PREDICTORS OF AXILLARY LYMPH NODE INVOLVEMENT IN SCREEN-DETECTED BREAST CANCER

Wanqing Chen

March 2004

This Treatise is submitted in partial satisfaction of the requirements for the Degree of Master of International Public Health (Hons), University of Sydney.

ABSTRACT

Background: Axillary lymph node dissection as routine part of breast cancer treatment has been questioned in relation to the balance between benefits and morbidity. The purpose of this study is to determine the association of tumor size, age and histological grade with axillary lymph node metastasis, to determine if some patients could be exempted from axillary dissection.

Methods: The data are derived from BreastScreen NSW, the government sponsored population-based breast screening program. In New South Wales (NSW) Australia between 1995 and 2002, 7,221 patients with invasive breast carcinoma were diagnosed and 5,290 patients were eligible for this study. The relationship between incidence of positive axillary lymph nodes and three study factors (tumor size, age and histological grade) was investigated by univariate and multivariate analysis. Logistic regression models were used to predict probability of axillary metastases.

Results: The incidence of axillary lymph node metastases was 28.6% (95% CI: 27.4%-29.8%). Univariate analysis showed that age, tumor size and histological grade were significant predictors of axillary lymph node metastases ($p<0.0001$). Multivariate analysis identified age, tumor size and histological grade remained as independent predictors ($p<0.0001$). From multivariate analysis, patients with T1a ($\leq$ 5mm) and grade I tumors regardless of age had 5.2% (95% CI: 1.2%- 9.3%) frequency of node metastases. Patients 70 years or older with grade I, T1a and T1b (6-10mm) tumors had 4.9% (95% CI: 3.2%- 7.5%) and 6.6% (95% CI: 5.3%-8.3%) predicted frequency of node metastases.

Conclusions: Tumor size, age and histological grade are predictors of axillary lymph node metastases. Routine axillary lymph node dissection could be avoided in some patient groups with a low frequency of involved lymph nodes if the benefits are considered to exceed the risks.

ACKNOWLEDGMENTS

I am much indebted to my supervisor Professor Richard Taylor from the Department of Public Health and Community Medicine, University of Sydney, who provided tremendous help in completing this paper. He initiated the study, encouraged me to take on the project, trusted my abilities in analysing the precious data derived from BreastScreen NSW and granted me access to the data. He also reviewed the draft, and provided valuable expertise on this paper. He is the co-author for the submission of this paper.

I would also like to acknowledge the following people, who provided valuable advice on statistical analysis:

Associate Professor Judy Simpson from the Department of Public Health and Community Medicine, University of Sydney.
Mr Raj Supramaniam from the Cancer Epidemiology Research Unit, The Cancer Council New South Wales.
Mr Xue Qin Yu from the Cancer Epidemiology Research Unit, The Cancer Council New South Wales.

AUTHOR'S CONTRIBUTION

This project utilised data collected through the "BreastScreen NSW" program at the NSW Breast Cancer Institute.

Professor Richard Taylor from the Department of Public Health and Community Medicine, University of Sydney initiated the topic of the treatise.

The author's contributions to this treatise included:

- Literature review
- Statistical data analysis
- Interpretation of results
- Writing of the treatise

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

ABBREVIATIONS

ALND	Axillary lymph node dissection
SLN	Sentinel lymph node
ALNM	Axillary lymph node metastasis
SLNB	Sentinel lymph node biopsy
CI	Confidence interval
p	Probability

INTRODUCTION

Breast cancer is the leading contributor to cancer incidence and is the most common cause of cancer-related death among females in Australia. A total of 11,314 new cases and 2,521 deaths were registered for 2000.[1]

Axillary lymph node status is an important prognostic indicator for predicting survival and guiding adjuvant therapy in breast cancer patients. Axillary lymph node dissection (ALND) is considered the standard of care in patients with invasive breast cancer[2,3,4] and axillary dissection and histological examination is still the most accurate way for assessment of axillary status.

An important purpose of surgical removal of axillary lymph nodes is to provide prognostic information and guide effect adjuvant systemic therapy. Due to increasing recommendations of adjuvant therapy for node-negative patients with primary tumors larger than 10mm, the routine axillary dissection for staging purposes may not be required. Clinical analysis has proved that information from ALND did not alter management of women $\geq$ 70 years old, unless they were classified as high risk[5]. Sentinel lymph node biopsy (SLND) was introduced in 1991, and is used as an alternative to complete axillary lymph node dissection in all patients with breast cancer in some centres.

As for treatment, it has been shown that although axillary dissection reduces the incidence of tumor recurrence in axillary lymph nodes, it does not improve survival[6,7]. Some studies have suggested routine axillary lymph node dissection can be avoided in patients with pure tubular carcinomas measuring $\leq$ 1 cm due to a low frequency of axillary lymph node metastases (ALNM)[8,9].

The complications of ALND include lymphoedema, paraesthesia, pain and weakness of upper extremity that reduce in the quality of life[10-12]. With the increase in population-based screening, diagnosis of breast cancer at earlier stages has increased[2]. Most of

patients detected by screening have small tumor size without ALNM[13,14]. ALND may be unnecessary for some of them.

The purpose of this study is to analyze the relationship between incidence of axillary lymph node involvement and three study factors (age, tumor size and histological grade) and establish a model to identify subgroups that have low risk of ALNM and could avoid axillary dissection. The low risk is considered as frequency less than 10% axillary metastases[14,15].

MATERIALS AND METHODS

Patients

BreastScreen NSW is the government sponsored population-based breast screening program for women in the state of New South Wales (NSW), Australia. Women aged 50-69 years on the electoral roll are invited and re-invited for biennial screening; women 40-49 years, and 70 years or older are screened on request. All patients with breast cancer detected by the screening program in NSW from 1995 to 2002 were studied through a retrospective cross-sectional review. By 1995, BreastScreen NSW was operating in all areas in NSW, and 1995 was the earliest year breast cancer data were collected centrally. The latest year of available complete data was 2002.

Data

Data collection for each patient included: size of primary tumor, the number of axillary lymph nodes examined, the number of lymph nodes involved with tumor, histological grade of tumor and patient's age. Age categories were classified as: 40-49 years (age1), 50-59 years (age2), 60-69 years (age3) and 70 years or older (age4). Hormone receptor status was not reported nor collected. A frequency distribution of the tumor size data indicated evidence of rounding for each mm below the standard cut-offs, with a significantly higher frequencies on 5mm, 10mm, and so on, compared to integers immediately below. Thus size categories were classified as: $\leq$ 5mm(size1), 6-10mm (size2), 11-15mm (size3), 16-20mm (size4), 21-50mm (size5) and greater than 50mm (size6). Tumor size was also assigned a categorical T value using the TNM System of the American Joint Committee on Cancer[16]. Over the period of the study 7,221 invasive breast cancers were detected; 1269 patients who did not receive axillary lymph node dissection, or for whom the number of examined nodes was less than 5 were excluded. Less than 5 nodes retrieved were taken as evidence of inadequate dissection. Patients with items of missing data (662) were also excluded from the study, leaving 5,290 for analysis.

Analyses

Comparisons of the frequency of axillary lymph node involvement between groups were evaluated using a chi-square method for testing the null hypothesis of no association. Mantel-haenszel trend test was used test for linear trend and for significance for each variable for axillary lymph node involvement. For tumor size, an exponential model $y=ae^{bx}$ was used for curvilinear trend, where y represents frequency of lymph node metastasis, x represents tumor size group, a is the intercept and b is the coefficient (e is the base of the natural log). For age and histological grade, a linear test was applied.

Multiple analyses included all variables, which were also significant in the univariate analysis. Logistic regression was employed, and the lowest categorical groups were selected as references. The equation model developed from multivariate logistic regression was used to obtain the value of the predicted incidence of ALNM. Exact 95% confidence intervals were provided for the actual and estimated proportions. For the actual proportions of subgroups, $p+ 1.96\sqrt{p(1-p)/n}$ was used, p is proportion, n is the number of subjects. If $np<5$, Geigy Scientific Tables[17] was applied. All analyses were performed using SAS statistical software (Version 8.02).

Age-specific rates and mean of tumor size were used to evaluate selection bias by comparing excluded subjects with eligible subjects. The Pearson Chi-Squared test was applied for comparison of age groups. Student's two-sample t test was applied for comparison of mean tumor sizes.

RESULTS

The 98% of cases were T1 (79.3%) or T2 (19.3%) tumors. Overall, 1512 (28.6%) were found to have at least one positive axillary lymph node. The mean number of examined nodes was 14 (standard deviation [SD]=6.64). Median tumor size was 14 mm. Table 1 shows the distribution of variables with the proportion of subjects in each category who received ALND.

Selection bias

A significant difference of age structure was found between excluded group and eligible group. Excluded group had higher proportions of cases in older groups, for instance, 67.4% for age ≥ 60 years and 37.4% for age ≥ 70 years, compared with 54.1% and 20.3% in eligible group. The difference was statistically significant ($p<0.0001$) (Appendix 2). Moreover, excluded group had smaller tumor size with mean of 11.6mm (standard deviation [SD] = 9.21mm), compared with 16.2mm (SD = 10.42mm) for eligible group ($p<0.0001$).

Univariate analysis

The association between age and axillary lymph node involvement is statistically significant ($p<0.0001$). The age of patients was significantly higher in negative group (61.6 +9.3 years) than in the positive group (59.4+9.0 years). The positive rate decreased from 33.5% in age range of 40-49 years to 20.8% in age ≥ 70 years (Figure 1). The trend of node metastasis for age groups was markedly apparent ($p<0.0001$).

There is strong relationship between tumor size and axillary lymph nodes involvement. From the tumor size ≤ 5mm to greater than 50mm, the proportion of axillary lymph node involvement gradually increased from 9.5% to 86.7%, although there was not a significant difference between T1a and T1b. The trend for proportion of ALNM to the tumor size was apparent that metastasis rate increased as tumor size increased ($p<0.0001$) (Figure 2). A significant curvilinear trend was shown for proportion of ALNM by tumor size with $p<0.0001$.

A strong relationship was found between histological grade and axillary lymph node involvement. Grade I tumors had 19.9% axillary positive rate, compared with 31.8% for grade II and 36.1% for grade III (Figure 3). A similar linear trend was significantly found from node metastasis for histological grade ($P<0.0001$).

Multivariate analysis

On univariate logistic regression analysis tumor size, age and histological grade were identified as highly significant predictors of axillary lymph node involvement ($p<0.0001$). All the three variables were included in a multivariate modeling of the data. In multivariate analysis, age, tumor size and histological grade remained significant independent predictors of axillary lymph node involvement associated with incidence of ALNM (Table 2).

Subgroup analysis revealed that the patients with small tumor size and low grade had lower nodal involvement rate than those with bigger tumor size and higher grade; patients in lower age group had higher axillary lymph node metastasis rate than older (Appendix 1). Subjects with T1a and grade I tumors regardless of age had 5.2% (95% CI: 1.2%-9.3%) of axillary involvement (Table 3).

Predicted values

The predicted proportion of axillary nodal involvement based on three-variable equation from logistic model was shown in Table 4. The following equation developed for model was used: $P=1/[1+\exp(-Y)]$, where

$Y=\text{Logistic}(P)= -2.4112 + 0.3174 \times \text{size2} + 1.0817 \times \text{size3} + 1.5701 \times \text{size4} + 2.3333 \times \text{size5} + 4.1083 \times \text{size6} + 0.1275 \times \text{age2} - 0.1263 \times \text{age3} - 0.5537 \times \text{age4} + 0.3719 \times \text{grade II} + 0.3753 \times \text{grade III}$ (0 for reference groups: size1, age1 and grade I).

Two subgroups were identified as low risk of axillary metastasis: subjects aged 70 years, with T1a and grade I had 4.9% (95% CI: 3.2%-7.5%) axillary nodal involvement; aged 70 years with T1b and grade II had 6.6% (95% CI: 5.3%-8.3%) axillary nodal involvement.

DISCUSSION

In the current study we analyzed the data from 7,221 consecutive women diagnosed as invasive breast cancer by screening program during the period between 1995 and 2002 in NSW Australia. Due to the population-based native of the program and the large sample size, the result is likely to be representative.

In terms of axillary clearance, <5 lymph nodes examined was considered inadequate dissection[18], and these cases were excluded from analyses. The cases with missing data were also excluded. We analyzed data from 5290 women with invasive breast cancer as the eligible group. A selection bias could exist if the exclusion of cases had markedly different status characteristics. By comparing age-specific rates and median tumor size between excluded cases and eligible cases, we found there were significantly different age structure and mean tumor size. Based on the results, older patients and patients with smaller tumor size had lower axillary lymph node metastasis, so the selection bias may lead to the result being over-estimated.

In patients with breast cancer, axillary lymph node status is a powerful predictor of recurrence and prognosis. ALND has been a routine component of management of breast cancer for a century. The benefits of ALND are that it decreases the rate of axillary recurrence from 18% to 1.4%[6], determines prognosis, and indicates staging for further adjuvant therapy. 5- year survival rate is also related to the number of ALNM, 60% for patients with 1-3 positive nodes, but 31% for those with ≥4 positive nodes[19]. However, the benefits should be weighed against side effects of ALND such as lymphedema, nerve paraesthesia, extended recovery time and economic factors[20]. The NSABP B-04 trial suggests survival is unchanged, whether or not axillary node dissection is performed[6]. Furthermore, axillary irradiation could provide the same local control as surgery with fewer side effects[21]. The results of two randomized clinical trials from Canada and Denmark showed that loco-regional radiation significantly reduced local-regional relapses and increased 10-year survival rates[22,23]. Another trial reported

that inadequate treatment of the axillar caused significantly increased axillary recurrence and had an adverse impact on survival rates[24].

Sentinel lymph node biopsy (SLNB) is an alternative to axillary lymph node clearance of all patients. SLNB has been widely accepted because it is less invasive and reasonably accurate[25-27]. Axillary dissection is then only performed when the histopathology of the sentinel node is positive. If the result is negative, the chance that remaining nodes are involved is small (<0.1%)[28]. Therefore, axillary dissection could be avoided for breast cancer patients with negative sentinel nodes. Although recent SLN biopsy studies around the world have suggested positive results, long-term data are needed before the new technique changes the standard surgical practice in breast cancer management. Some randomized trials, such as ALMANAC trial and NSABP- 32 trial, are ongoing and compare SLN biopsy with ALND in relation to local control and survival[29,30].

Recently, surgeons have become more conservative and the tendency for conservation therapy is clear. Elimination of ALND has been accepted for patients with ductal carcinoma *in situ* and microinvasive carcinoma[31-33]. Chua et al suggested that clinically node-negative patients with either a $\leq$ 5mm, lymphovascular invasion-negative tumor, or a $\leq$ 15mm tubular or mucinous carcinoma could avoid routine ALND[34]. The question remains: are there any factors that are indicators of ALNM, so that the risk of lymph node status can be evaluated and patients with potential low risk of axillary lymph node metastasis can avoid axillary dissection?

With population-based screening introduced, more breast cancers are detected at an early stage with small tumor and low risk of nodal metastasis. Two series reports a less than 10% risk of nodal involvement in women with a T1a or T1b tumor detected by screening[14,15]. In this study based on the Breast Screening program in NSW, 79% had T1 tumors and 19% had T2 tumors. Subject with a tumor $\leq$ 10mm had 11.7% nodal involvement. The existence of selection bias may overestimate the actual ALNM. Tumor size has been an identified predictive factor of axillary lymph node involvement as the

ALNM rate increases with tumor size increase[34-38]. In the present study, tumor size has shown strongest independent predictor of ALNM. Age and histological grade have also consistently been found to be related to ALNM in previous studies[36,38-41]. Other factors have been shown significant predictors for nodal involvement such as lymphatic or vascular invasion[42,43], primary tumor palpability[15,44], and estrogen and progesterone receptors[41].

Recently, the level of incidence of ALNM $\leq$ 5% has been defined as low risk to avoid ALND[45]. In our study, only one subgroup had less than 5% of nodal involvement; this group was patients $\geq$ 70 years old with T1a and grade I tumors. However, the upper 95% confidence interval of the rate was higher than 5% and was thus not significantly lower than 5%. From multivariate analysis, older patients with small tumor size and low grade are likely to have a low risk of axillary lymph node metastasis. Our result found patients with T1a and grade I, regardless of age had 5.2% (95% CI: 0.2%-9.3%) of axillary involvement. We also identified two low risk subgroups: T1a, grade I in age $\geq$ 70 years and T1b, grade I in age $\geq$ 70 with predicted metastasis rate (from logistic regression) of less than 10%. If patients and surgeons are willing to accept 10% as very low risk of nodal involvement and the value to avoid axillary dissection[38,44], routine ALND could be avoided in patients with T1a and grade I tumors, patients aged 70 years or older with T1a and T1b, grade I or II tumors.

In conclusion, tumor size, histological and age are predictors of axillary lymph node status that help to make decision if a patient have a low or high risk of nodal metastasis. These results could be clinically useful and help clinicians and patients to decide if axillary dissection can be avoided for some groups of patients.

REFERENCES

1. Australian Association of Cancer Registries: “Cancer in Australia 2000”. Canberra, Australia: Australian Association of Cancer Registries.

2. National Cancer Institute:”breast cancer Treatment- Health Professionals. Stage I, II and IIIA Breast Cancer.” Vol 2000. Toronto, Canada: National Cancer Institute, 2000.

3. Mirsky D, O’Brien SE, McCready DR, et al.: Surgical management of early stage invasive breast cancer (stage I and II). Cancer Prev Control 1997;1:10-17.

4. Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Can Med Assoc J 1998; 158(suppl 3):S1-S83.

5. Chua B, Ung O, Taylor R, Boyages J. Is information from axillary dissection relevant to patients with clinically node-negative breast cancer? The Breast J. 2003; 9: 478-84.

6. Fisher B, Redond C, Fisher ER, Bauer M, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med. 1985; 312: 674-81.

7. Dent DM, Gudgeon CA, Murray EM. Mastectomy with axillary clearance versus mastectomy without it: late results of a trial in which patients had no adjuvant chemo-, radio- or endocrine therapy. S Afr Med J. 1996; 86: 670-671.

8. McDivitt RW, Boyce W, Gersell D. Tubular carcinoma of the breast. Clinical and pathological observations concerning 135 cases. Am J Srug Pathol 1982;6:401-11.

9. Morrow M. Role of axillary dissection in breast cancer management. Ann Surg Oncol 1996;3:233-4.

10. Beaulac SM, McNair LA, et al. Lymphedema and quality of life in survivors of early-stage breast cancer. Arch srug 2002;137:1253-7.

11. Ivens D, Hoe AL, Podd TJ, et al. Assessment of arm morbidity from complete axillary dissection. Br J Cancer.1992; 66:1368-1373.

12. Kissin MW, Querci della Rovere G, Easton D, Westbury G. Risk of lymphoedema following the treatment of breast cancer. Br J Surg. 1986; 73: 580-584.

13. Cady B, Stone MD, Schuler JG, et al. The new era in breast cancer: invasion, size, and nodal involvement dramatically decreasing as a result of mammographic screening. Arch Surg. 1996; 131: 301-308.

14. Tabar L, Duffy SW, Vitak B, Chen HH, Prevost TC. The natural history of breast carcinoma. What have we learnt from screening? Cancer. 1999; 86: 449-62.

15. Fein DA, Fowble BL, Hanlon AL, et al. Identification of women with T1-T2 breast cancer at low risk of positive axillary nodes. J surg Oncol 1997; 65: 34-9.

16. Bears OH, Henson DE, Hutter RVP, Kennedy BJ, editors. Manual for staging of cancer. 4th ed. Philadelphia: JB Lippincott 1992: 149-54.

17. Lentner C, Diem K, Seldrup J, editors. Geigy Scientific Tables. 8th ed. Basle, Switzerland: CIBA-GEIGY Limited 1982.

18. Graversen HP, Blichert-Toft M, Andersen JA, Zedeler K. Breast cancer: risk of axillary recurrence in node-negative patients following partial dissection of the axillar. Eur J Surg Oncol. 1988; 14(5): 407-12.

19. Fisher B, Bauer M, Wickerham L, Redmond C, Fisher ER. Relation of number of positive axillary lymph nodes to the prognosis of patients with primary breast cancer. Cancer 1983; 52: 1551-7.

20. Cady B. The need to reexamine axillary lymph node dissection in invasive breast cancer. Cancer 1994;74:505-8.

21. Early Breast Cancer Trialists Collaborative Group: Effects of radiotherapy and surgery in early breast cancer. N Engl J Med 333:1444-5, 1995.

22. Ragaz J, Jackson SM, Le N et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl. J. Med. 1997; 337: 956-62.

23. Overgaard M, Hansen PS, Overgaard J et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N. Engl. J. Med. 1997; 337: 949-55.

24. Fentiman IS. Hedley Atkins Breast Unit, Guy's Hospital, London, U.K. Long-term follow-up the first breast conservation trial: Guy's wide excision study. The Breast. 2000; 9: 5-8.

25. Veronesi U, Pagaelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, et al. Sentinel node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph nodes. Lancet 1997;349:73:350-3.

26. Cox CE, Salud CJ, Harrinton MA. The role of selective sentinel lymph node dissection in breast cancer. Surg Clin North Am 2000;80:1759-1777.

27. Nora MH, Baiba JG, Armando EG. The time has come to change the algorithm for the surgical management of early breast cancer. Arch Surg 2002;137:1131-6.

28. Turner RR, Ollila DW, Krasne DL, Giuliano AE. Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. Ann Surg. 1997;226:271-8.

29. Clarke D, Khonji NI, Mansel RE. Sentinel node biopsy in breast cancer: ALMANAC trial. World J. Surg. 2001; 25 (6): 819-22.

30. Krag DN, Julian TB, Harlow SP et al. NSABP-32: Phase III, randomized trial comparing axillary resection with sentinel lymph node dissection: a description of the trial. Ann. Surg. Oncol. 2004; 11(3 Suppl): 208S-10S.

31. Silverstein MJ, Rosser RJ, Gierson ED, Gamagami P, Colburn WJ, Handel N, et al. Axillary lymph node dissection for intraductal carcinoma: is it indicated ? Cancer 1987; 59:1819-24.

32. Silverstein MJ, Waisman JR, Colburn WJ, Furmanski M, Lewinsky BS, Cohlan BF, et al. Intraductal breast cancer carcinoma with and without microinvasion: is there a difference in outcome? Proc Am Soc Clin Oncol 1993; 12:56.

33. Wong JH, Kopald KH, Morton DL. The impact of microinvasion on axillary node metastases and survival in patients with intraductal breast cancer. Arch Surg 1990; 125: 1298-1302.

34. Chua B, Ung O, Taylor R, Boyages J. Frequency and predictors of axillary lymph node metastases in invasive breast cancer. ANZ J. Surg. 2001; 71: 723-28.

35. Ahlgren J, Westman SO, Arnesson LG. Predictors of axillary lymph node metastases in a screened breast cancer. Acta Oncol. 1994; 33: 603-8.

36. Maibenco DC, Weiss LK, Pawlish KS, Severson RK. Axillary lymph node metastases associated with small invasive breast cancer. Cancer 1999; 85: 1530-6.

37. Giuliano A, Barth AM, Spivack B, Beitsch PD, Evans SW. Incidence and predictors of axillary metastasis in T1 carcinoma of the breast. J. Am. Coll. Surg. 1996; 183: 185-9.

38. Olivotto IA, Jackson JSH, Mates D, Andersen S, Davidson W, Bryce CJ, Ragaz J. Prediction of axillary lymph node involvement of women with invasive breast carcinoma. Cancer 1998;83:948-55.

39. Mustafa IA, Cole B, Wanebo HJ, Bland KI, chang HR. The impact of histopathology on nodal metastases in minimal breast cancer. Arch Surg 1997;132:384-90.

40. Choong PL, Desilva CJS, Dawkins HJS, Sterrett GF, Robbins P, Harvey JM, et al. Predicting axillary lymph node metastases in breast carcinoma patients. Breast Cancer Res Treat 1996;37:135-49.

41. Ravdin PM, De laurentiis M, Vendely T, clark GM. Prediction of axillary lymph node status n breast cancer patients by use of prognostic indicators. J Natl Cancer Inst 1994;86:1771-9.

42. Chadha M, Chabon AB, Friedmann P, Vikram B. Predictors of axillary lymph node metastases in patients with T1 breast cancer: a multivariable analysis. Cancer 1994; 73:350-3.

43. De Larentiis M, Gallo C, De Placido S, Peronne F, Pettianato G, Petrella G, et al. A predictive index of axillary nodal involvement in operable breast cancer. Br J Cancer 1996;73: 1241-7.

44. Bath A, Craig PH, Silverstein MJ. Predictors of axillary lymph node metastases in patients with T1 breast carcinoma. Cancer 1997;79:1918-22.

45. Craig PH, Silverstein MJ. Small invasive carcinomas: the role of axillary lymph node dissection. IN: Bland KI, Copeland III EM. The Breast: Comprehensive management of Benign and Malignant Diseases. Philadelphia: W.B. Saunders, 1998.

Table 1 Distribution of subjects by tumor size, age and histological grade

Variable	Category	Number of patients	Proportion (%)
Tumor size (mm)	0-5 (T1a)	262	5.0
	6-10 (T1b)	1324	25.0
	11-15 (T1c)	1584	29.9
	16-20 (T1c)	1025	19.4
	21-50 (T2)	1020	19.3
	>50 (T3)	75	1.4
Age (years)	40-49	544	10.3
	50-59	1884	35.6
	60-69	1790	33.8
	≥ 70	1072	20.3
Histological grade	I	1817	34.3
	II	2383	45.0
	III	1090	20.6

Table 2 Association between axillary lymph node involvement and tumor size, age and histological grade

Variable	ALN Positive		Univariate		Multivariate*	
	n	% (95%CI)	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Tumor size (mm)				**<0.0001**		**<0.0001**
T1a (0-5)	25	9.5 (6.0-13.1)	1.00+		1.00+	
T1b (6-10)	161	12.2 (10.4-14.0)	1.31 (0.84-2.05)	0.23	1.37 (0.88-2.15)	0.16
T1c (11-15)	369	23.3 (21.2-25.4)	2.88 (1.88-4.42)	**<0.0001**	2.95 (1.92-4.54)	**<0.0001**
T1c (16-20)	352	34.3 (31.4-37.2)	4.96 (3.22-7.64)	**<0.0001**	4.81 (3.11-7.42)	**<0.0001**
T2 (21-50)	540	52.9 (49.8-56.0)	10.67 (6.94-16.40)	**<0.0001**	10.31 (6.69-15.90)	**<0.0001**
T3 (>50)	65	86.7 (79.1-94.3)	61.62 (28.16-134.83)	**<0.0001**	60.84 (27.68-133.74)	**<0.0001**
Age (years)				**<0.0001**		**<0.0001**
40-49	182	33.5 (29.5-37.5)	1.00+		1.00+	
50-59	609	32.3 (30.2-34.4)	0.95 (0.78-1.16)	0.62	1.14 (0.91-1.42)	0.26
60-69	498	27.8 (25.7-29.9)	0.77 (0.62-0.94)	**0.01**	0.88 (0.71-1.10)	0.27
≥ 70	223	20.8 (18.4-23.2)	0.52 (0.42-0.66)	**<0.0001**	0.58 (0.45-0.74)	**<0.0001**
Histological grade				**<0.0001**		**<0.0001**
I	361	19.9 (18.1-21.7)	1.00+		1.00+	
II	758	31.8 (29.9-33.7)	1.88 (1.63-2.17)	**<0.0001**	1.45 (1.24-1.69)	**<0.0001**
III	393	36.1 (33.3-39.0)	2.27 (1.92-2.69)	**<0.0001**	1.46 (1.21-1.75)	**<0.0001**

+ Reference category

* Size, age and histological grade

Bold p values are less than 0.05

Table 3 Frequency of cases with axillary lymph node metastases for age, tumor size and histological grade categories and 95% CI (%)

	T1a ≤ 5(mm)		
	Histological grade		
Age (years)	I	II	III
40-49	**0/12(0.0) (0.0-26.5)***	3/13(23.1) (5.0-53.8)*	2/10(20.0) (2.5-55.6)*
50-59	**4/43(9.3) (2.6-22.1)***	4/3 (12.5) (3.5-29.0)*	2/14(14.3) (1.8-42.8)*
60-69	**1/39(2.6) (0.1-13.5)***	3/25(12.0) (2.6-31.22)*	2/14(14.3) (1.8-42.8)*
≥ 70	**1/21(4.8) (0.1-23.8)***	**1/16(6.3) (0.2-30.2)***	**0/9(0.0) (0.0-33.6)***
All ages	**6/115(5.2) (1.2-9.3)**	11/8 (12.8) (5.7-19.9)	6/47(12.8) (3.2-22.3)
	T1b 6-10(mm)		
	Histological grade		
Age (years)	I	II	III
40-49	5/42(11.9) (2.1-21.7)	9/49(18.4) (7.5-29.2)	2/17(11.7) (1.5-36.4)*
50-59	28/221(12.7) (8.3-17.1)	26/192(13.5) (8.7-18.4)	6/57(10.5) (2.6-18.5)
60-69	**20/235(8.5) (4.9-12.1)**	26/182(14.3) (9.2-19.4)	10/54(18.5) (8.2-28.9)
≥ 70	**8/133(6.0) (2.0-10.1)**	14/112(12.5) (6.4-18.6)	7/30(23.3) (8.2-38.5)
All ages	**61/631(9.7) (7.4-12.0)**	75/535(14.0) (11.1-17.0)	25/158(15.8) (10.1-21.5)
	11-15(mm)		
	Histological grade		
Age (years)	I	II	III
40-49	8/46(17.4) (6.4-28.3)	17/69(24.6) (14.5-34.8)	7/27(25.9) (9.4-42.5)
50-59	55/238(23.1) (17.8-28.5)	84/253(33.2) (27.4-39.0)	27/91(29.7) (20.3-39.1)
60-69	40/211(19.0) (13.7-24.2)	46/211(21.8) (16.2-27.4)	30/102(29.4) (20.6-38.3)
≥ 70	19/136(14.0) (8.1-19.8)	31/156(19.9) (13.6-26.1)	5/44(11.4) (2.0-20.7)
All ages	122/631(19.3) (16.3-22.4)	178/689(25.8) (22.6-29.1)	69/264(26.1) (20.8-31.4)

* np<5 (n-number of case, p-proportion of ALNM), 95% confidence interval obtained using Geigy Scientific Tables.

Bold values are proportion less than 10%.

Table 4 Frequency of axillary lymph node metastases for age, tumor size and histological grade categories derived from logistic regression model and 95% CI (%)

	T1a ≤ 5(mm)		
	Histological grade		
Age (years)	I	II	III
40-49	8.2(5.4-12.5)	11.5(7.6—17.0)	11.5(7.6-17.2)
50-59	9.2(6.2-13.5)	12.9(8.8-18.5)	12.9(8.8-18.6)
60-69	7.3(4.9-10.9)	10.3(6.9-15.0)	10.3(6.9-15.2)
≥ 70	**4.9(3.2-7.5)**	7.0(4.6-10.5)	7.0(4.5-10.6)
	T1b 6-10(mm)		
	Histological grade		
Age (years)	I	II	III
40-49	11.0(8.6-13.9)	15.2(12.1-18.8)	15.2(11.9-19.2)
50-59	12.3(10.3-14.6)	16.9(14.3-19.8)	16.9(14.0-20.3)
60-69	9.8(8.1-11.8)	13.6(11.4-16.2)	13.6(11.1-16.6)
≥ 70	**6.6(5.3-8.3)**	9.3(7.5-11.5)	9.3(7.5-11.5)
	11-15(mm)		
	Histological grade		
Age (years)	I	II	III
40-49	20.9(17.2-25.2)	27.7(23.4-32.6)	27.8(23.1-33.1)
50-59	23.1(20.2-26.3)	30.3(27.1-33.8)	30.4(26.6-34.6)
60-69	18.9(16.4-21.8)	25.3(22.3-28.5)	25.3(21.8-29.2)
≥ 70	13.2(11.0-15.8)	18.1(15.3-21.2)	18.1(15.0-21.8)

Y=Logistic(P)= -2.4112 + 0.3174 × size2 + 1.0817 × size3 + 1.5701 × size4 + 2.3333 × size5 + 4.1083 × size6 + 0.1275 × age2 – 0.1263 × age3 – 0.5537 × age4 + 0.3719 × grade II + 0.3753 × grade III.

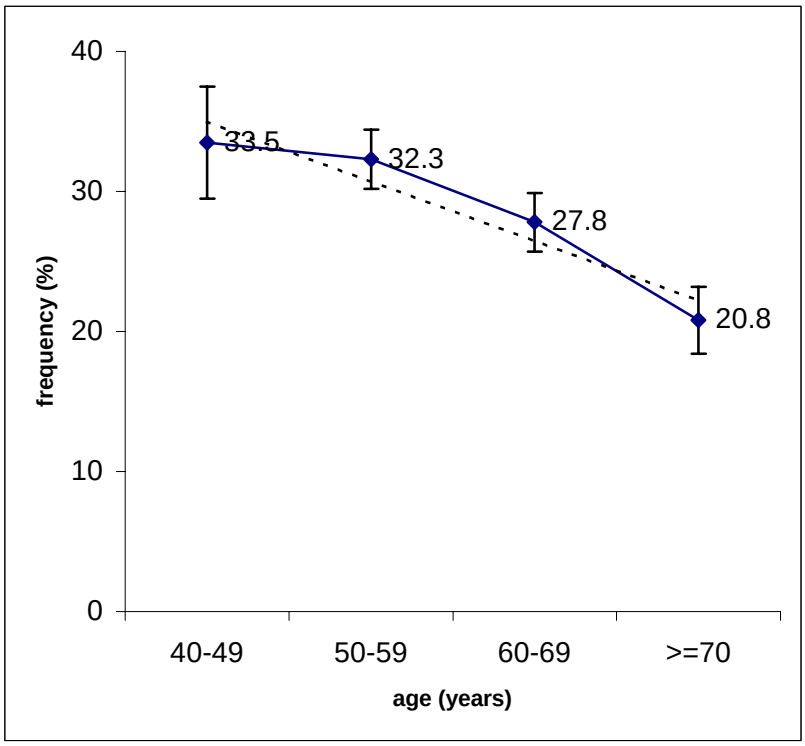
Where P= proportion of axillary lymph node metastasis rate.

P=1/[1+exp(-Y)]

95% CI=1/[1+exp(-y +/- 1.96 × SE (Y)]

Bold subgroups are upper limits of 95% confidence interval <10%.

Figure 1 Proportion of ALNM by age groups



$y=a+bx$. P<0.0001.

The equation is $y=39.25-4.26x$.

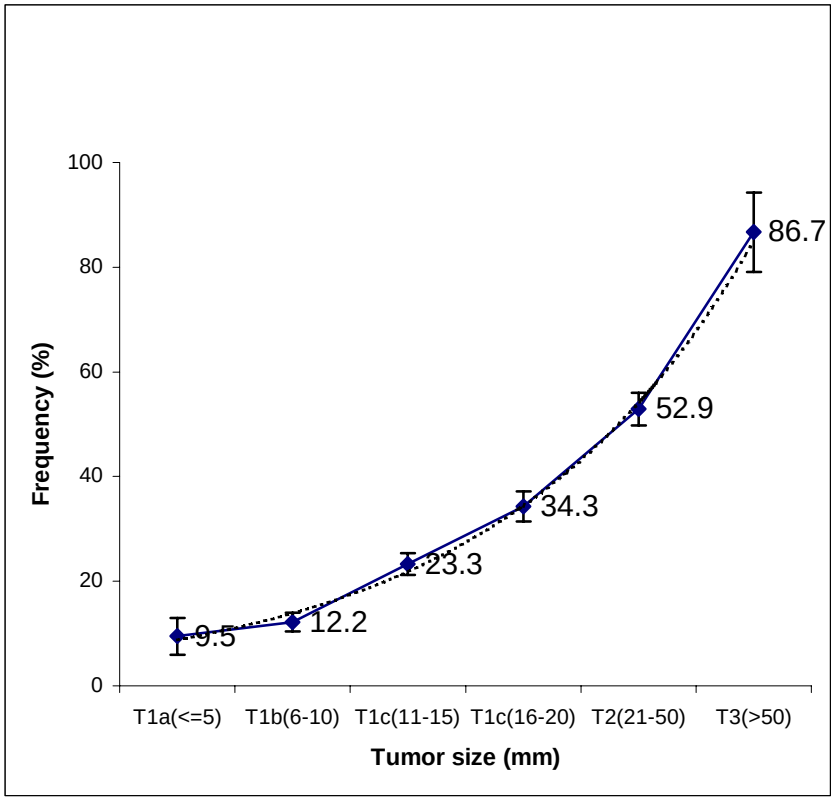
y=proportion of frequency of axillary lymph node metastasis

x=age group, for instance, group 1 (40-49 years) x=1.

a=39.25

b= - 4.26

Figure 2 Proportion of ALNM by tumor size



$y=ae^{bx}$. p<0.0001.

The equation is $y=5.62e^{0.45x}$.

y=proportion of frequency of axillary lymph node metastasis

x=tumor size group: for instance, for group 1 (tumor size≤ 5mm) x=1.

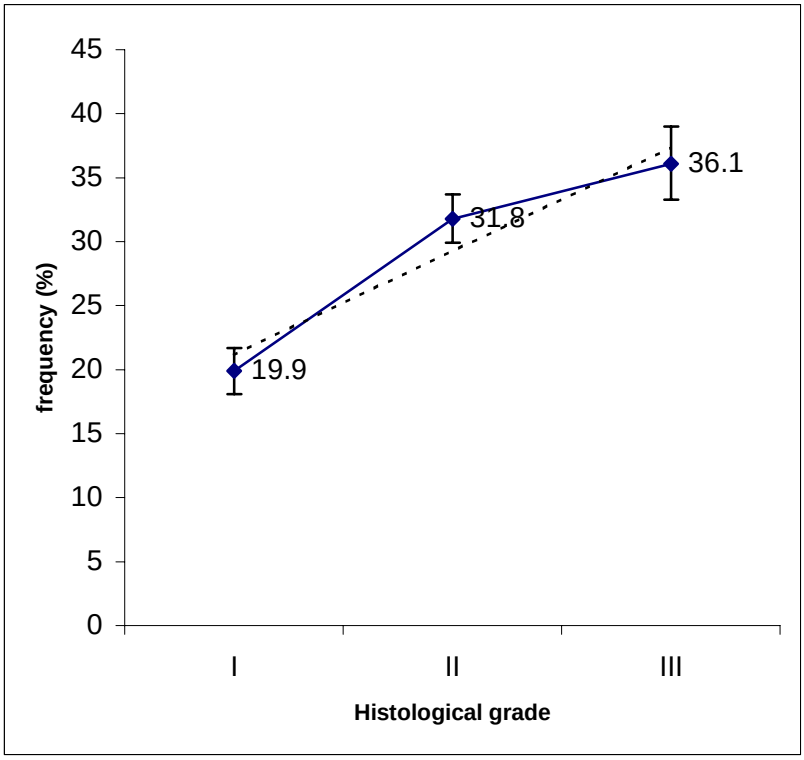
a=5.62

b=0.45.

…… Trendline

____ Empirical data

Figure 3 Proportion of ALNM by histological grade



$y=a+bx$. P<0.0001.

The equation is $y=13.07+8.10x$.

y=proportion of frequency of axillay lymph node metastasis

x=histological grade, for instance, grade I x=1.

a=13.07

b=8.1

Appendix 1-- Proportion of cases with axillary lymph node metastases for age, tumor size and histological grade categories (%)

	≤ 5(mm)		
	Histological grade		
Age (years)	I	II	III
≤ 50	**0/15(0.0)**	4/16(25.0)	2/12(16.7)
>50	**6/100(6.0)**	7/70(10.0)	6/49(12.2)
≤ 55	**3/41(7.3)**	6/30(20.0)	4/28(14.3)
>55	**3/74(4.1)**	**5/56(8.9)**	4/33(12.1)
≤ 60	**4/59(6.8)**	7/49(14.3)	6/38(15.8)
>60	**2/56(3.6)**	4/37(10.8)	**2/23(8.7)**
≤ 65	**5/80(6.3)**	7/56(12.5)	7/46(15.2)
>65	**1/35(2.9)**	4/30(13.3)	**1/15(6.7)**
≤ 70	**5/97(5.2)**	10/73(13.7)	8/52(15.4)
>70	**1/18(5.6)**	**1/13(7.7)**	**0/9(0.0)**
	6-10(mm)		
	Histological grade		
Age (years)	I	II	III
≤ 50	7/58(12.1)	13/63(20.6)	3/22(13.6)
>50	**54/573(9.4)**	62/472(13.1)	22/136(16.2)
≤ 55	21/157(13.4)	24/155(15.5)	7/47(14.9)
>55	**40/474(8.4)**	51/380(13.4)	18/111(16.2)
≤ 60	37/291(12.7)	38/258(14.7)	9/84(10.7)
>60	**24/340(7.1)**	37/277(13.4)	16/74(21.6)
≤ 65	46/412(11.2)	50/349(14.3)	12/109(11.0)
>65	**15/219(6.8)**	25/186(13.4)	13/49(26.5)
≤ 70	54/513(10.5)	64/439(14.6)	19/133(14.3)
>70	**7/118(5.9)**	11/96(11.5)	6/25(24.0)
	11-15(mm)		
	Histological grade		
Age (years)	I	II	III
≤ 50	15/67(22.4)	31/92(33.7)	9/38(23.7)
>50	107/564(19.0)	147/597(24.6)	60/226(26.5)
≤ 55	40/176(22.7)	71/216(32.9)	25/85(29.4)
>55	82/455(18.0)	107/473(22.6)	44/179(24.6)
≤ 60	67/304(22.0)	105/338(31.1)	38/131(29.0)
>60	55/327(16.8)	73/351(20.8)	31/133(23.3)
≤ 65	89/413(21.5)	132/444(29.7)	53/182(29.1)
>65	33/218(15.1)	46/245(18.8)	16/82(19.5)
≤ 70	106/518(20.5)	155/561(27.6)	64/226(28.3)
>70	16/113(14.2)	23/128(18.0)	5/38(13.2)

Bold values are proportion of ALNM less than 10%.

Appendix 2--Age structure comparison between excluded and eligible group

	Eligible group	Excluded group			
Age (years)	Number (%)	Number (%)	X^2	Degree of freedom	P
40-49	544 (10.3)	146 (7.9)	11.12	1	**0.001**
50-59	1884 (35.6)	476 (25.0)	71.98	1	**<0.0001**
60-69	1790 (33.8)	572 (30.0)	9.31	1	**0.002**
≥ 70	1072 (20.3)	712 (37.4)	219.51	1	**<0.0001**
All age	5290 (100)	1906 (100)	229.77	3	**<0.0001***

Bold p values are less than 0.05

*Overall Pearson Chi-Square test and p value with 3 degree of freedom.

Appendix 3--Interaction test between age and histological grade & good-of-fit test for final model

Model	**-2Log L**	**Wald χ^2**	**P**
Base Mode (BM)	5836.84		
BM+agegp*grade	5827.50	36.91 (9DF)	0.39

Wald test for the interaction between age and histological grade, p>0.05

χ^2	DF	P	c
2.8302	**7**	**0.9003**	**0.723**

The model fits the data well using Hosmer-Lemeshow goodness-of-fit test (χ^2=2.8302, 7DF, P=0.723). 70.7% of pairs are concordant and c =0.723.