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ANALYSIS OF TUMOR MARKER CA 15-3 AND HORMONE RECEPTOR STATUS RELATED TO METASTATIC INVOLVEMENT OF INTERPECTORAL (ROTTER'S) LYMPH NODES

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Summary

The study was aimed at analyzing metastatic involvement in interpectoral (Rotter's) lymph nodes related to tumor marker CA 15-3 and hormone receptor status.

The study includes 172 female patients undergoing surgery for breast cancer at the University Hospital for Tumors, Zagreb, Croatia from November 2001 to August 2003. In addition to the standard surgical procedure, interpectoral (Rotter's) lymph nodes were removed in all of the patients. Levels of the serum tumor marker CA 15-3 was determined prior to surgery and hormone receptors status were determined after the surgery.

Rotter's lymph nodes were identified in 67% of the patients, with metastatic involvement revealed in 20% of the Rotter's nodes. Metastatic involvement of Rotter's nodes in patients with negative and positive axillary lymph nodes was 4% and 35%, respectively. Of 35 Rotter's node-positive patients, 31.4% had elevated serum levels of tumor marker CA 15-3, with the level statistically significantly higher in Rotter's positive patients compared to those with negative (or absent) Rotter's nodes (χ^2=8.22, p= 0.0004). Hormone receptor status showed statistically significant difference in the expression of estrogen receptors and no statistically significant difference in progesteron receptors between patients with and those without positive Rotter's nodes (χ^2=3.68; p=0.05 and χ^2=0.07;p=0.79).

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 undiagnosed and non-extirpated. Tumor marker CA 15-3 is more frequently elevated in patients with positive Rotter's lymph nodes. Estrogen receptors are as well more frequently negative in such patients. Progesteron receptors show no difference in patients with positive or negative Rotter's lymph nodes. As the nodes can be surgically removed without additional mutilation, the exploration of Rotter's lymph nodes should be introduced into routine clinical practice and the elevated values of tumor marker CA 15-3 could be warning for possible positive interpectoral nodes.

KEY WORDS: *breast cancer, tumor marker CA 15- 3, hormone receptor status, interpectoral (Rotter's) lymph nodes*

ANALIZA TUMORSKOG MARKERA CA 15-3 I HORMONSKOG STATUSA U ONDOSU NA METASTATSKU ZAHVAĆENOST INTERPEKTORALNIH (ROTTEROVIH) LIMFNIH ČVOROVA

Sažetak

U radu je analizirana zahvaćenost interpektoralnih (Rotterovih) limfnih čvorova metastazama u odnosu na vrijednosti tumorskog markera CA 15-3 i hormonski status.

Analizirane su 172 bolesnice s rakom dojke operirane u Klinici za tumore, Zagreb od studenog 2001. do kolovoza 2003. U svih su bolesnica, uz standardnu operaciju, uklonjeni i interpektoralni (Rotterovi) limfni čvorov. Prije operacije su izmjerene vrijednosti tumorskog markera CA15- 3, a nakon operacije vrijednosti hormonskih receptora.

Rotterovi limfni čvorovi otkriveni su u 67% bolesnica, od kojih je 20% bilo zahvaćeno metastazama. U bolesnica s negativnim aksilarnim limfnim čvorovima metastatska zahvaćenost Rotterovih limfnih čvorova iznosila je 4%, a u bolesnica s pozitivnim aksilarnim limfnim čvorovima 35 %. Od 35 bolesnica s pozitivnim Rotterovim limfnim čvorovima u njih 31, 4% bio je i povišen tumorski marker CA 15- 3 što je statistički znakovito viša vrijednost u odnosu na žene s rakom

dojke s negativnim (ili neprisutnim) Rotterovim limfnim čvorovima (χ^2=8,22, p= 0,0004). Hormonski status pokazuje statistički znakovitu razliku u ekspresiji estrogenskih receptora, a u ekspresiji progesteronskih receptora takva razlika između bolesnica sa ili bez pozitivnih Rotterovih čvorova nije uočena (χ^2=3,68; p=0,05 and χ^2=0.07;p=0,79).

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. Vrijednosti tumorskog markera češće su povišene u bolesnica s pozitivnim Rotterovim čvorovima. Estrogenski su receptori u tih bolesnica također bili češće negativni, a progesteronski receptori ne pokazuju razlike između bolesnica s pozitivnim i onima s negativnim Rotterovim čvorovima. Kako se ti čvorovi mogu ukloniti bez dodatne mutilacije, otkrivanje Rotterovih limfnih čvorova treba postati redovitom kliničkom praksom, a pritom povišene vrijednosti tumorskog markera CA 15-3 mogu upozoravati na eventualno pozitivne interpektoralne limfne čvorove.

KLJUČNE RIJEČI: *testovi koagulacije krvi, operacija malignih solidnih tumora, heparin male molekulske mase*

INTRODUCTION

The study is aimed at exploring the level of Rotter's lymph node involvement in breast cancer patients with levels of the serum tumor marker CA 15-3 and their relation to hormone receptor status. Finally, the obtianed results may come in handy as guidelines on routine removal of Rotter's nodes in breast cancer patients.

The study includes 172 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
3. Rotter's lymph node involvement in relation to hormone receptor status
4. Rotter's lymph node involvement in relation to preoperative levels of the serum tumor marker CA 15-3

PATIENTS AND METHODS

The study includes 172 female patients undergoing surgery for breast cancer at the Department of Surgery, University Hospital for Tumors, Zagreb, Croatia from November 2001 to August 2003. 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. After a confirmed breast cancer diagnosis, a portion of the material was sent for testing of hormone receptors for both estrogen and progesterone (6, 7, 8, 9,10). Tumors were classified according to the World Health Organization Classification of Tumors (11), and the grade of differentiation according to the Bloom-Richardson grading scheme (12).

Hormone receptor status was evaluated on tumor tissue cytosol specimens. Scatchard analysis was used to determine hormone-binding parameters (13,14). Hormone receptor levels are considered to be negative when estrogen and progesterone receptor levels are less than or equal to 5 and 10 fmol/mg protein, respectively. Levels exceeding the above are considered to be positive.

The statistical method used to analyze the data was χ^2- 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 84 years of age (median 57.8 years). Reagrding localization, in 89 patients the tumor was present in the right breast (51.7%), and in the remaining

83 it was located in the left breast (48.3%); 110 (64%) patients underwent breast cancer mastectomy, and in 62 (36%) 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 preoperative assessment of the serum tumor marker was done in all 172 patients. The levels were found to be elevated in 23/172 patients (13.4%).

Pathohistologic evaluation showed invasive ductal carcinoma in 152 (88.4%), mucinous carcinoma of the breast in 7 (4.1%), lobular carcinoma in 11 (6,4%) and papillary and medullary carcinoma of the breast in 1 (0.6%) patient each. Of 152 invasive ductal carcinomas, 22 (14.5%) were grade I, 86 (56.6%) grade II, and 44 (28.9%) grade III Due to either technical unfeasiblity or tumor size, levels of estrogen and progesteron receptors were assessed in 146 and 148 patients, respectively. Estrogen receptors were positive in 44 (30.1%) patients, while 72 (48.6%) patients were found to be progesterone receptor positive.

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 nodes in 80/172 (46.5%), while 92/172 (53.5%) patients were axillary lymph node positive. Interpectoral fat tissue of 56/172 (32.6%) patients did not contain any lymph nodes, while at least 1 lymph node was found in 116/172 (67.4%). Tumor cell-positive Rotter's lymph nodes were found in 35/172 (20.3%), and 81/172 (47.1%) patients had tumor-negative nodes. Of patients with pathohistologically confirmed Rotter's nodes (116/172), 30.2% were positive (with metastatic tumor cells), and the remaining 69.8% were negative.

From a total of 80 patients with negative axillary lymph nodes, in 33/80 (41.2%) Rotter's lymph nodes were not found, and in 47/80 (58.75%) patients the presence of Rotter's nodes was pathohistologically confirmed; 3/80 (3.75%) had positive Rotter's lymph nodes.

Of patients with positive axillary lymph nodes (92/172 patients or 53.5%), in 23/92 (25.0%) Rotter's lymph nodes were not found, and in 69/92 (75.0%) the presence of Rotter's lymph nodes was not confirmed; 32/92 (34.8%) had positive Rotter's lymph nodes, while the nodes were negative in 37/92 (40.2%).

Of 35 Rotter's node-positive patients, 24 (68.6%) had tumor marker CA 15-3 levels within normal range, and in 11 (31.4%) patients the levels were elevated. Tumor marker CA 15-3 levels was statistically significantly higher in Rotter's node-positive patients (χ^2=8,22, p= 0.0004) compared to patients without positive Rotter's lymph nodes (Figure 1).

Eight (26.7%) Rotter's node-positive patients also had elevated estrogen receptor levels (8/30) in whom estrogen receptor measurements were performed for either technical unfeasibility or tumor size). In addition, higher progesterone receptor levels were found in 13 (43.3%) patients with positive Rotter's lymph nodes. Hormone receptor status showed statistically significant difference in the expression of estrogen receptors and no statistically significant difference in progesteron receptors between patients with and those without positive Rotter's nodes (χ^2=3,68; p=0,05 for estrogen receptors and χ^2=0,07; p=0,79 for progesteron receptors) (Figures 2).

Tumor marker	Elevated	Normal
CA 15-3	23(13%)	149(87%)

Marker Ca 15-3 with positive Rotter's lymph nodes	Elevated	Normal
	11(31%)	24(69%)

Figure 1. Levels of tumor marker CA 15-3 in patients with metastatically involved lymph nodes in correlation with levels of CA 15-3 in all patients undergoing surgery (χ^2-test, p= 0.01)

Hormone receptor status	E +	E -	P+	P-
	44 (30%)	102 (70%)	72 (49%)	76 (51%)

Hormone receptor status with Rotter's nodes	E +	E -	P +	P -
	8 (27%)	22 (73%)	13 (43%)	17 (57%)

Figure 2. Levels of hormone receptors in patients with positive Rotter's lymph nodes in correlation with levels of hormone receptors in all patients undergoing surgery

DISCUSSION

Preoperative diagnosis of Rotter's lymph nodes in routine clinical practice is rather unsafe. According to some authors, Rotter's lymph nodes can be detected by ultrasound in 10-35% cases. Results obtained by a majority of authors show metastatic involvement in Rotter's lymph nodes in about 10% of patients (15).

Our results show that Rotter's node metastases are not so rare, and that breast cancer can be locally controlled by surgery in the early stages of the disease. This problem of breast cancer treatment has been tackled by Yamasaki and Kodama (16).

In this study, Rotter's lymph nodes were identified in 116 patients, accounting for (compared to previous experience and literature data) a surprising 67.4 percent. Of the 116 patients with Rotter's lymph nodes, 35 had at least one metastatic lymph node which accounts for 30.2%, or compared to the overall number of patients studied, an astonishing 20.3%. Our results showing that preoperative tumor maker CA 15-3 levels exceeded the normal range in only 23 (13.4%) of the 172 studied patients are particularly interesting. Actually, in patients with Rotter's node metastases, higher marker levels accounted for 31.4% (11/35), and among patients without Rotter's node metastases, levels of the tumor marker were elevated in only 8.7% (12/137). Considering estrogen receptors, they are as well more frequently negative in patients with positive Rotter's lymph nodes. Progesteron receptors show no difference in patients with positive or negative Rotter's lymph nodes.

CONCLUSION

Taking into cosideration the above, removal of Rotter's lymph nodes may play a particular role in the treatment of breast cancer. Tumor marker CA 15-3, if elevated, could alarm the surgeon and make him at least explore interpectoral space to search for possible positive Rotter's lymph nodes, so they would not be left behind the surgery. Also the values of estrogen and progesteron receptors are very important in further therapy for breast cancer patients and together with the status of all metastatic involved lymph nodes which should include interpectoral (Rotter) lymph nodes it makes the better view at the stage of desease as well as prognosis. 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.

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