

The Comparison of Radiocolloid, Methylene Blue and Combined Methods for Detecting Sentinel Lymph Node for Axillary Staging in Breast Cancer Patients

Meme Kanserli Hastalarda Aksiller Evreleme Amaçlı İntraoperatif Sentinel Lenf Nodu Saptanmasında Radyokolloid Metilen Mavisini ve Kombine Yöntemlerin Karşılaştırılması

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ÖZET

GİRİŞ ve AMAÇ: Çalışmanın amacı sentinel lenf nodu saptanmasında radyonüklid ve metilen mavisini metotlarının başarı oranlarını karşılaştırmak ve meme kanseri bulunan hastalarda bu teknik veya teknik kombinasyonlarının başarı oranlarını değerlendirmektir.

YÖNTEM ve GEREÇLER: Bu prospektif çalışmada Şubat 2006 ve Mart 2010 tarihleri arasında Ankara Onkoloji Eğitim ve Araştırma Hastanesine başvuran 287 meme kanseri hastası değerlendirilmiştir. Sadece metilen mavisini metodu uygulanan hastalara Grup I, sadece radyokolloid madde metodu uygulanan hastalara Grup II, hem metilen mavisini hem de radyokolloid madde uygulanan hastalara ise Grup III adı verildi. Hastalar gruplara rastgele olarak dağıtıldı. Her bir tekniğin başarı oranları ve toplam başarı oranları karşılaştırıldı.

BULGULAR: Tüm gruplar ele alındığında sentinel lenf nodu saptanmasında toplam başarı oranı %83,3 olarak hesaplandı. Gruplara ayrı ayrı bakıldığında Grup I (tek başına metilen mavisini) için başarı oranı %80, Grup II (tek başına radyokolloid madde) için %84,9 ve Grup III (kombine grup) için %90,6 başarı oranı hesaplandı. İstatistiksel olarak Grup I ve Grup II arasında fark görülmezken ($p=0,425$) Grup I ve Grup III arasında istatistiksel olarak anlamlı fark izlendi ($p<0,05$).

TARTIŞMA ve SONUÇ: Vital boyaların ve radyoaktif koloidal maddelerin tek başına kullanımında sentinel lenf nodu saptanması başarı oranları yüksektir ancak metotlar kombine edildiğinde bu başarı oranı anlamlı şekilde artmaktadır.

Anahtar Kelimeler: Metilen mavisini, radyokolloid, sentinel lenf nodu biyopsisi, meme kanseri

ABSTRACT

INTRODUCTION: The aim of this study to compare the success rates of radionuclide and methylene blue methods in detecting sentinel lymph nodes and evaluate the success rates of techniques or technique combinations in breast cancer patients.

METHODS: In this prospective study we evaluated 287 breast cancer patients referred to Ankara Oncology Training and Research Hospital between February 2006 and March 2010. Patients whom we performed methylene blue method alone was named as Group I, radiocolloid substance method alone as Group II and both methylene blue and radiocolloid method as Group III. Patients dispatched groups randomly. We calculated the overall success rate and success rates of each techniques separately.

RESULTS: When considered for all groups overall sentinel lymph node detecting success rate was 83,3%. When considered for each group, success rate was 80% for group I (methylene blue alone group), 84,9% for group II (radiocolloid substance alone group) and 90,6% for group III (combined group). Statistically there was

no difference between group I and group II ($p=0,425$) but there was a statistical difference between group I and group III ($p<0,05$).

DISCUSSION and CONCLUSION: The usage of vital dyes and radioactive colloidal substances alone has high success rates but combined method increases the success rate obviously.

Keywords: Methylene blue, radiocolloid, sentinel lymph node biopsy, breast cancer.

INTRODUCTION

Theoretically, sentinel lymph node is the first node that takes the lymphatic flow of the breast and it is conceivable that tumor cells that break apart from the normal breast tissue first appear in this node by this lymphatic flow. Sentinel lymph node that is negative for tumor cells reflect that remainder axilla is tumor free too and surgeon avoid for unnecessary dissection for reducing morbidity. From the first reports of Guiliano in 1994, currently sentinel lymph node biopsy replace standard axillary dissection in clinically axillary negative breast cancer patients.

There are some methods that help to detect axillary sentinel lymph node intraoperatively. Beside the vital dyes like isosulfan blue, methylene blue and patent blue dye, there are various pharmaceuticals that makes lymph nodes visible and helps to detect them easily. Each of this methods have different success rates of detecting sentinel lymph nodes, moreover with combination of some methods this rates can be increased.

In this study we compared the success rates of radionuclide and methylene blue methods in detecting sentinel lymph nodes and evaluate the success rates of techniques or technique combinations in breast cancer patients referred to surgical clinic of Ankara Oncology Training and Research Hospital.

MATERIAL and METHODS

In this prospective study we evaluated 287 breast cancer patients referred to Ankara Oncology Training and Research Hospital between February 2006 and March 2010. We performed breast conserving surgery and sentinel lymph node dissection to predict axillary involvement. We performed three different methods to detect sentinel lymph nodes intraoperatively; methylene blue, radiocolloid substance and combined method, and evaluate the success rates of them.

We formed three different groups that we performed three different sentinel lymph node detecting method. Patients whom we performed methylene blue method alone was named as Group I, radiocolloid substance method alone as Group II and both methylene blue and radiocolloid method as Group III. Patients dispatched groups randomly. We calculated the overall success rate and success rates of each techniques seperately. Success rates are evaluated according to patient age, menopausal status, location of tumor in breast, tumor size and grade, and primary biopsy method performed.

Preoperative pathologic diagnosis of patients established by excisional, incisional or tru-cut biopsy. Patients with proved breast cancer hospitalized and investigation for distant metastasis applied. Written consent obtained from all suitable patients for breast conserving surgery. Datas like patient age, menopausal status, location of tumor in breast, tumor size and grade, and primary biopsy method performed were recorded.

All operations performed under general anesthesia and three different methods beforementioned performed for detecting sentinel lymph node. In only methylene blue performed group I, 1% 4-6cc methylene blue solution applied periareolar and peritumoral before surgical procedure started and all applications performed subdermal. In patients who had excisional biopsy cavity, we applied the solution around, not inside, the cavity. Following injection we waited for 10 minutes and after that search the blue painted lymph node in axillary region. In only radiocolloid performed group II, 1 mCi Tc-99m nanocolloid applied peritumoral and/or intradermal, 4-12 hours

before surgery. We performed lymphoscintigraphy to all patients preoperatively to determine involvement of lymph node. After admission of radioactive substance we search the sentinel lymph node with the help of gamma probe in the axillary region. In the combined group, group III, we performed both of these methods at the same time.

We calculated the success rates of each group and compared these results with variables like patient age, menopausal status, tumor location and size, tumor grade and primary biopsy method performed.

Statistical calculations were performed using SPSS for Windows V16.0 (SPSS Inc., Chicago, IL, U.S.A.). To determine the differences between groups we used One-Way ANOVA test. Chi-square and Fisher's Exact Chi-square tests are used for comparing qualitative data. The level of significance was set at $p < 0.05$.

RESULTS

Two hundred and eighty seven patients operated because of breast cancer between February 2006 and March 2010 are included to study. All of the participants were women. Patients are included to three different groups that we performed three different sentinel lymph node detecting methods. There were 170 patients in Group I (methylene blue group), 53 patients in Group II (radiocolloid group) and 64 patients in Group III (combined group).

Mean patient age was 50,2 years (26-79). There were 43 patients under age 40 (14,9%), 109 patients between 40-50 (37,9%) and 135 patients over 50 years old (47%). Forty-eight percent of all participants (n=139) were premenopausal. In preoperative period we performed excisional biopsy to 215 patients (74,9%), incisional biopsy to 32 (11,1%), tru-cut biopsy to 24 (8,3%) and fine needle aspiration biopsy to 16 (5,5%). According to location of tumor, 210 (73,1%) was in upper outer quadrant (UOQ), 34 (11,8%) was in upper inner quadrant (UIQ), 23 (8%) was in lower outer quadrant (LOQ) and 20 (6,9%) was in lower inner quadrant (LIQ). Seventy-three (25,4%) patients had T1, 165 (57,4%) had T2 and 49 (17,2%) had T3 tumor. Fifty-six (19,5%) patients had grade I, 140 (48,7%) had grade II and 91 (31,7%) had grade 3 tumor. According to patient age, menopausal status, primary biopsy method, tumor location, size and grade there were no statistical differences between three groups (Table 1).

When considered for all groups overall sentinel lymph node detecting success rate was 83,3%. (Table 2) We detected at least 1 sentinel lymph node in 239 of 287 patients and could not find any node in 48 (16,7%) patients. When considered for each group, success rate was 80% for group I (methylene blue alone group), 84,9% for group II (radiocolloid substance alone group) and 90,6% for group III (combined group). Statistically there was no difference between group I and group II ($p=0,425$) but there was a statistical difference between group I and group III ($p<0,05$).

According to patient age, success rate for under 40 age population was 79% (n=34), for 40-50 age was 83,4% (n=91) and for over 50

age was 84% (n=114). There was no statistical difference of success rate between three groups according to age ($p=0,72$). Also success rate for premenopausal group was 84% (n=117) and postmenopausal was 82,4% (n=122). There was no difference between three groups for success rate according to patients menopausal status ($p=0,24$).

The overall success rate for patients who had excisional biopsy primarily was 83,7% (n=180). This rates were 78,1%, 83,3% and 87,5% for incisional, tru-cut and fine needle aspiration biopsy respectively. There was no statistical difference for success rate according to primary biopsy method overall but between three groups combined group is

statistically superior than the other groups (Table 3).

The overall success rates were 84,7%, 70,5%, 82,6% and 90% for UOQ, UIQ, LOQ and LIQ tumors respectively. For UOQ tumors there were no statistical difference between three groups but success rates increase for the other locations of the breast for combined group (Table 4).

The overall success rates were 80,8%, 86% and 85,7% for T1, T2 and T3 tumors.

Combined method is statistically better for all tumor sizes (93,3%, 92,1% and 90,9% respectively). According to tumor grade, overall success rates were 80,3%, 82,1% and 86,8% for grade I-II and III tumors respectively. There was no statistical difference for success rate according to tumor grade between three groups.

Table 1. Patient characteristics and distribution by groups

	Group I (170) n(%)	Group II (53) n(%)	Group III (64) n(%)	Total (287) n(%)	p Value
Age					
Age<40	26(15,2)	8(15)	9(14)	43(14,9)	0,969
40≤Age<50	65(38,2)	18(33,9)	26(40,6)	109(37,9)	
Age≥50	79(46,4)	27(50,9)	29(45,3)	135(47)	
Menopause					
Premenopausal	81(47,6)	26(49)	32(50)	139(48,4)	0,739
Postmenopausal	89(52,3)	27(50,9)	32(49)	148(51,5)	
Biopsy Method					
Excisional	125(73,5)	37(69,8)	53(82,8)	215(74,9)	0,048
İncisional	26(15,2)	1(1,8)	5(7,8)	32(11,1)	
Tru-cut	8(4,7)	11(20,7)	5(7,8)	24(8,3)	
Fine needle aspiration	11(6,4)	4(7,5)	1(1,5)	16(5,5)	
Tumor Location					
Upper Outer Quadrant					0,474
Upper Inner Quadrant	121(71,1)	39(73,5)	50(78,1)	210(73,1)	
Lower Outer Quadrant	21(12,3)	8(15)	5(7,8)	34(11,8)	
Lower Inner Quadrant	14(8,2)	2(3,7)	7(10,9)	23(8)	
	14(8,2)	4(7,5)	2(3,1)	20(6,9)	
Tumor Size					
T1	44(25,8)	15(28,3)	14(21,8)	73(25,4)	0,8
T2	91(53,5)	36(67,9)	38(59,3)	165(57,4)	
T3	36(21,1)	2(3,7)	11(17,1)	49(17,2)	
Tumor Grade					
Grade1	34(20)	11(20,7)	11(17,1)	56(19,5)	0,765
Grade2	84(49,4)	26(49)	30(46,8)	140(48,7)	
Grade3	52(30,5)	16(30,1)	23(35,9)	91(31,7)	

Table 2. Sentinel lymph node finding success rates according to groups

	Group I (170) n (%)	Group II (53) n(%)	Group III (64) n(%)	Total (287) n(%)
SLN Detected	136(80)	45(84,9)	58(90,6)	239(83,3)
SLN Not Detected	34(20)	8(15)	6(9,3)	48(16,7)

Table 3. The success rates of methods according to primary biopsy method

	Methylene Blue (Group I)	Radiocolloid (Group II)	Combined (Group III)
Excisional Biopsy	%80,8	%86,4	%88,6
Incisional Biopsy	%73	%100	%100
Tru-cut Biopsy	%75	%81	%100
Fine Needle Aspiration Biopsy	%90,9	%75	%100

Table 4. The success rates of methods according to tumor location

	Methylene Blue (Group I)	Radiocolloid (Group II)	Combined (Group III)
Upper Outer Quadrant	%83,4	%84,6	%88
Upper Inner Quadrant	%57,1	%87,5	%100
Lower Outer Quadrant	%71,4	%100	%100
Lower Inner Quadrant	%92,8	%75	%100

DISCUSSION

In this study we evaluated the success rates of three different sentinel lymph node detecting methods and factors that can effect these rates. Two hundred-eighty seven patients divided into three groups randomly and we performed methylene blue in group I, radiocolloid in group II and both in group III for detecting sentinel nodes. Accordingly, success rate for methylene group was 80%. Some researchers disapprove methylene blue for its small particle size but there are many records in the literature that rebut this.¹ Koller and colleagues² reported 98%, Simmons et al.³ 90%, Chen et al.⁴ 75%, Yu et al.⁵ 97%, Nour A⁶ 91,1% and Wang et al⁷ 83,8% success rates with methylene blue. The result of 80% in this study suits with literature.

The technique with methylene blue is time consuming and can be challenging for the surgeon. To simplify this, different methods emerges. Applying radiocolloid substances with gamma probe and lymphoscintigraphy, raised the success rates in the literature. In this study success rate of radiocolloid alone was 84,9%. Krag and colleagues acquired 82% success rate in his study regarding 18 patients, with Tc 99m sulphide colloid and gamma probe.⁸ This technique seems easier and less time consuming than methods with vital dyes. Pijpers et al. showed 97.8% success rate with

Tc 99m colloid albumin in 1997.⁹ They concluded that methods with radioactive colloidal substances are better and easier than methods with vital dyes for determining sentinel lymph node. In the same year Veronesi et al. acquired 98% success rate with radiocolloid alone.¹⁰ Gulec et al. showed 94% success rate with Tc 99m sulphide colloid alone and concluded that radiocolloid method is less time consuming than vital dye methods.¹¹ In Dunnwald's study with 93 patients, the rate was 85%.¹² Whether this technique seems successful, the differences of rates between reports are due to radioactive substance used, its activity, its injection volume and location of injection. Indeed, these rates are better than vital dyes despite differences.

In 1995 Pijpers et al. suggested that success rates could be raised with combining vital dye and radiocolloid methods in malign melanoma patients.¹³ In 1998 Cox and colleagues confirmed this result for breast cancer in their guideline study. In their study they found sentinel lymph node in 440 of 466 patients (94.4%) with combined method and concluded that combined method is superior.¹⁴ Liberman et al. suggested that combined method is superior than methods alone with their success rate of 91%.¹⁵ Such as our study, in 1999 Hill divided 500 patients into three groups and show 80%, 85% and 93% success

rates for blue dye, isotope and combined group respectively.¹⁶ These numbers suits with this study.

In our study we also evaluated the factors that can effect determining location of the sentinel lymph node. As for that, we compared age, menopausal status, tumor location, grade, size and primer biopsy method. In EORTC 10981-22023 AMAROS study, 1953 patients were suitable for sentinel node biopsy. The success rate was 97%. They indicate once again that combined method is better than the methods used alone. They suggested that factors effect these rates are age, pathologic tumor size, tumor histology, year of the procedure and method used.¹⁷

There are some reports suggesting that sentinel lymph node determining rate decrease with increasing age. McMasters and colleagues¹⁸ suggest that success rates significantly decreases age over 50, Chakera et al.¹⁹ age over 56 and Chagpar et al.²⁰ age over 60 in his study with 4151 patients. This can be due to increase of axillary fat tissue with age and decrease of lymphatic flow.²¹ Also the increase of fat tissue in lymph nodes with age can decrease approaching of vital dyes or radiocolloid substances.²² Similarly, in AMAROS study, they observed decrease of success rate over 70 years old but the highest rates were between 50-69 age group. In our study success rate of patients over 50 years old was higher than younger ones. This can be due to difference of age ranges from other studies and less number of young population in the study. Also it is known that body mass index could change these rates but it is not questioned in our study. Menopausal status can effect the rate as the same reasons as age. Koizumi et al, concluded that factors that effect involvement of radioactive substance in sentinel lymph node are body mass index, age and menopausal status.²³ In our study there was no difference between groups according to menopausal status.

In the literature there are some reports suggesting that primer biopsy method, even excised tissue volume, could effect sentinel lymph node detecting.²² Miner TJ et al. suggest that primer biopsy method has no effect on sentinel lymph node.²⁵ Such as in 2006 Marchal F et al. concluded the same result.²⁶ But in patients with excisional biopsy performed previously, someone could expect that success rate must decrease because of the ruined lymphatic flow around the tumoral tissue. Krag D. et al. suggest that if sentinel node biopsy scheduled for the patient, excisional biopsy must be avoided. In our study results of combined method were better than the methods alone, independent from primer biopsy method.

It is relatively more difficult to detect sentinel lymph node in inner quadrant tumors. It is because of masking internal mammary nodes with injection site. Also the long distance between inner quadrant tumors and axillary lymph nodes makes waiting for longer time for approaching of vital dyes or isotope to the nodes. Krag et al. showed that success rates are lower in inner quadrant tumors independent from sentinel node detecting technique. Ahrendt et al suggest the same result and they concluded that success rate of inner quadrant tumors are lower independent from body mass index and age but success rate of outer quadrant tumors are dependent to them.²⁶ When radiocolloid substance applied, radioactivity could make it hard to search for sentinel node in axilla for upper outer quadrant. Cody HS et al. suggest that blue dye method alone is superior than radiocolloid method for upper outer quadrant tumors.²⁷ Morrow et al. suggest that the highest success rate for sentinel lymph node is obtained from upper outer quadrant tumors.²⁸ In our study we concluded that combined method is superior than methods used alone independent from tumor location. In metylene blue group, best success rate was in lower inner quadrant but

this can be due to less number of patient in that group.

Marchal F et al showed that tumor size has no effect on detecting sentinel lymph node. Ahrendt and Morrow suggest the same result in their studies. But all of the researchers are agreed that success rates decrease in non-palpable tumors. In our study overall success rates did not change according to tumor size but combined method was superior in all tumor sizes.

Increase of tumor grade is corelated with increase in number of metastatic nodes. In the existence of metastatic lymph nodes, lymphatic blockade of tumor cells does not let dye or radiocolloid flow. For this reason theoretically someone could expect that sentinel lymph node success rate must decrease while tumor grade increase. Hence, Marchal et al suggest that success rates are lower in lower grade patients. On the top of it, in our study success rates increase while tumor grade increase too. These results are ineffective and multivariate analyses must be done.

In any case, the usage of vital dyes and radioactive colloidal substances alone has high success rates, factors like primary biopsy method, patient age, tumor location, tumor size and grade causes inadequacy and the usage of both methods together (combined method) seems to resolve this inadequateness. Combined method increases the success rate obviously. Also leading of radioactive substance to target directly and visibility of vital dyes macroscopically are shortening the process and making it easier.

Conflict of interest: None

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