

Review Article

Update on Management of Non-Palpable Breast Lesion

A Nafisa¹, SKF Ahmed², MA Alam³, SS Murad⁴, ASMT Rahman⁵, S Ahmed⁶

Abstract:

Halstedian radical mastectomy is practiced over 40 years as surgical treatment of breast cancer. For the last twenty years, breast conserving surgery (BCS) has been more practiced in the treatment of breast cancer as it provides oncological safety as well as cosmesis. Non palpable breast lesions are being increasingly diagnosed in the recent years as a result of introduction of breast cancer screening, high quality digital mammography and increase in public awareness. Accurate localisation of small, nonpalpable breast lesions is mandatory for accurate surgical management. The purpose of this article is to review the techniques systematically those have been used to locate non-palpable breast lesions which could easily be introduced in Bangladesh. Breast conserving surgery means complete removal of the tumour with a concentric margin of surrounding healthy tissue with maintenance of acceptable cosmesis. It should be followed by radiation therapy (RT) to achieve an acceptably low rate of local recurrence. Breast conserving surgery with radiotherapy has same survival benefit as mastectomy. BCS plus RT provided better outcome than mastectomy for early breast cancer and should be offered as a preferred treatment option. Experience, logistical support, and multidisciplinary approach is key to success. Radiological support with ultrasound or stereotactic localization with wires and /or ultrasound skin marking are key to have accurate wide local excision of non palpable lesions which is gold standard. Other newer techniques such as radio guided occult lesion localisation (ROLL), magnetic seeds, radiofrequency seeds localisation are a feasible and safe method of breast lesion localization as well and gaining popularity slowly.

Key words: Non palpable breast lension, Breast cancer.

Introduction:

Breast cancer is the most common cancer and the second leading cause of death amongst women worldwide¹. In the United States, it is the leading cause of death in women in forties². In recent years, the size

1. Dr. Ali Nafisa, MBBS, FCPS (Surgery), Associate Professor, Department of Surgery, Anwer Khan Modern Medical College, Dhaka.
2. Dr. SK Farid Ahmed, MBBS, FRCS, Breast & Oncoplastic Breast Surgeon, Wycombe Hospital, Buckinghamshire Healthcare, NHS Trust UK. Visiting Consultant and Advisor, Anwer Khan Modern Breast Care Unit and Research Centre, Dhaka.
3. Dr. Md. Ahasanul Alam, MBBS, Assistant Registrar, Department of Vascular Surgery, National Institute of Cardiovascular Disease, Dhaka.
4. Dr. Shoeb Sarwar Murad, MBBS, MS (Orthopaedics), Assistant Professor, Dept. of Orthopedic surgery, Anwer Khan Modern Medical College, Dhaka.
5. ASM Tanjilur Rahman, MBBS, FCPS (Surgery), Junior consultant, Department of Surgery, Faridpur Medical College Hospital, Faridpur.
6. Dr. Salma Ahmed, MBBS, Medical Officer, Department of Surgery, Anwer Khan Modern Medical College Hospital, Dhaka.

Address of correspondence :

Dr. Ali Nafisa, MBBS, FCPS (Surgery), Associate Professor, Department of Surgery, Anwer Khan Modern Medical College, Dhaka. Mobile: +88-01770301037, E-mail: alinafisadr@gmail.com

of tumors detected has been decreased because of earlier detection as a result of increased population awareness and utilization of mammographic screening programs. Breast cancer screening results in detection of non-palpable breast lumps (i.e. lumps that cannot be felt by palpation by a doctor). Screen detected invasive cancer are 5 per thousand, 2.7 per thousand were < 15 mm in diameter and more than one third of excised breast lesions were clinically occult¹. In screening programme, approximately 15% of all lesions are shown to be malignant in different studies^{3,4}. Screening mammography has increased the detection of non-palpable breast cancer (both invasive and in situ)⁵. The American Cancer Society estimates 200,000 breast cancer diagnosed in 1988. About 60,000 (30%) non palpable lesions were identified in screening mammography and 80.9% of women underwent single operation with preoperatively proven non palpable breast cancer⁶, 74.1% of women who had breast-conservation amongst them⁷. Percutaneous imaging-guided core biopsy may enable most of these women to undergo a single operative procedure for definitive surgical treatment⁸.

A meta analysis of seven randomized trials studying women aged 40-49 years has demonstrated a statistically significant 24% reduction in breast cancer mortality due to screening intervention⁹. This outcome may be improved by annual two-view screening with high-resolution mammography^{10,11} and for Bangladesh it should be 30-40 years¹².

The challenge remains to accurately locate small non-palpable lesions intraoperatively for optimal therapeutic outcome. A secondary important goal is to remove the smallest amount possible of healthy glandular tissue for optimal cosmesis. Currently, the most widely adopted approach (80% in one survey) in breast-conserving surgery for excising non palpable breast lesions is wire-guided localization (WGL)¹.

What is non palpable breast lesion:

Nonpalpable breast lesion is one that is not palpable during physical examination but detected in imaging incidentally or in screening. Most of the DCIS (ductal carcinoma in situ) even upto 5 cm lesions may be non palpable. Larger invasive cancers can be non-palpable in huge breasts. In the last couple of decades as a result of screening small, clinically occult carcinomas are being diagnosed increasingly. This leads the surgeons to reconsider the optimal treatment of this sub-group. Tumor stage has a well established association to the prognosis. Stage I disease, particularly less than 1 cm, is associated with very low recurrence and death rates. Although 35% of non-palpable breast carcinomas have metastatic capacity, and axillary lymph node metastases¹³.

Diagnostic Challenge:

Screening detected breast lesion requires histopathological confirmation of its tissue type. Percutaneous imaging-guided core biopsy is a faster, less invasive, and less expensive alternative to surgical biopsy for diagnosing breast lesion¹⁴. For women with breast cancer diagnosed by surgical biopsy, treatment often requires a second operation to achieve complete resection of the tumor and/or to evaluate the axilla¹⁵. Interventional procedures are very important in clarifying non-palpable breast lesions. The introduction of localization techniques has dramatically increased the ability to find out small cancers as well as cosmetic results. Most surgeons and patients want a one-stage procedure. Core biopsy is easier in collection, preparation and pathological interpretation of specimens¹⁶. Sensitivity and specificity are higher for core biopsy than for Fine Needle Aspiration Cytology (FNAC). The benefit of core biopsy is to have a structural details regarding invasiveness of cancerous cells through basement membrane of ducts

(differentiate between DCIS and invasive carcinoma which is not possible on FNAC), grades, ER, PR, HER2, Ki67, and lymphovascular invasion (LVI) status with certainty¹⁷. These are the major determinants for making decision and choosing better treatment modalities. Ultrasound of the breast is an important adjunct to mammography and clinical examination of both palpable and non-palpable breast lesions.

Traditionally the biopsy technique used to evaluate non-palpable lesions has been needle localized breast biopsy (Stereotactic or sonographic guidance). This method involves surgical excision of breast tissue around the needle or wire used and has been the gold standard for the last three decades because the reliability is 99-100%¹⁷.

Diagnostic procedure :

1. Wire localization

Needle localization biopsies of non-palpable breast disease have a higher proportion of detection of non-invasive lesions (DCIS) and early stage breast cancers than biopsies in palpable breast disease. For excisional biopsy positive margins and re-excision rates are reported to be 55-83%.

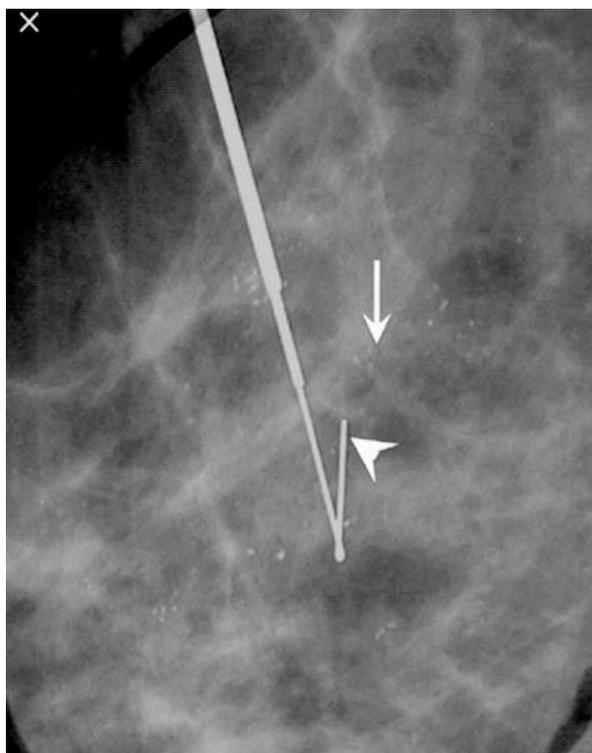


Figure 1: Stereotactic needle localization



Figure 2: Wire guided needle



Figure 5: Weight measurement of the specimen



Figure 3: Pre-operative wire localization

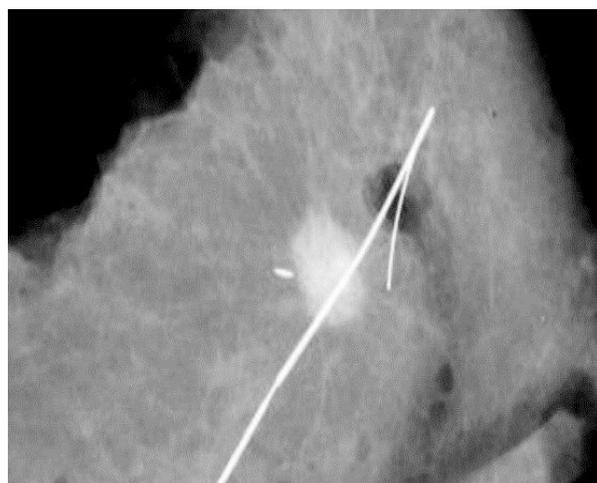


Figure 6: X-ray of specimen with wire localization in situ to see radiological marging clearance



Figure 4: Specimen with orientation



Figure 7: With bracketed wire localization. For few cases, two wires use for proper localization.

For women with calcifications shown to be carcinoma, additional surgery was recommended if postoperative mammography performed approximately 2 weeks after surgery showed residual calcifications at the biopsy site. Preoperative needle localization helps in precise re-excision of residual malignant calcification^{18,19}. Complications include wire dislocation/migration, penetration of the pleural space or the wire retracting into the breast^{20,21}.

Factors of unsuccessful needle localized breast biopsy are two or more lesions per breast, small lesions, small specimens and microcalcifications²².



Figure 8: Mobile digital X-ray cabinet for assessment of radiological free margin of specimen per operatively

2. Intra Operative Ultra Sonogram (IOUS) and IOUS guided surgery

"The IOUS surgical technique" has been described. It normally relies on the surgeon to mark the projected tumour margins on the skin of the breast before the first incision is made. The surgeon then inserts the probe into the wound multiple times in an effort to determine the relation between the tumor and the surrounding tissue once surgery proper has started. Once the excision has been completed, the specimen is examined ex vivo (i.e., ultrasound examination of the excised specimen), followed by additional shaving excisions if one of the excision margins is found to be too close to the edge of the tumour. Intraoperative ultrasound may help maintain low incidence of reoperation after breast-conserving surgery²³. Patients who underwent lumpectomies using IOUS were less likely to have an involved margin or to require re-excision²⁴. The lumpectomy volumes in the IOUS group were smaller than in the lumpectomy alone group²⁵.

3. Radioguided Occult Lesion Localization Technique (ROLL)

In ROLL technique intratumoural injection of a large-diameter radiotracer, Tc 99m-labeled human albumin colloid (Macrotec, diameter of 10-150m) is given. It should be performed under stereotactic mammographic or US guidance. It allows greater accuracy of lesion localization. Furthermore, 0.1L of water-soluble nonionic iodinated contrast medium is administered to check the exact position of the radiotracer at the time of injection. One hour later, the patient undergoes front and lateral view planar scintigraphic imaging, using a 99mTcO4 flood to check the radiographic correlation²⁶. The patient is admitted to the operating room for surgical resection of the lesion. Preoperatively before the induction of general anesthesia, the surgeon uses a hand-held gamma probe to identify and mark the site of the lesion by locating the area of maximal radioactivity, this allowing the incision to be concentrated exactly over the tissue disorder. The parenchyma substance is verified with the probe to rule out residual areas of high radioactivity. During the surgical procedure, a radiologic study is performed to confirm total resection of cases that had been previously demarcated by mammography²⁷.

4. Radioguided Seed Localization Technique (RSL)

RSL involves a small titanium seed (4x0.8mm), which is labeled with I-125 and emits 27keV of gamma radiation, compared to Tc-99, which has 140keV of this radiation. The half-life of this substance is estimated to be 60 days²⁸.

5. Radiofrequency seed

Wire-free miniature RFID tag approximately 11mm long and 2mm in diameter, each Tag includes a unique identification number displayed by the reader and a polypropylene cap designed to prevent its migration in tissue. The Tag is visible under X-ray and ultrasound and has no contraindication for patients with nickel allergies.

Single-Use Sterile Probe: The Surgical Probe is a pencil-sized, single-use sterile probe that will guide the surgeon towards the Tag during the operation. The 8mm diameter of the probe allows for small incisions.

Portable Handheld Reader: The handheld Reader displays the distance to the Tag in millimeters and the Tag's ID number on a bright screen, making it easy to read during the procedure. The LOCALIZER™ system can read the tag at up to a 60mm distance and is designed to function without interference from the other equipment in the theatre²⁹.



Figure 9: Radiofrequency seed : A: Before incision-sterile probe to guide the surgeon, B: Probe finding the tag location, C: Resected specimen and D: Per operative Xray of specimen to see radiological clear margin

Problems with frozen section biopsy:

It is especially true that frozen section might not yield a definite diagnosis when the gross lesion is small <1cm in dimension. Permanent sections from the frozen block might have sufficient freezing artefacts to render these sections sub-optimal or even useless for diagnosis. Sampling error which leads to a false-negative diagnosis when frozen section is used to diagnose DCIS. Patients do not know the exact diagnosis pre-operatively, so they cannot be adequately informed. As a negative margin status has become a pre-requisite for breast conserving therapy, it is possible to evaluate the margins by frozen section but is not always accurate³⁰. Hospitals where breast cancer surgery is performed should have a multidisciplinary approach as this is associated with a greater likelihood that women will receive effective local and systemic adjuvant treatments. Pre-operative diagnosis of a breast carcinoma is desirable allowing the specialist to plan a one-stage therapeutic operation; it also allows the patient time to 'come to terms' with the entirety of her management plan. Invasive cancers tend to be small, of low histologic grade and have a low incidence of lymph node involvement, with a high proportion of ductal carcinoma in situ and also a high proportion of lobular carcinoma³¹.

Surgical management of Axilla

Sentinel lymph nodes were evaluated by paraffin section, and immunohistochemistry and more recently over ten years, OSNA using molecular biology technique counting copies of CK19mRNA³¹. If sentinel lymph nodes were tumour-free, no further axillary surgery was performed. If sentinel lymph nodes contained tumour, axillary dissection was performed during the same operative procedure. Underestimation contributed to the need for additional surgery in 25.3% of women who required³². If percutaneous biopsy shows DCIS and surgery shows infiltrating carcinoma, the patient may require a second operation to evaluate the axilla. The finding of tumor in sentinel nodes was the third most common reason for more than one operation³¹.

Pathological challenge :

Morphological assessment of the degree of differentiation has been shown in numerous studies to provide useful prognostic information in breast cancer. In the Nottingham/Tenovus Primary Breast Cancer Study the most commonly used method, described by Bloom & Richardson, has been modified in order to make the criteria more objective. The revised technique involves semi quantitative evaluation of three morphological features-the percentage of tubule

formation, the degree of nuclear pleomorphism and an accurate mitotic count using a defined field area. A numerical scoring system is used and the overall grade is derived from a summation of individual scores for the three variables; three grades of differentiation are used. Since 1973, over 2200 patients with primary operable breast cancer have been entered into a study of multiple prognostic factors³².

Pathologists do need specimen accurately oriented with details history on histology request form. Report should contain details of Types, grading, size, margins, ER, PR, HER2, LVI, Ki67 .

Adjuvant treatment:

Postoperative chemotherapy was less frequently employed in treating patients with mammographically detected breast cancer. Palpable invasive breast cancer need adjuvant chemotherapy for 67% of the women. For non palpable breast cancer it is only 31%. More conservative surgery and less chemotherapy did not pose any adverse effect on the excellent outcome of patients with mammographically discovered breast cancer. Their five-year overall survival and disease-free survival rates were both 100%. In contrast, the five-year overall and disease-free survival rates were 70% and 62% respectively among patients with palpable breast cancer. The mean size of invasive cancers detected as non palpable mammographic abnormalities was 1.3 cm, and 94% of these patients had negative lymph nodes. The five-year survival rate was 100%, which is significantly better than 70% observed in patients with palpable breast cancer. Patients rarely had recurrent disease³³. One study demonstrated excellent local control and overall survival in patients with non palpable breast cancer who were treated by breast-conserving surgery and radiation. One study further pointed out that none of these patients received adjuvant chemotherapy. One would assume that the quality of the patient's life is likely to be improved when breast conserving treatment is an option, and when it is possible to avoid chemotherapy among women with mammographically detected breast cancer³⁴.

Although majority may be offered adjuvant RT post BCS, omission of WBRT in women age 65 or above with PN0, ER+ve breast cancer after BCS with endocrine therapy, results in only 4.1% 5 years IBTR (ipsilateral breast tumour recurrence) found on PRIME 2 trial. ER positives are offered Tamoxifen 20 mg once daily for 10 years and post menopausal women with aromatase inhibitor for 5-10 years. Small percentages will be HER2 +ve, may be treated with Herceptin along with chemotherapy.

Conclusion:

From the Halstedian radical mastectomy to the more aesthetic breast conserving surgery (BCS), the last 40 years have witnessed a fascinating evolution in the role of surgery in the treatment of breast cancer. Complete removal of the tumour with a concentric margin of surrounding healthy tissue with maintenance of acceptable cosmesis, and should be followed by radiation therapy to achieve an acceptably low rate of local recurrence. Breast Conserving Surgery + Radiotherapy = Mastectomy. RCT showed no survival benefit in mastectomy. BCS plus RT provided better outcome than mastectomy for early breast cancer and should be offered as a preferred treatment option. Radiological support with US or stereotactic localization with wires and /or US skin marking are key to have accurate excision of non palpable lesions, is gold standard. Other newer techniques involves radio guided occult lesion localisation (ROLL), Magnetic seeds are a feasible and safe method of breast lesion localization as well and gaining popularity slowly. Wire guided Wide Local Excision method involves surgical excision and has been the gold standard for the last three decades because the reliability is 99-100%.

Conservative treatment of breast cancer is oncologically safe and involves team work. The first excision is the best excision. Specimen oriented, not opened/divided, fresh, clear margins are key and 1 mm clear margin histologically is deemed safe. Good Information to the patient about local recurrence, survival, therapeutic alternatives and experience, logistical support, and multidisciplinary approach is key to success. Optimization of patient selection for breast conservation, improvements in preoperative assessment of the extent of disease, advances in percutaneous biopsy technology to minimize histologic underestimation, and improved use of sentinel lymph node biopsy may allow more women to achieve therapeutic results in one operation.

References :

1. Chan BK, Wiseberg-Firtell JA, Jois RHS, Jensen K, Audisio RA. Localization techniques for guided surgical excision of nonpalpable breast lesions. *Cochrane Database Syst Rev.* 2015 Dec 31; (12): CD009206.
2. Department of Health and Human Services. Vital Statistics of the United States. *Cancer Mortality 1988:988.*
3. Al-Sobhis, Helvie M, Pass H, Chang A. Extent of lumpectomy for breast cancer after diagnosis by stereotactic core versus wire localization biopsy. *Ann Surg Oncol.* 1999; 6:330-35.
4. Blanks RG, Moss SM, McGahan CE, Quinn MJ, Babb PJ. Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990-8: comparison of observed with predicted mortality. *BMJ* 2000; 321: 665-69.

5. Luini A, Zurrida S, Paganelli G, Galimberti V, Sacchini V, Monti S, et al. Comparison of radioguided excision with wire localization of occult breast lesions. *Br J Surg.* 1999; 86: 522-25.
6. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. *Cancer Statistics, 2001.* *CA Cancer J Clin.* 2001; 51:15-36.
7. Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography. A meta-analysis. *JAMA* 1995; 273:149-54.
8. Ernst MF, Roukema JA. Diagnosis of non-palpable breast cancer: A review. *The Breast* 2002; 11(1):13-22.
9. Hendrick RE, Smith RA, Rutledge JH 3rd, Smart CR. Benefit of screening mammography in women aged 40-49: a new meta-analysis of randomized controlled trials. *J Natl Cancer Inst Monogr.* 1997; (22):87-92.
10. Feig SA. Estimation of currently attainable benefit from mammographic screening of women aged 40-49 years. *Cancer* 1995; 75:2412-9.
11. Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, et al. Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial. *Cancer* 1995; 75(10):2507-17.
12. Nafisa A, Tasnim T. Pattern of Breast Diseases in Patients Attending a Teaching Hospital in Bangladesh. *Bangladesh Medical College Journal* 2015; 20(1):8-11.
13. Liberman L. Percutaneous image-guided core breast biopsy: state of the art at the millennium. *AJR* 2000 ; 174:1191-119.
14. *Breast imaging reporting and data system (BI-RADS), 2nd ed.* Reston, VA: American College of Radiology, 1995.
15. Britton PD. Fine needle aspiration or core biopsy. *Breast* 1999; 8:1-4.
16. D'Angelo PC, Galliano DE, Rosemurgy AS. Stereotactic excisional breast biopsies utilizing the advanced breast biopsy instrumentation system. *Am J Surg.* 1997; 174(3):297-302.
17. Guray M, Sahin AA. *Benign Breast Diseases: Classification, Diagnosis, and Management.* *The Oncologist* 2006; 11:435-49.
18. Perre CI, Hoyneck van Papendrecht AA, Sierink HD, Muller JW. The non-palpable, radiographically suspicious breast lesion: an analysis of 101 cases. *Neth J Surg.* 1990; 42(3):69-71.
19. Bristol J, Jones PA. Transgression of localizing wire into the pleural cavity prior to mammography. *Br J Radiol.* 1981; 54:139-140.
20. David PS, Wechsler RJ, Feig SA, March DE. Migration of breast biopsy localization wire. *Am J Roentgenol.* 1988; 50:787-88.
21. Jackman RJ, Marzoni FA Jr. Needle-localized breast biopsy: why do we fail? *Radiology* 1997; 204(3):677-84.
22. Olsha O, Shemesh D, Carmon M, Sibirsky O, Abu Dalo R, Rivkin L, et al. Resection margins in ultrasound-guided breast-conserving surgery. *Ann Surg Oncol.* 2011; 18:447-52.
23. Davis KM, Hsu CH, Bouton ME, Wilhelmson KL, Komenaka IK. Intraoperative ultrasound can decrease the re-excision lumpectomy rate in patients with palpable breast cancers. *Am Surg.* 2011; 77:720-5.
24. Fisher CS, Mushawah FA, Cyr AE, Gao F, Margenthaler JA. Ultrasound-guided lumpectomy for palpable breast cancers. *Ann Surg Oncol.* 2011; 18:3198-203.
25. Van Riet YE, Jansen FH, van Beek M, van de Velde CJ, Rutten HJ, Nieuwenhuijzen GA. Localization of nonpalpable breast cancer using a radiolabelled titanium seed. *Br J Surg.* 2010; 97(8):1240-5.
26. Postma EL, Verkooijen HM, van Esser S, Hobbelink MG, van der Schelling GP, Koelemij R, et al. Efficacy of "radioguided occult lesion localisation" (ROLL) versus "wire-guided localisation" (WGL) in breast conserving surgery for non-palpable breast cancer: A randomised controlled multicentre trial. *Breast Cancer Res Treat.* 2012; 136(2):469-78.
27. Rampaul RS, Bagnall M, Burrell H, Pinder SE, Evans AJ, Macmillan RD. Randomized clinical trial comparing radioisotope occult lesion localization and wire-guided excision for biopsy of occult breast lesions. *Br J Surg.* 2004; 91(12):1575-7.
28. Hologic LOCALizer Wire-free Guidance System. Available from: <https://www.hologic.com/hologic-products/breast-skeletal/localizer-wire-free-guidance-system#resources> [Accessed 3rd March 2019]
29. McGugin C, Spivey T, Coopey S, Smith B, Gadd M, Hughes K, et al. Radiofrequency identification tag localization is comparable to wire localization for non-palpable breast lesions. *Breast Cancer Res Treat.* 2019; 177(3): 735-39.
30. Klimberg V S, Harms S, Korourian S. Assessing margin status. *Surg Oncol.* 1999; 8: 77-84.
31. Liberman L. Pathologic analysis of sentinel lymph nodes in breast cancer. (editorial). *Cancer* 2000; 88:971-77.
32. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. The value of histological grade in breast cancer: experience from a large study with long term follow up. *Histopathology* 1991; 19(5):403-10.
33. Helena RC, Bernard Cole, Kirby IB. Nonpalpable Breast Cancer in Women Aged 40-49 Years: A Surgeon's View of Benefits From Screening Mammography. *JNCI Monographs* 1997; 22:145-49.
34. Haffty BG, Kornguth P, Fischer D, Beinfield M, McKhann C. Mammographically detected breast cancer: results with conservative surgery and radiation therapy. *Cancer* 1991; 67:2801-4.