necessary to check the diagnostic accuracy of this procedure through controlled trials involving a more extended lymph node dissection in the neck. The clinical significance of this technique in thyroid cancer remains to be determined.

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Conference abstract
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Early detection of the regional lymph nodes' metastases by biopsy of the guard lymph nodes in melanoma patients - Our experience

KEYWORDS: Melanoma; Sentinel Lymph Node Biopsy; Diagnosis

Sentinel, or the guard lymph node is the first node on the way of the lymph drainage, from the place of the primary tumor to the regional lymph nodes. Extempore biopsy of the sentinel lymph node enables us to detect, or not, eventual metastases in the stated lymph node, before they appear, and also in other lymph nodes, which influences decision on dissection of the inspected region. Tested persons and methodology of work: From 1999 to 2000, 47 patients, operated for the skin melanomas, were completely tested and the results processed. The biopsy included radical excision of melanoma, biopsy of enlarged regional lymph nodes, biopsy of the sentinel lymph nodes in the melanoma with thickness of over 1 mm and II level of the skin involvement by Clark, and dissection of the regional lymph nodes, depending on extempore finding of the tested lymph nodes. The skin melanoma localizations by regions were as follows: head and neck 1 patient (2.12%); torso 22 patients (46.80%); upper extremities 10 patients (21.27%); lower extremities 14 patients (29.78%). From total number of processed patients, 7 were with melanoma thickness up to 0.75 mm (14.9%); 12 had melanoma thickness over 1.5 mm (25.53%); and 24 patients had melanoma thickness of over 3 mm (51.06%). Biopsy of the sentinel lymph node was performed in 12 patients (25.53%) and in 7 patients (14.89%) biopsy of enlarged lymph node was performed, while 5 patients (10.63%) had positive extempore finding of the tested lymph node. Dissection of the regional lymph nodes was performed in the patients with positive guard, or preoperatively palpable lymph nodes. In patients with negative HP finding of the lymph node (without metastases), operation was finished with radical excision of the skin malignant epithelial tumor. Biopsy of the guard lymph node is relatively new, and to some extent, sovereign method, which, with use of preoperative lymphoscintigraphy, may have an important role in disease staging, and in that way help surgeon in making decision on type of the surgical treatment.

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Importance of extempore control of the sentinel lymph node in the extremities' skin melanoma

KEYWORDS: Sentinel Lymph Node Biopsy; Diagnosis; Melanoma

Investigation of the role of lymph drainage and the existence of the sentinel lymph nodes found the biggest application in the extremities' skin melanoma, considering the prediction of the metastases spreading and learning of the lymph ways. Sentinel lymph node detection and the secondary deposits are of enormous importance since it enables dissection of the lymph node region on time. In that way, additional surgical interventions are avoided in a sense of postponed dissections, and it has been proven that detection of macrometastases improves survival. This method has been tested and accepted at the Surgical Department of our Institute since 1997. From 1997 to 2002 we performed 37 sentinel lymph node biopsies for skin melanoma using Metilen blau and Patent blue V for frozen section, and HE hystopathology staining. The method of vital dye should be combined with the method of lymphoscintigraphy. The method is carried out with patent blue V and Metilen blue with which the best results are obtained. Specificity and sensitivity of this method is in a very high what justifies the use of this method as a routine in the clinical practice.

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Sentinel lymph node biopsy in breast cancer: Our experiences

KEYWORDS: Breast neoplasms; Sentinel Lymph Node Biopsy; Neoplasm Staging

Determination of axillary nodal status (ANS) is the most important particular prognostic information on the patients with invasive breast cancer (IBC), essential for the staging and adjuvant chemotherapy. Conventional surgical approach, which involves axillary lymph node dissection (ALND) is often associated with considerable morbidity that could be avoided by applying less aggressive procedures. It primarily refers to early breast cancer in patients with low risk of axillary nodal metastases (ANM), with clinical negative axilla and in those cases where the adjuvant treatment could be designed on the basis of information obtained by pathological analysis of tumor. Intraoperative lymphatic mapping, identification and analysis of the sentinel lymph node could predict the status of axillary lymph nodes. Sentinel lymph node (SLN) is defined as the first lymph node to receive drainage from a primary tumor. By injecting patent blue vital dye subdermally, either around the primary tumor diameter less than 3 cm or directly in the walls around tumor cavity after excision biopsy of neoplasm in patients with clinical negative axilla. Blue stained nodes were identified, removed by surgical exploration and analyzed intraoperative by frozen section and definitive paraffin findings. The finding obtained by intraoperative analysis of frozen section was compared with final paraffin finding, which was obtained after axillary dissection as a part of conservative or radical surgical approach. We enrolled 64 patients with breast cancer. The sentinel lymph node was identified successfully in 53 (82%). Frozen section accurately predicted axillary nodal status in 49 patients (92.4%), on definitive paraffin section predictive value was 96.22% (accurately predicted ANS in 51 patients). Sensitivity (number of positive SLNB divided by the number of patients with ANM multiplied by 100) was 59% for intraoperative findings (10 positive SL on the frozen section) and 71% (12 patients) on the definitive findings 17 patients with axillary nodal metastases. Specificity (number of negative SLNB divided by number of patients without axillary lymph node metastases multiplied by 100) was 83% (39 negative SLNB patients out of 47 node negative patients). Overall accuracy (total number of true positive and true negative SLNB divided by the total number of the patients that were enrolled in study) was 76% for intraoperative results (49 out of 64) and 79% for definitive results (51 out of 64). In two patients with "ex tempore" negative SLNB micrometastases were found in definitive examination but in cases of two patients with definitive negative SLN some other positive axillary lymph nodes were found (false negative result that could indicate skip metastases). In 14 patients who each had only one positive axillary lymph node SN were accurately detected in 7 intraoperative accurate examination and 9 definitive findings. This study confirms that identification of the sentinel lymph node with vital blue dye is technically possible in our conditions and that histologic characteristics of the SLN probably reflect axillary lymph node status. Some outstanding questions need other investigations: Is this procedure quite safe to be included in the routine breast cancer treatment of the patients with low risk for regional metastases (clinically negative axilla, tumors diameters less than 0.5 or 1 cm, with favorable histological features, well differentiated tumors, low gradus, ER+, and for postmenopausal patients aged over 60 years)? Which technique should be used: vital blue dye or lymphoscintigraphy with radiocolloid mapping, or both? Is it necessary to check SLN for occult micrometastases with immunohistochemical staining or RT-PCR? Is frozen section of SLN enough accurate and secure to represent the basis for clinical decision taking? Is it either, just a current fashion in oncology surgery or procedure that will replace ALND for most breast cancer patients with clinically negative axilla?

Conference abstract
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Histopathological approach of sentinel lymph node biopsy examination

KEYWORDS: Sentinel Lymph Node Biopsy; Neoplasm Staging; Immunohistochemistry

Sentinel lymph node (SLN) examination has becoming one of the most advantageous and useful tools for more precise staging procedure of variety of solid malignancies, especially malignant melanoma, breast cancer and recently, thyroid cancer. With preoperative radioactive lymphoscintigraphic mapping, followed by intra- and postoperative histopathological examination of SLN, it is possible to significantly improve detection rate of regional lymph node metastases. Furthermore, using combined serial sectioning and immunohistochemistry, 65% of patients with malignant melanoma and 10%-15% of breast cancer patients that were initially node negative are generally found positive for SLN metastases. Concerning the possibility of understaging SLN positive patients, the following issues arise for all solid malignancies: frozen section examination should include 1-3 slices per node, depending on the size; paraffin-embedded samples require intensive routine histopathological workload with serial sectioning and tumor-specific immunohistochemistry on at least 3 layers, including 30%, 50% and 75% of SLN thickness, with expectance of less than 9.5% of missed metastases, which appear to be time- and cost-effective. Eventual improvements of detection accuracy could be obtained by cell separation technique and pellet examination, as well as with high sensitivity techniques, especially RT-PCR, but both are still remaining to be evaluated for a routine procedure of standard samples. While SLN negativity in breast cancer patients implies almost certain metastases-free lymph nodes status, the same, still, does not rule-out possibility of false negativity in melanoma patients. Overall, regardless of the extent of histopathological labor, SLN examination significantly improves accurate staging of solid malignancies, updating the adequacy of treatment modalities, with major improvements still remaining to develop.

Conference report
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Adverse reactions to isosulfan blue dye and patent blue dye during sentinel lymph node mapping

KEYWORDS: Sentinel Lymph Node Biopsy; Neoplasms; Rosaniline Dyes+adverse effects

The sentinel node hypothesis is predicated on the fact that a metastasis will traveled on a direct path from the primary tumor through the efferent lymphatic channels to the first draining lymph node in the regional lymphatic basin, the sentinel node (1). The challenge for implementation of sentinel lymph node biopsy (SLNB) is to develop a reliable minimally invasive technique that identifies all possible sentinel nodes (2). Lymphatic mapping with blue dye and sentinel lymphadenectomy is being increasingly used in the management of patients with melanoma, breast cancer and other solid tumor of epithelial localization (1).

The intraoperative method of lymphatic mapping and sentinel lymph node biopsy is rapidly becoming the preferable method because it provides accurate staging the axilla with low morbidity in patients with carcinoma of the breast (3,4). Also, this technique is a quality alternative to axillary dissection for breast cancer (5). Namely, it has recently been reported that selective sentinel lymph node biopsy can spare about 80% of patients with solid tumors from radical lymph node dissection (6), because SLN accurately reflects the status of the axillary nodes in patients with early-stage breast cancer (7). That is why SLN mapping is gaining widespread acceptance (7).

The lack of complications and the short time needed to perform this technique are attractive features (8). Identification of the SLN requires the use of different vital dyes (isosulfan blue dye, patent blue dye) and/or (99m) Tc-labeled colloid to trace the lymphatic drainage of a neoplasm (9).

Reviewing the actual literature on the adverse reactions to isosulfan blue and patent blue dye during SLN mapping for epithelial malignancies, we have analyzed the different reports on spectrum of mild to severe reactions, which have to be promptly recognized and, sometimes, aggressively treated.

Isosulfan blue (IB) has usually demonstrated a 1.5% incidence of adverse reactions. All the reactions are of an allergic type. Localized swelling at the site of administration and mild pruritus of hands, abdomen and neck have been reported within several minutes following administration of the drug. A

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death has been reported following the intravenous administration of compounds similar to IB. Severe reactions to IB may be manifested by edema of the face and glottis, respiratory distress or shock; such reactions may prove fatal unless promptly controlled by such emergency measures as maintenance of a clear airway and immediate use of oxygen and resuscitative drugs. Like other sensitivity phenomena, severe reactions are more likely to occur in patients with a personal or family history of bronchial asthma, significant allergies, drug reactions or previous reactions to triphenylmethane dyes.

In one of the largest prospective studies to adverse reactions to IB, carried out in USA, thirty-nine of 2392 patients (1.6%) had a documented allergic reaction during the mapping procedure (9).

Most reactions (69%) produced urticaria, blue hives, a generalized rash, or pruritus. The incidence of hypotensive reactions was 0.5%. In this trial, patients with a sulfa allergy did not display a cross-sensitivity to IB (9).

Out of two patients with reported hypotension and hypoxia in report of Laurie et al. (10), one required intubation, while another one suffered prolonged hypotension. Both patients recovered without sequelae (10).

Blue urticaria as a previously unreported adverse event associated with IB has been reported by Sadiq et al. (1).

With 639 consecutive SLNBs for breast cancer performed by Albo et al., 1.1% of patients had severe anaphylactic reactions to IB requiring vigorous resuscitation, while in one patient, the anaphylactic reaction required termination of the operation (5).

Five cases with adverse reactions to IB, of 267 patients, were reviewed by Cimmino et al. (11). The two patients with anaphylaxis experienced cardiovascular collapse, erythema, perioral edema, urticaria, and uvular edema. The blue hives in 3 patients resolved and transformed to blue patches during the course of the procedures. The incidence of allergic reactions in this series was 2.0% (11).

The three cases that varied in severity from treatable hypotension with urticaria and erithema to severe cardiovascular collapse with or without bronchospasm or urticaria, were reported by Leong et al., out of 406 patients who underwent intraoperative lymphatic mapping with IB (6).

Hoskin and Granger report that absorption of the dye into the circulation may interfere with pulse oximetry, causing falsely low readings (12). IB as a cause of pulse oximetry desaturation is also reported in some other studies (13,14).

Lymphatic mapping with blue dye may cause severe adverse reactions and therefore operating room personnel who participate in intraoperative lymphatic mapping where isosulfan blue is used must be aware of the potential consequences. That is why this procedure require a setting of anesthesiology protocol, which may consider the next:

(a) the lymphographic procedure which involves the use of IB should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the procedure to be performed,

(b) after subcutaneous administration of IB, competent personnel and emergency facilities should be available for at least 30 to 60 minutes, since severe delayed reactions have been known to occur with similar compounds,

(c) as physicians expand the role of SLN mapping, they should consider the use of histamine blockers as prophylaxis and have emergency treatment readily available to treat the life-threatening complication of anaphylactic reaction.

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Concept of sentinel nodes in gynecologic malignancies

KEYWORDS: Sentinel Lymph Node Biopsy, Lymph Node Excision

The concept of sentinel node identification is already established as part of standard practice in the surgical management of breast cancer and melanoma. However sentinel node biopsy has become a standard diagnostic procedure to assess lymph node status of various tumors including gynecological malignancies. The status of regional lymph nodes is important prognostic factor of survival in patients with early cancers of vulva, cervix and uterus. Sentinel node identification has the potential to improve the treatment of patients with gynecologic cancer with improved detection of lymph node metastases. Radical resection of vulvar and cervix cancers along with extensive lymphadenectomy remains the standard care for these cancers. In vulvar and cervical carcinomas sentinel node identification may significantly reduce extensive radical procedures, the number of patients undergoing unnecessary extensive lymphadenectomy in the absence of disease and decrease morbidity in gynecologic malignancies. The concept of sentinel node biopsy represents diagnostic non invasive or minimally invasive procedures that provide accurate preoperative staging of lymph node status.