THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

Examination of lymph node involvement in solid neoplasms – Sentinel lymph node biopsy

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UNIVERSITY OF DEBRECEN
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The Examination takes place at the Library of the Ophtalmology Clinic, Medical and Health Science Center, University of Debrecen, at 11.00. a.m., 26th of November, 2012.

Head of the **Defense Committee**:	Prof. Dr. András Berta, D.Sc.
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	Dr. Sándor Bende, Ph.D.

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1. Introduction

The modern, optimal treatment of patients with different neoplasms can be achieved, in most cases, with the stage adapted, combined modality therapy according to international protocols. In case of solid tumors the presence and exact number, or the absence of lymph node metastases are among the most important prognostic factors. Adjuvant chemotherapy, as well as, prognosis of the patient is determined primarily by the TNM stage. Preoperative imaging techniques provide a much more accurate determination of the T and M stage than that of the N stage. The correct status of lymph node metastases can be obtained only by histology following an optimally extended node dissection. The removal of more lymph nodes, on the other hand, incerases operative time, the rate of complications, and if negative may be considered unnecessary. Contemporary techniques are most helpful during intraoperative decision making by labeling the sentinel node, which is than examined histologically during the operation (SLN). If the SLN contains tumor deposit(s) extended dissection is warranted, while in case of negativity the patient can be spared of the possible complications.

During my work in the field of general surgery I focused on the detection of lymph node involvement of two of the most frequent types of cancer (breast and gastric cancer), where the extension of the dissection may substantially increase the rate of complications. Apart from the anatomical differences in the lymphoid drainage of the two organs, there are common features in the surgical technique which make a paralell examination feasible. In tumors of both organs the first potentially affected lymph node, the sentinel node, reflects reliably the status of the nodes in the second and third line, which is supported by data of numerous publications.

In 2002, 1.15 million new patients were diagnosed with mammary cancer in the world, one quarter of these in Europe. One half of the patients had no proven lymph node metastasis. The incidence of lymph node positivity in the 990.000 newly diagnosed early gastric cancer patients is 14%, while in Hungary the N stage positivity of the more prevalent advanced tumors is between 52-82%, depending on tumor size as well.

Determination of the accurate lymph node status, as well as, decreasing morbidity serve the basic interest of patients. We tested the „dye only" labeling technique of sentinel nodes and applied the Maruyama computer program in cases of gastric cancer. The efficacy of FNAB and core biopsy, as well as, their added value to imaging techniques were determined in cases of radial scar lesions of the female breast. The present theses is a summary of our results.

2. Specific aims

2.1. To determine the accuracy of preoperative percutaneous biopsies (FNAB, core biopsy, CB) in radial scar type lesions of the breast.

2.2. To calculate the added value of core biopsy avoiding the two-step surgical treatment (SNB) of radial scar.

2.3. To define the accuracy of the single agent (Patent blue) sentinel lymph node mapping in gastric cancer for the first time in Hungary.

2.4. To evaluate the accuracy of the single agent (Patent blue) sentinel lymph node mapping according to injection site (submucosal versus subserosal) in gastric cancer for the first time in the Eastern European region.

2.5. To examine the accuracy of the Maruyama computer program (MCP) and to detemine it's potential role in the stage-adapted surgery in gastric cancer.

2.6. To compare the accuracy of the Maruyama computer program and sentinel lymph node biopsy in prediction of lymph node involvement in gastric cancer.

3. Patients and Methods

3.1. In the “radial scar study” 45 consecutive patients were investigated with a mean age of 53.3 (range: 40 to 81) years from 01/2005 to 12/2009 at the Kenézy Breast Center among standardized circumstances. Inclusion criteria were “black star” appearance with long, thin spicules radiating from a radiolucent central area containing a fibroelastic core on mammograms. Exclusion criteria were other malformations on the mammogram and/or previous ipsilateral surgical procedure. Mammography was carried out with a GE Senograph 700T Mammo Unit in 31 cases and later with a GE alpha-RT Unit and Profect type (FUJI) phosphorous-disc digital technology in 14 cases. Complementary radiograms (aimed-enlarged and lateral), breast and axillary ultrasound (US) examination were performed with a Siemens Adara device and synchronous US guided FNAB and core biopsies were taken in all cases. FNAB was performed with 23G needles by the Cameco syringe pistol in local anesthesia. Two samples per patient were retrieved and fixed in alcohol immediately. After that, 2 to 5 cores per case were extracted with the Bard Magnum 14G needle instrument. These preoperative percutaneous biopsies were done by the same radiologist and both the preoperative and postoperatve specimens were analyzed by the same pathologist.

All lesions were non-palpable and smaller than 1 cm, which necessitatad ultrasound guided wire placement. I performed the oncoplastic procedures with periareolar or lateral incisions and remodellation of the breast tissue. In cases of invasive tumors the sentinel nodes were labeled with blue dye (Bleu Patenté V Sodique Guerbet 2.5%, F-95943 Roissy CdG, cedex, France) and intraoperative frozen section examinations were performed. After the surgical procedure the postoperative pathological findings were compared to the results of preoperative percutaneous biopsies. I investigated the sensitivity, specificity, false-negative rate, negative predictive value and positive predictive value of FNAB and CB. The diagnostic

value of CB was evaluated in comparison to that of FNAB, with the potential benefit of avoiding a second (SNB) surgical procedure.

3.2. A comparative study evaluating the accuracy of Maruyama computer program and single agent (Patent blue) sentinel lymph node mapping was prospectively controlled from February 2008 to April 2011 at the Department of General Surgery of the „Gyula Kenézy" Teaching Hospital, Debrecen, Hungary. 21 females and 19 males with a mean age of 64.1 (range: 50 to 80) years were enrolled. The average body mass index (BMI) was 22.6 (range: 17.1 to 27.6) Exclusion criteria were gastric stump tumor, cardia cancer, distant metastases and involvement of the surrounding organs (T4). Forty consecutive patients were evaluated by the Maruyama computer program. The calculation required the following prognostic factors in every patient: age, gender, position of the tumor (upper, middle, and lower third of the stomach, anterior or posterior wall, lesser or greater curve), Bormann's classification or early gastric cancer classification according to the Japanese Endoscopy Society, depth of infiltration, and histological type. Based on these data, the computer model calculated the proportion of the potentially positive nodes at each lymph node location (station 1-16).

All the patients underwent open gastric resection with blue dye mapping and modified D2 lymph node dissection. Sampling of station 10 and compartment 3 nodes (13 to 16) was optional, in case of macroscopic signs of infiltration, so we did not routinely calculate the values of these stations. After laparotomy, the lesser sac was opened (if it was needed) and 4 X 0.5 mL blue dye (Bleu Patenté V Sodique Guerbet 2,5%, F-95943 Roissy CdG, Cedex, France) was injected in four quadrants around the tumor. First 16 patients were marked submucosal by an endoscopist, the remaining patients' (n=23) injection was performed by the surgeon subserosaly. Lymphatic drainage was observed for up to 10 minutes following

injection. Blue stained lymph nodes were marked and modified D2 lymph node dissection was performed after gastric resection or total gastrectomy. The calculations of the MCP values, the staining method and the lymphadenectomy were supervised by the author. The position of lymph nodes was labelled according to the Japanese Classification of Gastric Carcinoma (JCGC). The sentinel lymph nodes were examined intraoperatively by frozen section and postoperatively the sentinel lymph nodes were sectioned at 0.2 mm intervals and hematoxylin and eosin (HE) staining and, immunohistochemistry examinations were performed with DAKO Monoclonal Mouse Anti-Human Cytokeratin (clone AE1/AE3; dilution 1:30; Dakocytomation; Glostrup; Denmark). Only negative sentinel nodes were examined for micrometastases.

To compare the MCP values and the results of the SLN mapping, I had to define a ‘cut-off level’, by using the calculation of the receiver-operating characteristics analysis (ROC). This logistic regression model indicates the probability of concordance between the predicted probability and the proven diagnosis of lymph node metastasis. I estimated the sensitivity and specificity with several cutoff points of the Maruyama program expected percentage values obtained by the ROC analysis for each of the 12 lymph node (LN) stations. I defined the best cutoff points for every LN station and the common critical cutoff point to maximize the test validity.

The detection rate has been calculated as the number of successful identifications of SLN in relation to the total number of SLN biopsy procedures. The sensitivity has been given as, the number of patients with positive SLN among total number of patients with a histopathologic evidence of lymphatic tumor spread. False negative rate has been defined as 100 % - sensitivity. Specificity has been calculated as the number of negative SLN biopsy results in relation to the sum of negative SLN biopsy results plus false positive results. Negative predictive value has been calculated as the number of negative results per the sum of negative

results and false negative results, while the positive predictive value has been quantified as the number of positive results per the sum of positive results plus false positive results. Statistical analysis of equivalence between the marking methods (subserosal versus submucosal) and between the results of MCP and SLN mapping was based on calculating ratios of test performance indicators (those of the SLN mapping method divided by those of the MCP procedure). Equivalence was established when the 95% exact confidence interval around such a ratio was fully contained within the range 0.8 to 1.25. The median follow up was 19 months (range: 1 to 39).

4. Results

4.1. In 6 cases (13.3%) the postoperative histology was invasive ductal carcinoma mimicking RS morphology. In 28 patients (62.2%) neither malignant tumor nor ductal carcinoma in situ (DCIS) could be detected on postoperative histological examination. In 8 cases (17.8) DCIS and in 3 patients (6.7%) invasive ductal carcinoma were associated with RS. In the non-malignant group (n =28) FNAB was non-diagnostic in 15 cases (53.6%). All the invasive ductal tumors (6 cases) were diagnosed with CB preoperatively, while FNAB was non-diagnostic (C1) in 2 cases, proved suspicious for malignancy (C4) in 2 patients and was positive (C5) in 2 cases. In 3 cases of invasive malignant tumor associated with radial scar, core biopsy was positive in 1 patient, while FNAB was negative or non-diagnostic in all of them. In the group of DCIS associated with radial scar the core biopsy detected malignancy in 5 cases and FNAB was positive (C5) in 1 case and was suspicious for malignancy (C4) in another case. In this cohort of patients the FNAB had an added value (C4, C5) in two cases with negative results of CB. The preoperative FNAB was non-diagnostic in 20 cases (44.4%). This high rate of false diagnosis was due to the acellular central scar of the RS. The core needle biopsy samples were evaluable in all cases. In the present series, the sensitivity of preoperative percutaneous biopsies (FNAB and CB) was 17.6% and 70.6%, specificity was the same (100%), false-negative rate was 82.4% and 29.4%. Negative predictive value was 48.1% and 84.8%. Applying both types of biopsies the results improved significantly. The lack false positive cases resulted in a 100% positive predictive value. The sensitivity increased to 82.3%, and the negative predictive value was 90.3%, while the false negative rate decreased to 17.6%.

In 9 cases (20%) we had to perform a second operation (SNB), no preoperative biopsy had been performed. Had we done a preoperative cytology only, I would have had to perform a

two-step procedure (SNB) in 7 patients (16%). Using of preoperative core biopsy, SNB was needed only in 2 cases (4%) to establish the proper diagnosis. The intraoperative frozen section and the postoperative histological examination of sentinel lymph nodes were negative in all cases of invasive tumors. SNB was not indicated in the DCIS group due to it's size, grade and histological results (non-comedo). The resection margins were adequate in all cases

4.2. In the comparative „gastric cancer study" I investigated 40 consecutive patients. Fifteen patients had signet-ring cell carcinoma, 18 patients had moderately differentiated adenocarcinoma and 7 patients had poorly differentiated adenocarcinoma. The tumor was localized in the upper third of the stomach in 8 cases, in the middle third of the stomach in 10 cases, and in the lower third of the stomach in 22 cases. The depth of invasion was T1 in 10, T2 in 11 and T3 in 19 patients. Total gastrectomy was performed in 14, and subtotal gastrectomy in 26 cases. A total of 795 lymph nodes were removed, and 19.9 lymph nodes per patient were examined in average (range 10 to 38 lymph nodes per patient). The mean number of blue nodes was 4.25 per patient.

In two patients with lower third tumors labeling of lymph node station 10 was hardly detectable. Both of them had a circular tumor. The first patient had a T3, grade 3, papillary adenocarcinoma with lymphatic vessel invasion and five lymph nodes were labelled (LN no.3, no.6, no.7, no.8, no.10), while the other patient had a T3, grade 3, signet-ring cell carcinoma and twelve lymph nodes were stained (LN no.5, no.6, no.7, no.8, no.10, no.11 and no.12).

The best cutoff point was estimated for every LN station and a critical cutoff point of 12% of the MCP expected percentage maximized the test validity. In 2 cases with metastases in LN station 9 and 12 the MCP calculated 0%, so the sensitivity was zero with any cutoff level, as in 2 other cases with metastases in LN station 10.

The sensitivity, specificity, negative predictive value, positive predictive value and accuracy of MCP were calculated with „12%-cutoff point" and with the „best-cutoff point" station by station. The sensitivity was 91.3%, specificity was 52.9% in the "12% group" and 91.3% and 64.7% in the "best group", respectively. Positive predictive value, negative predictive value and the accuracy was 72.4%, 81.8% and 75% in the "12% group" and 77.8%, 84.6%, 80% in the "best group".

In 39/40 cases sentinel lymph nodes were successfully identified, resulting in a detection rate of 97.5%. Seventeen patients (42.5%) were histologically node negative, in 16 patients both sentinel lymph nodes and non-sentinel lymph nodes were negative. In one case there was no sign of labeling, the BMI of this patient was 26.8. In 22/23 cases at least one SLN showed tumor involvement, with a false negative rate of 1/23 (4.3 %). In this single false negative case the tumor was T3 in extension, and grade 3 with perineural invasion histopathologically and the macroscopically involved lymph nodes could be found during the operation. In the sixteen SLN negative cases micrometastases were not found in the sentinel nodes. Results of the intraoperative frozen sections (SLN) correlated completely with the postoperative pathological findings. Sensitivity was 95.7%, and the specificity was 100%. Negative predictive value was 94.1% and the positive predictive value was 100%. The accuracy was 97.5%. These statistical values were investigated in relation to the injection site (submucosal versus subserosal). The specificity and positive predictive value was 100% in both groups, while the sensitivity, negative predictive value and detection rate was 100% in the submucosal group and 92.3%, 91%, 96% in the subserosal group. These parameters were proven equivalent based on 95% of confidence interval. The only false negative case in the subserosal group resulted a 7.7% of false negative rate.

The sentinel lymph nodes were located in the D1 compartment in 22 cases (57%), in 12 cases (32%) both in the D1 and D2 compartments and in four cases (11%) in the D2 compartment

only. Regarding lymph node involvement of the patients, SLN-s alone were positive in 6/23 cases (26%). Two of them could be found in the D2 compartment only. In 17 cases other lymph nodes were also involved. The D1 compartment only was involved in 8/17 (47%) cases, D1 and D2 compartments in 9/17 (53%) cases. In the group of T1 tumors (n=9), SLN were not involved. In the T2 group (n=11), 8 patients were SLN positive ones and 4 of them were non-sentinel positives, as well. Only 5/19 (26.3%) patients were lymph node negative in the T3 group.

No side-effects of blue dye mapping could be observed. The postoperative period of the 40 patients was uneventful without any surgical or non surgical complication. During the follow up period of 19 months we have lost 6 patients due to progressive disease. Four of the patients succumbed to progression of pT3 tumors with lymphovascular invasion and two patients had pT2 signet-ring cell carcinoma. All six patients had positive SLN and in four cases only one sentinel node was positive.

Results of the MCP and sentinel lymph node biopsies were equivalent only in sensitivity based on 95% confidence interval (CI) of ratio of indicators. Specificity, negative predictive value, positive predictive value and accuracy with SNB method were superior to those of MCP. The computer program with the „best cutoff point" (station by station) had a somewhat better statistical result than with the „12% cutoff point"; however, the area under the curve of SNB was higher. The difference was statistically significant between SNB and MCP with the „12% cutoff point" (p=0.0043) and between SNB and MCP with the „best cutoff point" (p=0.0003). The area under the curve of MCP with the „best cutoff point" was higher than MCP with the „12% cutoff point", although the difference was not significant (p=0.1441). I evaluated the accuracy of the MCP applied to first level lymph nodes, due to the low value of area under the ROC curve in station 9, 10 and 12. However, the accuracy and the statistical features (sensitivity, specificity, positive predictive value, negative predictive value) did not

change, because patients with false negative second level lymph nodes had false negative lymph node in the first level also. The accuracy of the MCP in sentinel node positive patients was 91% and only 75% in the complete group of the forty patients.

The sensitivity of the MCP in the cohort of SLN positive patients was 91% and the PPV was 100%. So, these features of the MCP and SNB was proven equivalent in the sentinel node positive group. In these patients the specificity and NPV could not be defined, due to the lack of negative cases. The accuracy of the Maruyama computer program in prediction of lymph node metastasis in stations 7 to 12 was 50% in sentinel node positive patients. This accuracy increased to 72%, when the sentinel node could be found in the compartment 2.

5. Conclusions

5.1. In the clinical practice preoperative percutaneous biopsies help us to select the optimal surgical procedure in patients with breast cancer. In the present study, invasive tumor mimicking RS was present in 6/45 cases (13%). DCIS or invasive ductal carcinoma were associated with RS in 11/45 patients (25%). The high rate of false negative preoperative results the RS like lesions should not be regarded as benign lesions, therefore surgical excision is mandatory.

In 9 cases we had to perform a second operation (SNB) as well. This means a disadvantage for the patient because the detection rate by the sentinel lymph node method is lower in a second operation. With the parallel application of FNAB and core biopsy, the detection rate was greatly improved. In our series SNB was needed only in 2 cases (4%) to establish the correct diagnosis.

5.2. Prospective randomized trials found a higher morbidity and mortality rate following extended lymph node dissection of patients with gastric cancer compared to those undergoing D1 dissection only. Forty percent of Western European patients have an unnecessary extended lymph node dissection in cases of R0 resection. Unfortunately, preoperative diagnostic tools have a low sensitivity and specificity in defining the lymph node involvement of patients with gastric cancer.

Although, it is difficult to draw definitive conclusions, due to the small sample size of our prospective, consecutive study, the detection rate of SLN-s was 97.5%, with a 95.7% sensitivity, 4.3% of false negative rate and a 100% specificity using the blue dye alone

technique. In patients with T1 and T2 gastric tumors I did not find false negative case, so the sensitivity was 100% in this group.

The influence of BMI on SLN detection is well known. In our investigation, the single non marking patient's BMI was higher than average (26.8 versus 22.8). This increase in BMI is not dramatic, but BMI calculations do not reflect the distribution of fat inside the body.

The two cases of positive SLNs confined to the D2 compartment only, call attention to the possibility of skip metastases. Using the blue dye-alone marking method we can avoid an insufficient (limited) lymph node dissection.

The statistical equivalence of the submucosal and the subserosal dye injection technique was showed in this study. Based on these findings we prefer the logistically easier, time sparing subserosal marking method except for the cases of non palpable tumors, when the endoscopist labels the SLNs intraoperatively.

This comparative, standardized study demonstrated a similar degree of reliability of MCP to international results, with 91.3% of sensitivity, 64% of specificity and 80 % of accuracy at the best cutoff point. The false negative rate was 8.7%. These statistical features are superior to the results of preoperative imaging diagnostic tools.

The sensitivity of MCP and SNB was proven equivalent, while the specificity, negative predictive value, positive predictive value and accuracy were higher with SNB. It is generally accepted, that metastases in the SLNs indicate D2 lymphadenectomy.

We analyzed the relevance of the MCP in sentinel node positive patients. The accuracy was higher by 16% than in the group of our total forty patients.

In summary, this comparative study showed a lower clinical impact of the Maruyama computer program compared to SNB; however using these two methods in a parallel fashion could be useful in preoperative decision making for the appropriate extension of lymphadenectomy and individualize stage-adapted surgery in gastric cancer.

New observations

1. **Based on the results of the above detailed, first Hungarian study, we recommend simultaneous use of FNAB and core biopsies, to improve the accuracy of preoperative diagnosis in the cases of radial scars of the female breast.**

2. **The accurate diagnosis renders an SNB unnecessary, which is less efficient when carried out as a second, complimentary operation.**

3. **The result of the present study demonstrated the feasibility of sentinel lymph node mapping with blue dye only technique in T1-T2 gastric tumors.**

4. **The subserosal marking method proved to be easier and more time sparing in the cases of palpable tumors during open surgical procedures, while the non-palpable tumors can be labeled submucosally by the endoscopist intraoperatively.**

5. **Calculated by our standardized study the Maruyama computer program showed an accuracy of 80%, specificity of 64%, and sensitivity of 91.3%. The false negative rate was 8.7%. The statistical features of the Maruyama computer program is superior to those of current preoperative diagnostic imaging tools. The routine use of the program is suggested in surgical departments to increase the number of eliminated metastatic lymph nodes.**

6. The sensitivity of Maruyama computer program and sentinel lymph node biopsy was proven equivalent, while the specificity, negative predictive value, positive predictive value and accuracy were higher with SNB. The accuracy of the MCP in sentinel node positive patients was higher by 16% than in the group of the total of our forty patients. The sensitivity and the positive predictive value of the MCP and SNB was proven equivalent in the sentinel node positive group.

It will be a fascinating question of the future whether the simultaneous, widespread use of the Maruyama program and SNB will serve better the tailoring of a stage adapted operation for patients with gastric cancer.

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Candidate: Dezső Tóth
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List of publications related to the dissertation

1. **Tóth, D.**, Sebő, É., Sarkadi, L., Kovács, I., Kiss, C., Damjanovich, L.: Role of core needle biopsy in the treatment of radial scar.
   Breast. Epub ahead of print (2012)
   DOI: http://dx.doi.org/10.1016/j.breast.2012.02.009
   IF:2.491 (2011)

2. **Tóth D.**, Kathy S., Csobán T., Kincses Z., Török M., Plósz J., Damjanovich L.: Gyomortumorok őrszemnyirokcsomó-jelölésének prospektív, összehasonlító vizsgálata: Submucosus kontra subserosus jelölés.
   Magyar Seb. 65 (1), 3-8, 2012.
   DOI: http://dx.doi.org/10.1556/MaSeb.65.2012.1.1

3. **Tóth, D.**, Török, M., Kincses, Z., Damjanovich, L.: Prospective, comparative study for the evaluation of lymph node involvement in gastric cancer: Maruyama computer program versus sentinel lymph node biopsy.
   Gastric Cancer. Epub ahead of print (2012), p. 13-19, p. 13-19. -
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4. **Tóth, D.**, Kincses, Z., Plósz, J., Török, M., Kovács, I., Kiss, C., Damjanovich, L.: Value of sentinel lymph node mapping using a blue dye-only method in gastric cancer: A single-center experience from North-East Hungary.
   Gastric Cancer. 14 (4), 360-364, 2011.
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List of other publications

5. **Tóth, D.**, Kathy, S., Csobán, T., Kincses, Z., Plósz, J., Török, M.: Prospective, consecutive study for sentinel lymph node mapping in gastric cancer: Hungarian experiences. *World J. Surg. 35*, s291, 2011.

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Acta Chir. Hung. 38 (2), 187-189, 1999.

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