RESEARCH ARTICLE

Predictive Role of Tumor Size in Breast Cancer with Axillary Lymph Node Involvement - Can Size of Primary Tumor be used to Omit an Unnecessary Axillary Lymph Node Dissection?

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Abstract

Background: Breast cancer is the most common cancer among women worldwide. The aim of this study was to investigate the relationship between tumor size and axillary lymph node involvement (ALNI) in patients with invasive lesions, to find the best candidates for a full axillary dissection. Additionally, we evaluated the association between tumor size and invasive behavior. The study was based on data from 789 patients with histopathologically proven invasive breast cancer diagnosed in Shohada University hospital in Tehran, Iran (1993-2009). Cinical and histopathological characteristics of tumors were collected. Patients were divided into 6 groups according to primary tumor size: group I (0.1-≤1cm), II (1.1-≤2cm), III (2.1-≤3cm), IV (3.1-≤4cm), V (4.1-≤5cm) and VI (>5cm). The mean(±SD) size of primary tumor at the time of diagnosis was 3.59±2.69 cm that gradually declined during the course of study. There was a significant correlation between tumor size and ALNI (p<0.001). A significant positive correlation between primary tumor size and involvement of surrounding tissue was also found (p<0.001). The mean number of LNI in group VI was significantly higher than other groups (p<0.05).We observed more involvement of lymph nodes, blood vessels, skin and areola-nipple tissue with increase in tumor size.We found 15.3% overall incidence of ALNI in tumors ≤2 cm, indicating the need for more investigation to omit full axillary lymph node dissection with an acceptable risk for tumors below this diameter. While in patients with tumors ≥2 cm, 84.3% of them had nodal metastases, so the best management for this group would be a full ALND. Tumor size is a significant predictor of ALNM and involvement of surrounding tissue, so that an exact estimation of the size of primary tumor is necessary prior to surgery to make the best decision for management of patients with invasive breast cancer.

Keywords: Breast cancer - tumor size - axillary lymph node - prognostic factors

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Introduction

Breast cancer is the most frequently diagnosed cancer among women and the leading cause of cancer death in females worldwide. It accounts for 30% of all female cancers and 15% of all cancer related death among women (Artaman, 2010; Garcia et al., 2011; Jemal et al., 2011). In Iran the incidence of the disease is rising, patients present with advanced stage of disease and they are younger than western population (about 10 years) than their western counterparts (ASR=25.06) (Harirchi et al., 2000; Mousavi et al., 2007). Because of high incidence rate of breast cancer among women, it is essential to identify effective strategies to manage this disease in populations. This is particularly depended on screening programs and early detection of cancer, information about risk factors, incidence of cancer in a population and the relationship between tumor characteristics and its invasive manner (Wasserberg et al., 2002).

Early detection of breast cancer, through organized mammographic programs, is an effective method to reduce death and morbidity associated with breast cancer (Ernst et al., 2002; Giuliano et al., 2011).Of known risk factors, age has the strongest influence on breast cancer incidence; roughly, half of all new cases are among women between 50 and 69 years of age (Artaman, 2010). The presence or absence of axillary lymph node involvement (ALNI) is the most important prognostic indicator for patients with early stage breast cancer (Rosen et al., 1993; Cianfrocca and Goldstein, 2004; Westenend et al., 2005; Lee et al., 2010). Increasing the number of involved axillary lymph nodes (ALN) is associated with an increased probability of recurrence and mortality (Colleoni et al., 2005).Efforts have been made to identify factors which can predict

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the risk of axillary lymph node involvement. Prognostic factors that are considered valuable in predicting axillary nodal status for patients with invasive breast cancer include: age, vascular invasion, hormonal receptors, menopausal status, histological grade, nuclear grade, lympho-vascular invasion, DNA ploidy and palpability of the primary tumor. But only the size of primary tumor, as an independent factor, seems to have a statistically significant relationship with lymph node metastases (Ahlgren et al., 1994; Port et al., 1998; Gajdos et al., 1999; Mann et al., 1999; Bourez et al., 2002; Westenend et al., 2005).

During the last century axillary lymph node dissection (ALND) had been an effective surgical procedure in initial management of invasive breast cancer (Krag et al., 1993; Giuliano et al., 1994; Takei et al., 2009). Although ALND is associated with some complications such as pain, lymphedema and shoulder stiffness (Ernst et al., 2002, Robert, 2002; Armando et al., 2011), it is universally acknowledged that staging the axilla is mandatory for selecting the proper treatment of patients with invasive breast cancer (Kang et al., 1999; Lee, 2010). Predicting the status of axillary lymph nodes prior to surgery will help us to determine patients who have an acceptable low risk of ALNI to avoid an unnecessary full ALND. For many years the idea of omitting full axillary dissection for patients with small tumors has been a subject of controversy. Some authors believe that we can spare patients with small tumors (<1cm) from a full ALND because of the low risk of ALNM in these patients, but others think ALND must remain as standard of care in patients with invasive breast cancer (Mincey, 2001). It is a cause for concern if we can use the size of primary tumor as a reliable predictive factor of ALNI. Another challenge is sparing any special group of patients from an unnecessary ALND on the basis of their primary tumor size.

As an aid to make future decisions about management of patients with breast cancer, here we considered the clinical and histopathological features of patients with invasive breast cancer to identify characteristics of primary tumors highly associated with ALNI, in order to select a subset of patients with invasive breast cancer who are the best candidates for ALND to spare them from an unnecessary ALND. In addition, to identify the aggressive manner of breast malignant tumors we studied the relationship between tumor size and involvement of surrounding tissue, such as peritumoral vascular and skin, and areola- nipple invasion.

Materials and Methods

This study was based on data from 789 patients (aged from 18-90 year) with histopathologically proven invasive breast cancer who were admitted at the Division of surgery, Shohada University hospital, Shahid Beheshti University of Medical Science, Tehran-Iran during 1993-2009. The study group underwent breast conserving surgery and ALND (level 1, 2, 3) or modified radical mastectomy. All of histopathological diagnoses were established at the institute of Pathology of the University of Shahid-Beheshti. The local ethics committee approved the study protocol. The following variables were assessed: patient's characteristics (age and sex), clinical characteristics of tumor (side and location of tumor), and histopathological data of tumor (histologic type, tumor size, peritumoral blood vessel, skin, areola and nipple invasion). The number of nodes pathologically evaluated on the likelihood of finding at least one lymph node positive for disease. Moreover, we considered tumors with in situ components as invasive. Invasive carcinoma was divided into three types: type I (infiltrative ductal), II (infiltrative lobular) and III (not otherwise specified). Additional biologic predictive factors (e.g. overexpression of p53, epidermal growth factor receptor, c-erb2) and hormone receptor status (estrogen and progesterone) was not available for all patients. Therefore this information was not considered in the final analysis. During the last years of study sentinel lymph node biopsy (SLNB) was performed in some cases, followed by complete axillary dissection, regardless of the histological nodal findings. The patients who underwent SLNB were included in our study but were not considered separately, their data being included in the total number of dissected lymph nodes.

Inclusion criteria for our study were the following: (1) histologically proven invasive breast cancer; (2) known histopathological nodal status; (3) no distant metastases at the time of registration (4) no previous treatment for breast cancer (5) no previous or concomitant malignancy. Patients who had no remnant of primary tumor (T0) or had a metastasis from other organs to breast at the time of registration, unknown pathological nodal status, immeasurable primary tumor (TX), previous chemotherapy/radiotherapy, primary tumor size <0.1 cm because the smallest diameter was 0.1 cm and tumors <0.1 cm reported as microscopic clues of malignancy, suspicious diagnosis, ductal carcinoma insitu/lobular carcinoma insitu and Paget's disease of the nipple with no tumor were excluded from study. For patients who underwent bilateral axillary dissection we reported the number and involvement of nodes in both sides. With multifocal tumors the larger parameter was considered. The size of tumors was defined as the size of the larger diameter reported in the pathological examination following surgery. In all cases size of tumor reported on the basis of archival pathologic reports. Patients were categorized into 6 groups according to primary tumor size including: group I (0.1-≤1cm), II (1.1-≤2cm), III (2.1-≤3cm), IV (3.1-≤4cm), V (4.1-≤5cm) and group VI (>5cm). Clinical and histopathological variables were compared between all groups and then relationships between tumor size and its invasive manner (such as axillary lymph node, peritumoral blood vessel, skin, areola and nipple invasion) were evaluated.

Statistical evaluation

Descriptive statistics are reported as frequencies and percentages, or means and standard deviations. An independent t-test was considered to compare the scores of each of the measures and some of the parameters data between the two groups. The ANOVA model was utilized for statistical analyses of parameters between all groups. The Pearson correlation and linear regression model

Table 1. Histological and Tumor Characteristics of 789 Breast Cancer Patients

Parameters		Results
Total number of patients (n=789)		789
Age (year) (n=789)	Mean	48.93±12.60
	Range	18-90
Tumor side (n=789)	Right	407(51.5%)
	Left	374 (47.4%)
	Both side	8 (1.1%)
Tumor location (n=193)	UOQ	104 (53.9%)
	LOQ	18 (9.3%)
	UIQ	19 (9.8%)
	LIQ	12 (6.2%)
	Central	33 (17.1%)
	M.C	7 (3.6%)
Tumor Size (mean, cm) (n=675)	Mean	3.59±2.69
	Range	0.4-21
Tumor size (n=675)	I (0.1-≤1)	33 (4.82%)
	II (1.1-≤2)	127 (18.81%)
	III (2.1-≤3)	164 (24.29%)
	IV (3.1-≤4)	138 (20.4%)
	V (4.1-≤5)	78 (11.5%)
	VI (>5)	135 (20%)
Axillary Lymph node (n=424)		4.37±6.12
	Yes	280 (66.03%)
	No	144 (33.96%)
Vascular invasion (n=184)	Yes	113 (61.4%)
	No	71 (38.6%)
Skin involvement (n=254)	Yes	75 (29.5%)
	No	179 (70.5%)
Areola- nipple involvement (n=250)		
	Yes	36 (14.4%)
	No	214 (85.6%)

was used to examine the relation between tumor size and its invasive manner. A p-value of less than 0.05 was considered statistically significant. Data were analyzed using SPSS, version 11.5 (FAQs).

Results

Patient profile and information on histological and tumor characteristics are summarized in Table 1. A total of 789 consecutive patients with invasive breast cancer were referred for interdisciplinary evaluation during 1993-2009, and their data were included in the database. We subsequently excluded patients who had metastatic disease at presentation (n=12), previous chemotherapy (n=8), patients whom primary tumor could not be assessed (n=29), patients who had no evidence of primary tumor (n=32), unknown pathological nodal status (n=11), micro residue of primary tumor (n=16), Paget's disease of nipple without tumor (n=4), suspicious diagnosis (n=2). The mean age of all participated patients was 48.93±12.6 years (ranged from 18-90 years). The lowest and highest mean ages of breast cancer were 46.48±13.7 year in 1993 and 51.18±15.28 year in 2009, respectively (Figure 1). Although there was fluctuation in mean age of patients over the period of 17 years, women 20-24 years of age had the lowest frequency and those 46-51 years of age had the highest incidence of breast cancer. The incidence rate of invasive breast cancer was increased among women 46 and older.

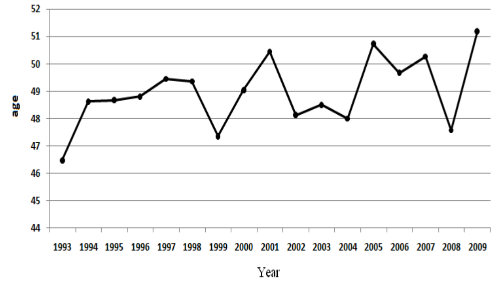

Figure 1. Incidence of Cancer According to Mean age

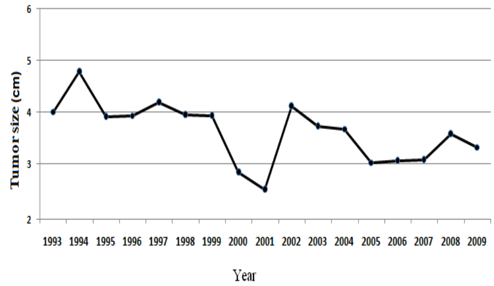

Figure 2. The Mean of Tumor Size between Years 1993-2009

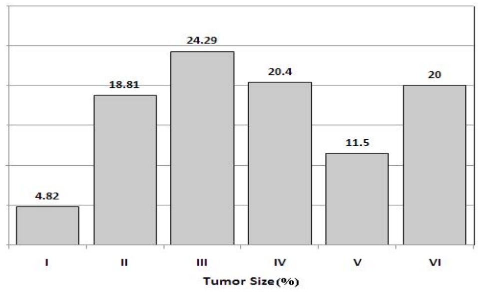

Figure 3. The Percentage of Patients Classified into 6 Groups

Results from histological and tumor characteristics were evaluated in each patient and compared (Table 1). In 51.5% of cases, tumor was detected in right side and in 47.4% of cases the location of tumor in breast was in left side. In 1.1% of cases tumors were bilateral. The tumor site was found more commonly in the upper outer quadrant (UOQ) (53.9% of cases), followed by central tumors (17.1%), upper inner quadrant (UIQ) (9.8%), lower outer quadrant (LOQ) (9.3%), lower inner quadrant (LIQ) (6.2%) and multi centeric tumors (M.C) (3.6%). Considering the pathological type, invasive ductal carcinoma was the most common histopathological type (78.3%), followed by invasive lobular counted (9.2%). The mean size of primary tumor in 675 evaluated patients was 3.59±2.69 cm (ranged from 0.4-21cm). The number of the examined lymph nodes (LN) in all patients ranged from 1-50 lymph nodes with a mean of 4.37±6.12. Among the 424 patients, 280 patients (66.0%) showed pathologic involvement of lymph nodes. Figure 2 presents incidence trends by tumor size during the study time. During 1993-2009, the mean of tumor size showed a gradual decline; however there were some fluctuations during the period. Between 1995 and 1999, the rate for tumors (mean 4 cm) was relatively stable and then dropped sharply to just near 2.5 cm in 2001.

Patients were classified into 6 groups (I-VI) according to primary tumor size. As shown in Figure 3, the majority

Table 2. Correlation between Some Histological and Tumor Characteristics in Six Groups

Parameters	Patients evaluated	I	II	III	IV	V	VI	P value
Tumor Size (cm)	424	0.85±0.22	1.76±0.29	2.77±0.29	3.79±0.25	4.79±0.25	7.83±2.5	<0.001
Axillary lymph node (n)	424	2.34±3.82	2.44±3.81	4.47±7.54	4.88±5.89	4.38±5.81	5.94±6.63	<0.05
Yes	280	8 (2.8%)	35 (12.5%)	49 (17.4%)	61 (18.5%)	52 (21.7%)	75 (26.7%)	<0.001
No	144	5 (3.5%)	28 (19.4%)	35 (24.3%)	25 (17.4%)	26 (18.1%)	25 (17.4%)	
Skin involvement (n)	242							
Yes		7 (7.1%)	11 (12.5%)	13 (14.5%)	16 (19.3%)	15 (17.9%)	23 (28.7%)	<0.001
No		5 (2.4%)	23 (13%)	26 (14.8%)	33 (18.9%)	27 (15.4%)	43 (24.9%)	
Areola & nipple I.N (n)	253							
Yes		6 (4.7%)	7 (8.1%)	8 (13.5%)	10 (16.9%)	11 (18.2%)	16 (38.5%)	<0.001
No		7 (2%)	33 (15.7%)	32 (14.6%)	42 (19.7%)	39 (18.2%)	42 (19.7%)	
Vascular invasion (n)	184							
Yes		5 (3.6%)	17 (11.7%)	14 (14.4%)	24 (20.7%)	24 (20.7%)	31 (27%)	<0.001
No		2 (1.5%)	14 (20.6%)	15 (22.1%)	15 (22.1%)	7 (10.3%)	16 (23.5%)	

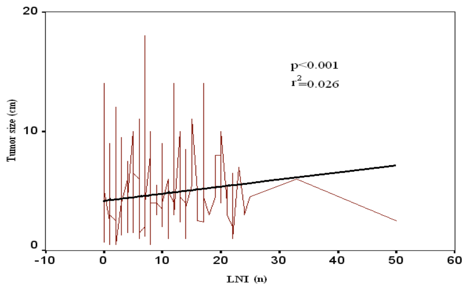

Figure 4. Linear Regression between Tumor Size and LNI. Their correlation is significant (p<0.001)

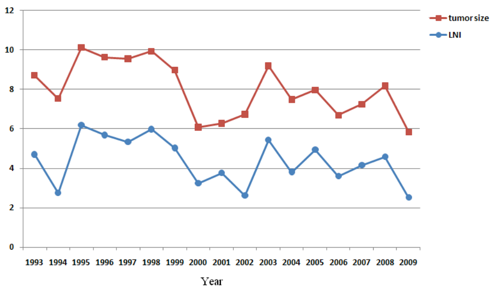

Figure 5. Variations of the Mean of Tumor Size and LNI Since 1993-2009

of cases (24.29%) were in group III (mean tumor size 2.77 cm); while group I constituted only 4.82% of the studied patients (mean tumor size 0.85 cm). This is subsequently followed by group IV (20.4%; mean tumor size 3.79 cm), VI (20%; mean tumor size 7.83 cm), II (18.81%; mean tumor size 1.76 cm) and V (11.5%; mean tumor size 4.79 cm), respectively. This difference was significant between groups ($p<0.001$).

Tumor invasive manner were as follows: 144 (33.96%) patients had node-negative disease and positive axillary nodes were detected in 280 (66.03%) patients for an overall incidence of 2.8% for group one, 12.5% in group two, 17.4% for group three, 18.5% for group four, 21.7% for group five and 26.7% for group six. Of 184 patients with reported peritumoral vascular status, 61.4% patients showed invasion. Skin and areola-nipple involvement in patients were 29.5% and 14.4% respectively (Table 1).

Correlation between tumor size and LNI is shown in Figure 4. Linear regression demonstrates a significantly positive correlation ($p<0.001$; $r^2=0.026$) between tumor size and axillary lymph node involvement.

It was also observed that, as the tumor size increased; more lymph nodes were involved. Figure 5 depicts the variations of mean tumor size and LNI during 1993-2009. As shown in figure, the trend for both was significantly similar during the period of time ($p<0.001$), in other words there is a significant positive correlation between size of primary tumor and ALNM during the studied period ($p<0.001$).

Table 2 shows the data of axillary lymph node involvement as well as peritumoral tissue involvement in six groups. There are significantly differences for the incidence of all variables between groups. The mean number of LNI in group VI was significantly higher than other groups ($p<0.05$). There was a significant difference in the mean number of other mentioned variables among all six studied groups ($p<0.001$).

Regarding the correlation between tumor size and involvement of axillary nodes, blood vessels, skin, areola and nipple, although there are some fluctuations (due to unequal number of patients in groups for these six variables), we found a significant positive correlation between primary tumor size and the other variables. The mean number of involved axillary nodes increased considerably from 2.34 in group I to 5.94 in group VI. The prevalence of areola involvement was also gradually increased from 4.7% in group I to 38.5% in group VI (Figure 1C). The percentage of patients with vascular involvement was considerably raised from 3.6% in group I to 27% in group VI. And the percentage of patients with skin involvement was gradually increased from 7.1% in group I to 28.7% in group VI (Figure 1).

Discussion

Nowadays, women with breast cancer constitute a large group of patients suffering from cancer. Considering the breast cancer as a major cause of morbidity and mortality, early detection of primary tumors is of great importance. Therefore, it is essential that a series of prevention and screening targets and goals are set out for early detection and treatment of the disease (Takei et al., 2009).

Many studies have shown that breast cancer incidence and death rates generally increase with age (Gajdos et al., 1999; Colleoni et al., 2005; Pappo et al., 2007; Stankov, 2011). According to the American Cancer Society reports, 95% of new cases and 97% of breast cancer deaths was occurred in women 40 years of age and older. Stankov (2011) demonstrated that the highest age-specific incidence rate was registered in age group of 70-74 years, whereas the highest number of cases was detected in age group of 60-64 years. In our study, while women 46-51 years had the highest frequency of breast cancer, women 20-24 years and older than 52 years of age had the lower incidence. This may explain the more aggressive nature of the disease among 46-51 years in Iranian patients. The decrease in incidence rates that occurs in women 52 years of age and older may reflect lower rates of screening, the detection of cancers by mammography and/ or incomplete detection. Moreover breast cancer typically produces no symptoms when the tumor is small and most treatable. Thus, it is very important for women to follow recommended screening guidelines for detecting breast cancer at an early stage, before symptoms develop. In our study, the number of patients with breast cancer increased during the last years. This is largely because of increase in screening programs . Possibly, some environmental factors came into play during the last years which then affected the incidence rate of breast cancer. For instance, increased exposure to pesticides or other chemicals could have caused the sudden increase. Or, the use of high-dosage birth control pills, which had just come onto the market, may also be to blame.

We also observed a decreasing trend in tumor size, which may be associated with increasing awareness about breast cancer and to a certain extent, with the introduction of the mammographic breast screening program in Iran since 1993. This result was comparable with other studies (Westenend et al., 2005; Pathy et al., 2011). The most common site for breast cancer was the upper outer quadrant that constituted 53.9% of the studied cases. This observation is confirmed by many authors (Bolkainy, 2000; Zaghloul et al., 2001).

Axillary node involvement is the most significant and durable prognostic factor for women with breast cancer (Gajdos et al., 1999). A common route of spreading breast carcinoma is first through the axillary lymph nodes, and the incidence of ALNI increases with larger tumors (Silverstein et al., 2001; Lee et al., 2010). Since past few decades ALND had been a part of standard method for determining axillary nodal status (Giuliano et al., 1994; Wasserberg et al., 2002; Takei et al., 2009). To identify patients at high risk of axillary metastases, we studied characteristics of primary tumors and their relationship with involvement of surrounding tissues. To investigate any relationship between tumor size and its invasive manner, we divided all patients into 6 groups according to the primary tumor size (I-VI). Our results demonstrate the strong relationship between the primary tumor size and ALNI. As the tumor size increased, the frequency of positive axillary nodes also increased. As shown in Table 2, group VI had higher ALNI compared to the other groups. Our result is comparable with other studies (Zaghloul et al., 2001; Colleoni et al., 2005). These finding suggested that the size of nodal involvement is an important prognostic factor that is significantly associated with increased risk of metastases. Because of this, finding cancer in one or more lymph nodes often affects the treatment plan. This study found an incidence of 2.8% for tumors less that 1cm and a 15.3% overall incidence of ALNI in patients with tumors≤ 2cm, which is similar to other studies (5-15% for T1a and T1b) (Silverstein et al., 2001; Lee et al., 2010). Bourez et al. (2002) found an incidence of 0-8.4% nodal involvement for T1a, 6.9-22.2% in T1b and 13.1-62.5% inT1c tumors in the review of ten studies. In another study overall incidence of ALNI for tumors ≤20 mm reported 29% (Yenidunya et al., 2011). Bader et al. (2002) reported that primary tumor size can be used to omit full ALND in patients with T1 tumors. In another study authors concluded that routine ALND could be omitted in clinically node negative patients with T1a disease (Chua et al., 2001). They recommended dissection for all other cases, as well as all patients with palpable axillary nodes. In our study we didn't have access to clinical data of palpability of primary tumors, so we couldn't analyze this variable that is the limitation of this study. In addition by analysis the correlation between size of primary tumor and involvement of surrounding components we found a considerable increase in involvement of skin, areola, nipple and vascular tissue. By considering all variables, group I had the least of total positive cases, which accounts 2.8% of total ALNI, 7.1% of total skin involvement, 4.7% of areola and nipple involvement and 3.6% of all vascular involvement. This finding shows a less aggressive manner of breast carcinoma in smaller tumors. Similarly, a considerable upward trend in groups II to VI for all studied variables confirms the idea that larger breast tumors have more aggressive manner. Full axillary clearance for patients with tumors <2cm is recommended as 84.3% of this patients will have nodal metastases. On the other hand for patients with tumors ≤2 cm 15.3% have nodal metastases and a full axillary dissection would be an overtreatment for the majority of this patients.

In conclusion, we found that tumor size is a significant predictor of axillary nodal status, which can be used to separate some patients from an unnecessary full axillary dissection. Although more studies are needed to be done for patients with small tumors to omit ALND with an acceptable risk. Larger diameter of tumor can predict the more probability of involving the surrounding tissue. So, an exact estimation of the size of primary tumor is necessary prior to surgery to make the best decision for management of patients with invasive breast cancer. Moreover, as the most of patients were in age range of 46-51, proper observation on performing screening methods before the peak age range is necessary.

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