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RELATION BETWEEN METASTATIC INVOLVEMENT OF INTERPECTORAL (ROTTER'S) LYMPH NODES AND LOCATION, SIZE AND GRADE OF BREAST CANCER

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Summary

The study was aimed at analyzing metastatic involvement in interpectoral (Rotter's) lymph nodes related to site, size and grade in primary breast cancer.

The study includes 210 female patients undergoing surgery for breast cancer at the University Hospital for Tumors, Zagreb, Croatia. In addition to the standard surgical procedure, interpectoral (Rotter's) lymph nodes were removed in all of the patients.

Rotter's lymph nodes were identified in 66.2% of the patients, with metastatic involvement revealed in 18.5% of the Rotter's nodes. Metastatic involvement of Rotter's nodes in patients with negative and positive axillary lymph nodes was 2.8% and 34.6%, respectively. Considering location of the tumor in patients with metastatic involvement of Rotter's nodes, it was shown that tumors located in the upper breast quadrants were more prone to metastasis to Rotter's nodes, demonstrating a significant positive correlation between tumor location within the breast and positive Rotter's lymph nodes (r=0.93, p=0.02). As regards tumor size, Rotter's nodes were identified in 15%, 20% and 60% of stage T1 (<2 cm), T2 (2-5 cm) and T3 tumors (>5 cm), respectively with a significant positive correlation (r=0.759, p=0.09). Also considering tumor grade it was shown that metastatic involvement of Rotter's lymph nodes was 3.8%, 17.6% and 31.6% of grade I,II and III, respectivly with a significant positive correlation (r=0.993, p=0.08).

The results show that one-fifth of breast cancer patients, or even one-third of them with positive axillary lymph nodes, are discharged with positive interpectoral lymph nodes that remain undiagnozed and non-extirpated. As the nodes can be surgically removed without additional mutilation, the exploration of Rotter's lymph nodes should be introduced into routine clinical practice. In upper breast quadrants, tumors were more prone to metastase in to Rotter's nodes, as well as higher tumor size and grade.

KEY WORDS: *breast cancer, interpectoral (Rotter's) lymph nodes*

METASTATSKA ZAHVAĆENOST INTERPEKTORALNIH (ROTTEROVIH) LIMFNIH ČVOROVA U ODNOSU NA LOKACIJU, VELIČINU I GRADUS RAKA DOJKE

Sažetak

U ovom je radu analizirana metastatska zahvaćenost interpektoralnih (Rotterovih) limfnih čvorova u odnosu na lokaciju, veličinu i gradus primarnog raka dojke.

Analizirano je 210 bolesnica s rakom dojke operiranih u Klinici za tumore u Zagrebu. U svih su bolesnica, uz standardni kirurški zahvat, uklonjeni i interpektoralni (Rotterovi) limfni čvorovi.

Rotterovi limfni čvorovi otkriveni su u 66,2% bolesnica, od kojih je 18,5% bilo zahvaćeno metastazama. Metastatska zahvaćenost Rotterovih čvorova uočena je u 2,8% bolesnica s negativnim aksilarnim čvorovima, odnosno u 34,6% bolesnica s pozitivnim aksilarnim čvorovima. S obzirom na lokaciju tumora u bolesnica s metastatskom zahvaćenosti Rotterovih čvorova, uočeno je da tumori u gornjim kvadrantima dojke češće metastaziraju u Rotterove limfne čvorove, što pokazuje znakovitu pozitivnu povezanost između lokacije tumora u dojci i pozitivnih Rotterovih čvorova (r=0,93, p=0,02). Kad je riječ o veličini tumora, Rotterovi su čvorovi otkriveni u 15% bolesnica sa stadijem tumora T1 (<2 cm), 20% sa stadijem T2

(2-5 cm) i 60% sa stadijem T3 (>5 cm) uz znakovitu pozivitnu povezanost (r=0,759, p=0,09). S obzirom na gradus tumora, također je uočena metastatska zahvaćenost Rotterovih limfnih čvorova u 3,8% bolesnica s gradusom I, 17,6% bolesnica s gradusom II i 31,6% bolesnica s gradusom III uz znakovitu pozitivnu povezanost (r=0,993, p=0,08).

Rezultati pokazuju da je jedna petina bolesnica s rakom dojke, ili čak jedna trećina s pozitivnim aksilarnim limfnim čvorovima otpuštena iz bolnice s pozitivnim interpektoralnim limfnim čvorovima koji nisu dijagnosticirani, pa tako ni uklonjeni. Kako se ti čvorovi mogu ukloniti bez dodatne mutilacije, otkrivanje Rotterovih limfnih čvorova treba postati redovitom kliničkom praksom. Tumori smješteni u gornjim kvadrantima dojke češće metastaziraju u Rotterove čvorove, kao i tumori veće veličine i višega gradusa.

KLJUČNE RIJEČI: *rak dojke, interpektoralni (Rotterovi) limfni čvorovi*

INTRODUCTION

The study is aimed at exploring the level of Rotter's lymph node involvement in breast cancer patients with positive (metastatically involved) axillary lymph nodes to obtain more detailed information about disease status and their prognostic value, which potentially have a substantial effect on adjuvant chemotherapy and postoperative irradiation. For many patients undergoing surgery without Rotter's lymph node removal, the nodes may be responsible for further spreading of the disease, indicating the therapeutic effect of this type of surgery. Finally, the obtianed results may come in handy as guidelines on routine removal of Rotter's nodes in breast cancer patients.

The study includes 210 female patients operated for primary breast cancer.

A special attention is paid to the analysis of:

1. Overall, surgically confirmed presence of Rotter's lymph nodes
2. Metastatic involvement in Rotter's lymph nodes in relation to:
   a) tumor location within the breast
   b) tumor size
   c) tumor grade

PATIENTS AND METHODS

The study includes 210 female patients undergoing surgery for breast cancer at the Department of Surgery, University Hospital for Tumors, Zagreb, Croatia. All the patients were operated on by the same surgical team. Standard preoperative evaluations included x-ray test of the lungs, spine and pelvis, abdominal and breast ultrasonography, mammography, complete laboratory tests, tumor marker CA 15-3. All operations were performed under general anesthesia using ordinary endotracheal intubation (1, 2, 3). All patients underwent surgical tumor biopsy, and surgery for biopsy confirmed breast cancer (either segmentectomy or breast cancer ablation) (4), as well as dissection of axillary nodes at all three levels and Rotter's lymph node extirpation (5). Pathohistologic evaluation of breast carcinoma performed with intraoperative frozen section biopsy was definitely confirmed on permanent tissue sections embedded in paraffin and stained with hemalaun-eosin. Tumors were classified according to the World Health Organization Classification of Tumors (6), and the grade of differentiation according to the Bloom-Richardson grading scheme (7).

The statistical method used to analyze the data was the correlation test with the obtained values expressed in percentage.

RESULTS

The study results showed that breast cancer patients were in the age bracket between 28 and 85 years of age (median 57 years). 113 (53,8%) patients underwent breast cancer ablation, and in 97 (46,2%) segmentectomy was performed.

All of the patients underwent radical dissection of axillary lymph nodes and removal of interpectoral fat tissue with Rotter's lymph nodes.

The location of the tumor within the breast assessed prior to surgery (clinical examination, mammography or ultrasonography) was as follows:

1. ULQ (upper lateral quadrant)
   - 101 patients (49%)
2. LLQ (lower lateral quadrant)
   - 32 patients (15%)

3. UMQ (upper medial quadrant)
   - 40 patients (19%)
4. LMQ (lower medial quadrant)
   - 10 patients (5%)
5. retromammillary region
   - 27 patients (12%)

The tumor's largest diameters (tumor size) measured by pathologist were classified in three groups according to the TNM classification. T1 tumors, <2cm in their largest diameter, were found in 129 (61,4%) patients; T2 tumors, 2–5 cm in their largest diameter, and T3 tumors, >5 cm in their largest diameter, were found in 71 (33,8%) and 10 (4,8%) patients, respectively. As T1 tumors can be further subclassified as T1a (0-5 mm), T1b (5–10 mm) and T1c (10–20 mm), 7 (3,3%) patients were subclassified into the T1a, 34 (16,2%) into the T1b and 87 (41,4%) into the T1c group.

Pathohistologic evaluation showed invasive ductal carcinoma in 185 (88.1%), mucinous carcinoma of the breast in 9 (4.3%), lobular carcinoma in 13 (6,2%), papillary, planocellular and medullary carcinoma of the breast in 1 (0.5%) patient each. Of 185 invasive ductal carcinomas, 26 (14.5%) were grade I, 102 (56.6%) grade II, and 57 (28.9%) grade III.

Pathohistologic examination of axillary lymph nodes and extirpated interpectoral fat tissue for potential presence of Rotter's lymph nodes showed no metastatic involvement or negative axillary lymph nodes in 106/210 (50,5%), while 104/210 (49,5%) patients were axillary lymph node positive. Interpectoral fat tissue of 71/210 (33,8%) patients did not contain any lymph nodes, while at least 1 lymph node was found in 139/210 (66,2%). Tumor cell-positive Rotter's lymph nodes were found in 39/210 (18,5%), and 171/210 (81,4%) patients had tumor-negative nodes or did not have praesent interpectoral (Rotter's) lymph nodes. Of patients with pathohistologically confirmed Rotter's nodes (139/210), 28,1% were positive (with metastatic tumor cells), and the remaining 71,9% were negative.

From a total of 106 patients with negative axillary lymph nodes, in 103/106 (97,2%) Rotter's lymph nodes were not found or the presence of metastasis in Rotter's nodes was not pathohistologically confirmed; 3/106 (2,8%) had positive Rotter's lymph nodes.

Tumor location	Rotter's lymph nodes positive	Rotter's lymph nodes negative
ULQ	19 (48%)	87
UMQ	11 (29%)	33
LLQ	3 (9%)	27
Retromammilar	5 (11%)	20
LMQ	1 (3%)	12
	39 (100%)	171

Figure 1. Metastatic involvement of Rotter's lymph nodes related to tumor location in breast (ULQ – upper lateral quadrant, UMQ – upper medial quadrant, LLQ – lower lateral quadrant, LMQ – lower medial quadrant).

Of patients with positive axillary lymph nodes (104/210 patients or 49.5%), in 68/104 (65,4%) Rotter's lymph nodes were not found or negative; 36/104 (34.6%) had positive Rotter's lymph nodes, while the nodes were negative in 37/92 (40.2%).

The median number of lymph nodes removed in 210 patients was 15.1 (minimum 5, maximum 28). The median number of positive lymph nodes in 104 axillary lymph node-positive patients was 5.4 (ranging from 1 to 21).

The average number of extirpated Rotter's lymph nodes in 116 patients with identified Rotter's lymph nodes was 2.7 (ranging from 1 to 12). Lymph node-positive patients had 2.2 nodes

	Metastatic involvement of Rotter's lymph nodes		
Tumor (T)	Negative	Positive	
T1a	6 (85.7%)	1 (14.3%)	7 (100.00%)
T1b	28 (82.4%)	6 (17.6%)	34 (100.00%)
T1c	76 (87.4%)	11 (12.6%)	87 (100.00%)
T2	56 (80.0%)	14 (20.0%)	70 (100.00%)
T3 i T4	4 (40.0%)	6 (60.0%)	10 (100.00%)
	170 (81.7%)	38 (18.3%)	208 (100.00%)

Figure 2. Positive Rotter's lymph nodes related to tumor size (T1a – tumor less than 5 mm, T1b – tumor size between 5 and 10 mm, T1c – tumor size between 10 and 20 mm, T2 – tumor size between 2 and 5 cm, T3 – tumor size larger than 5 cm).

	T1	T2	T3 i T4
All patients	128	70	10
Positive Rotter's nodes	18	14	6
%	15%	20%	60%

Figure 3. Positive Rotter's lymph nodes related to tumor size (T1 – tumor size less 20 mm, T2 – tumor size between 2 and 5 cm, T3 – tumor size larger than 5 cm).

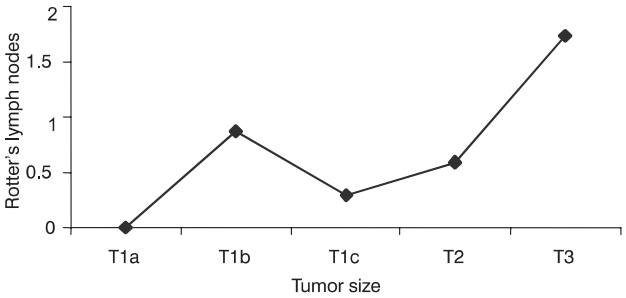

Figure 4. Relation between tumor size and the number of positive Rotter's lymph nodes (r=0.759, p=0.09).

(from 1 to maximum 5 positive Rotter's lymph nodes) extirpated on the average.

All patients were adjusted and analyzed for axillary and Rotter's lymph node involvement according to the location of tumor within the breast. With reference to the location of tumor within the breast among patients with Rotter's lymph node involvement, tumors were located as follows: ULQ 19 (48%), UMQ 11 (29%), LLQ 3 (9%), retromammillary region 5 (11%), and LMQ 1 (3%). A statistically significant positive correlation was identified between the tumor location within the breast and positive axillary lymph nodes (r= 0.995, p= 0.001), between the tumor location within the breast and positive Rotter's lymph nodes (r= 0.953, p= 0.012), and between positive axillary lymph nodes and positive Rotter's nodes (r= 0.93, p= 0.02) (Figure 1).

In relation to tumor size, positive Rotter's lymph nodes were identified in 18 (15%) of overall 128 T1 tumor patients; of them 1 in the T1a, 6 in the T1b, and 11 in the T1c group. Of 56 T2 and 10 T3, T4 tumor patients 14 (20%) and 6 (60%) were Rotter's node positive (Figures 2,3,4). A statistically significant positive correlation was identified (r=0.759, p=0.09).

Considering the tumor grade positive Rotter's lymph nodes were identified in 1 (3,8%) of overall 26 Grade I tumor patients. Of 102 grade II and 57 grade III tumor patients 18 (17,6%) for grade II and 18 (31,6%) for grade III were Rotter's node positive (Figures 5,6). A statistically significant positive correlation was identified (r=0.993, p=0.08).

	Metastatic involvement of Rotter's lymph nodes		
Gradus	negative	positive	all
I	25 (96.2%)	1 (3.8%)	26 (100.00%)
II	84 (82.4%)	18 (17.6%)	102 (100.00%)
III	39 (68.4%)	18 (31.6%)	57 (100.00%)
All	148 (80.0%)	37 (20.0%)	185 (100.00%)

Figure 5. Metastatic involvement of Rotter's lymph nodes related to tumor grade.

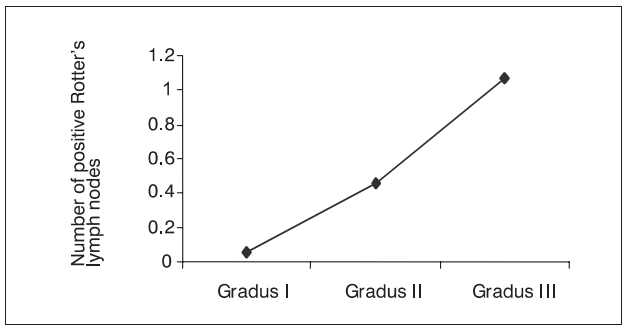

Figure 6. The number of positive Rotter's lymph nodes related to tumor grade (r=0.993, p=0.08).

DISCUSSION

The thesis that the removal of axillary lymph nodes should be considered both a therapeutic and diagnostic procedure, raises the question of Rotter's lymph nodes. The results can be used in the above conservative management of axillary nodes, but in case of positive lymph nodes, Rotter's lymph nodes should also be explored and removed.

Cody and colleagues confirmed Rotter' node metastases in only 2.6% of patients, with no difference in both size and localization compared to other patients (8). In cases where special techniques for lymph node assessment are used, the percentage increases to 19% as shown by Durkin and Haagensen (9). Other authors show that metastatic involvement in Rotter's node is more frequent in younger patients with a larger primary tumor of about 4 cm in diameter. Like Cody et al, Dixon and colleagues also consider that the identification of Rotter's node in patients with early carcinoma of the breast is of no greater practical significance (8,10). In a majority of cases, Rotter's node metastases are found in patients with already proven axillary metastases (11). Oran and colleagues report that 2 of 3 patients with metastases occurring only in interpectoral (Rot-

ter's) lymph nodes will develop massive distant metastases within less than 12 months from diagnosis (12). Survival of lymph node-positive patients also depends upon the number of positive lymph nodes. Almost all authors, and among them Rotter himself, suggest that lymph drainage, thus the route of metastasis dissemination from upper and deep breast structures passes through interpectoral lymph nodes (13).

In this study, Rotter's lymph nodes were identified in 139 patients, accounting for (compared to previous experience and literature data) a surprising 66,2 percent. Of the 116 patients with Rotter's lymph nodes, 39 had at least one metastatic lymph node which accounts for 28,1%, or compared to the overall number of patients studied, an astonishing 18,5%. Referring back to the thesis that the removal of axillary lymph nodes is considered to be both a therapeutic and diagnostic procedure, the question remains whether in our standard, routine clinical practice we dismiss for further treatment one-fifth of patients with their tumor, a potential source of further disease dissemination, still present. Also the location of the tumor in the breast, as well as tumor size and grade may inform us of possible presence of positive Rotter's lymph nodes. Surgeon should at least explore interpectoral area in patients with high risk for Rotter's lymph nodes metastases (patients with tumors located in upper quadrants, tumors greater than 2 cm, and grade III tumors). Another question is how can Rotter's node-positive patients be fitted into the actual TNM classification that not only does not include, but also does not even mention Rotter's lymph nodes. Metastatic involvement in Rotter's lymph nodes was identified in 3 axillary lymph node-negative patients accounting for, not at all irrelevant, 3.75%. How do these patients fit into the TNM classification? There is also a question of whether Rotter's nodes could be considered as «sentinel nodes» in patients with tumor located in the upper breast quadrants, as suggested by other authors as well. Bale and colleagues as well as Uren and colleagues who have also tackled the above question, discuss the occurrence of false-negative results of sentinel lymph node biopsy (14,15).

CONCLUSION

Taking into cosideration the above, removal of Rotter's lymph nodes may play a particular role in the treatment of breast cancer. With good communication between diagnostic and experienced and profiled surgical-pathologic teams, the identification and removal of Rotter's lymph nodes with metastatic involvement should not be a technical problem, especially since with the early postoperative rehabilitation program, it does not make any difference to the patient. Surgeons should explore interpectoral lymph nodes and search for the positive ones. The operation does not additionaly mutilate the patients. Patients with tumors in upper quadrants, higher tumor grade , and tumor size shuold undergo this exploration and extirpation of interpectoral lymph nodes. For many women undergoing surgery for breast cancer without Rotter's node removal, the nodes are responsible for further spreading of the disease, suggesting potential therapeutic benefits of this type of surgical management of breast cancer.

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