Breast Cancer (2014) 21:522–531
DOI 10.1007/s12282-012-0427-1

ORIGINAL ARTICLE

Procedures for location of non-palpable breast lesions: a systematic review for the radiologist

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Received: 3 September 2012 / Accepted: 15 October 2012 / Published online: 2 November 2012

Abstract Accurate location of small breast lesions is mandatory for proper surgical management. The purpose of this article is systematically review procedures used to locate non-palpable breast lesions, including a description of the current status, advantages, and disadvantages for each technique. A total of 47 articles were finally included: 7 articles for the wire location technique, 5 articles for the radioguided location technique, 13 articles that compare wire location with radioguided location, 3 articles for the carbon location technique, 2 articles that compare wire location with carbon location, and 17 articles for the clip location technique. The success of location and the clear margin are reported for each location technique and for the separate articles included; clip migration shift, also, is reported for the clip location technique. Odds ratio with related 95 % confidence intervals were also calculated for successful location. Comparative analysis or meta-analysis for all the different breast lesion location techniques is missing. Prospective investigations and randomized investigations for homogeneous populations are still needed to determine which is the most cost-effective modality among those used to date.

Keywords Breast cancer · Impalpable breast lesion · Hookwire location · Radioguided location · Carbon location · Clip marker location

Abbreviations

CI	Confidence interval
CL	Carbon location
MRI	Magnetic resonance imaging
ROLL	Radioguided occult location
WL	Wire location

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Background

With the worldwide introduction of mammographic screening programs and with women's increased awareness, small non-palpable breast lesions, usually smaller than 1 cm, are being detected with increasing frequency. Up to 25 % of breast lesions visualized by mammography or sonography are clinically non-palpable (i.e. not detectable by physical examination even if performed by an expert physician and based on topographic imaging data) (Table 1). Thus, appropriate management of non-palpable breast lesions has become an important issue with

Table 1 Prevalence of palpable and non-palpable breast lesions

Ref.	Overall number of lesions	Number of palpable lesions	Number of non-palpable lesions	Prevalence of non-palpable lesions (%)
Ernst et al. [1]	479	69	410	85.6
Cho et al. [49]	191	121	70	36.6
Berg et al. [50]	177	89	88	49.7
Londero et al. [51]	65	21	44	67.7
Lawrence et al. [52]	372	143	229	61.6

Table 2 Prevalence of benign and malignant lesions among non-palpable breast lesions

Ref.	Overall number of lesions	Number of benign lesions	Number of malignant lesions	Prevalence of malignancy (%)
Barros et al. [53]	115	58	57	49.6
Chen et al. [54]	182	142	40	22.0
Chen et al. [55]	35	21	12	34.3
Cho et al. [49]	70	49	21	30.0
Edkein et al. [8]	42	27	15	35.7
Gisvold et al. [56]	343	250	93	27.1
Landheer et al. [57]	36	26	10	27.8
Lawrence et al. [52]	229	157	72	31.4
Lee et al. [58]	59	40	19	32.2
Lehman et al. [59]	5	2	3	60.0
Liberman et al. [4]	103	28	75	72.8
Liberman et al. [60]	86	52	34	39.5
Phillips et al. [61]	11	6	5	45.5
Rao et al. [38]	50	19	31	62.0
Rose et al. [30]	230	134	96	41.7
Rosen et al. [43]	111	72	39	35.1
Chadwick et al. [62]	129	65	64	49.6
Intra et al. [29]	227	79	148	65.2
Allen et al. [63]	212	78	134	63.2
Gray et al. [64]	97	56	41	42.3
Luini et al. [34]	60	25	35	58.3
Mass et al. [65]	138	46	92	66.7
Arman et al. [66]	16	10	6	37.5

socioeconomic and emotional implications, moreover 9–63 % of these abnormalities are eventually found to be malignant [1] (Table 2).

It is necessary to accurately locate such occult lesions, with the objective of excising the smallest amount of tissue and yet to remove the entire lesion whilst achieving adequate clear margins. Location of the lesions is useful for radical resection of the tumor to:

– minimize the likelihood of local recurrence [2–4];
– provide a correlation of biopsied lesions revealed both by sonography and mammography [5, 6];
– locate the tumor bed in a locally advanced cancer patient after receiving preoperative neoadjuvant chemotherapy (given the frequently encountered marked response to treatment) [7, 8], and
– assess, after a stereotactic, vacuum-assisted breast biopsy, the accuracy of marker clip deployment for guiding subsequent needle location procedures and surgery [9].

Several techniques have been described for preoperative location, including wire-located breast biopsy (WL), radio-guided occult location (ROLL), clip location, and carbon location (CL). Other authors have already published reviews on techniques for location of breast lesions. Jakub et al. [10] reviewed the current status of radioactive seed location. Van der Ploeg et al. [11] and Lovrics et al. [12] have written reviews comparing ROLL and WL but without taking other modalities in consideration. The purpose of our study was to report all the techniques proposed for location of breast lesions, analyzing their current status and their advantages and disadvantages.

Methods

Search strategy and selection criteria

This study was approved by the ethics on research committee of our institution "National Cancer Institute of Naples IRCCS Pascale Foundation". Data for this review were identified by searches of the Pubmed database using a multimodal strategy and the search terms: breast clip placement or location, wire breast location, carbon breast location, radio-guided occult breast or seed location, titanium breast location, titanium or collagen or radiopaque clip breast location.

The inclusion criteria were: clinical study evaluating wire location, radio-guided location, carbon location, or clip location technique for non-palpable breast lesions; the presence of a criterion of performance evaluation for the considered breast location techniques; and availability of the full text. Only papers published in the English language from January 1987 to February 2011 were included. The references of these studies were also analyzed to identify original studies that were not identified by the search of the data. Exclusion criteria were: palpable tumors only included, not full text and not original research article type (abstract, editorial, case report, or review), and lack of reporting of clear margin status, of diagnostic success, or of clip migration.

Evaluation of outcomes

Comparisons among the several location techniques were conducted by choosing papers that reported the outcomes: successful location, clear margins, and clip migration (the last for the clip location technique only).

Successful location corresponded to the percentage of locations that did not fail. Causes of procedure failure typically include displacement of the location wire during surgery, deeply placed/relatively inaccessible lesion; lesion poorly defined in comparison with the surrounding breast tissue, and large breast size [13]. Another outcome considered was the percentage of clear margins after surgery. In accordance with the criteria defined by Solin et al. [14], a surgical margin is regarded as clear when at least 2 mm of normal breast tissue surround the carcinoma, as close when less than 2 mm of normal breast tissue surround the carcinoma, and as involved when carcinoma was found in the surgical margins. For the clip location technique another outcome was used—migration of the marker from

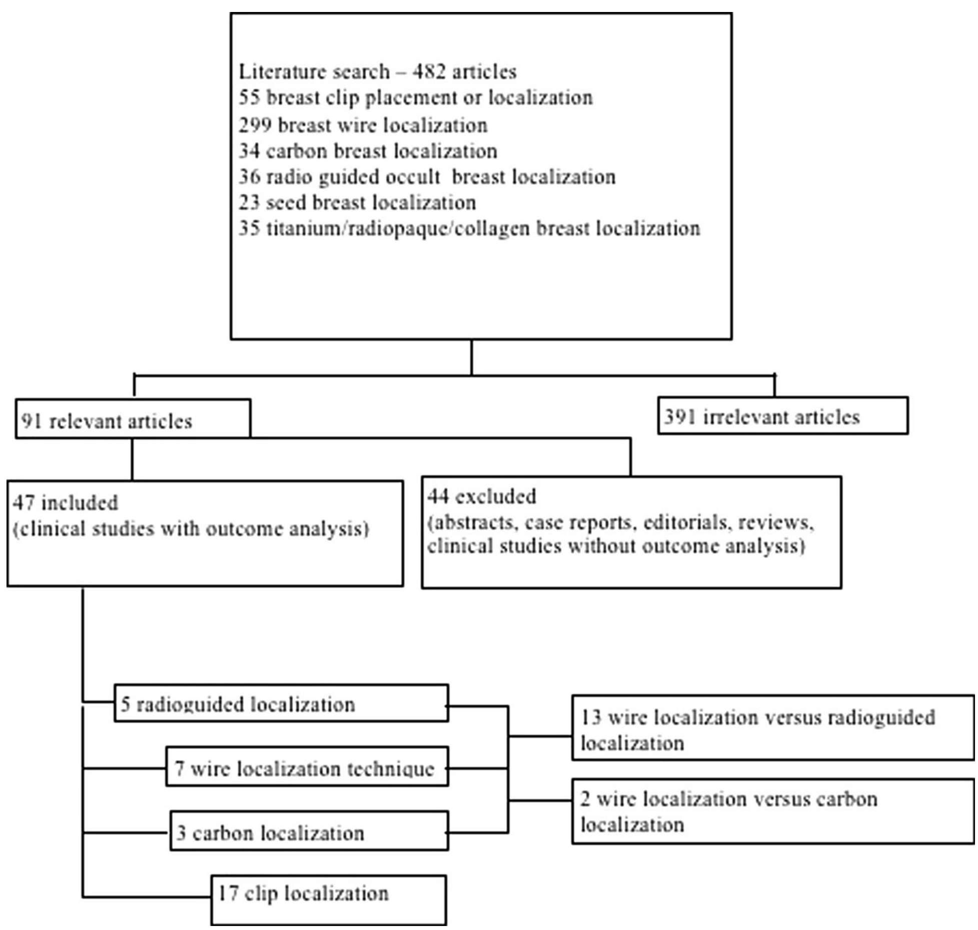

Fig. 1 Flow chart of article selection in our study

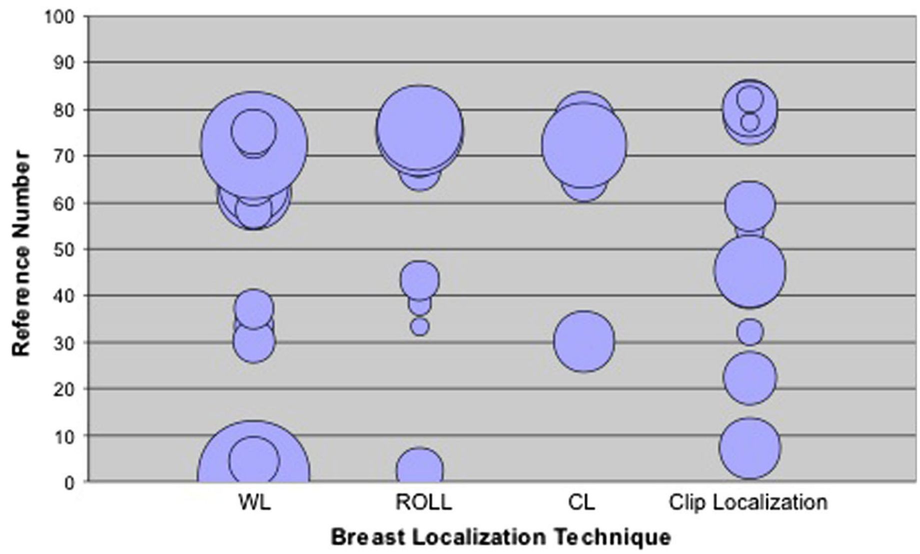

Fig. 2 Comparison of several location techniques. On the *vertical axis* is reported the study reference number. On *horizontal axis* is reported WL studies, ROLL studies, CL studies, and clip location studies. The sizes of the circles correspond to the number of lesions examined in each study

the initial site expressed in centimeters. Values were reported as average ± standard deviation.

The odds ratio is a measure of effect size, describing the strength of association or non-independence between two binary data values. An odds ratio is a measure of association between an exposure and an outcome. The 95 % CI is used to estimate the precision of the odds ratio. A large CI indicates a low level of precision of the odds ratio, whereas a small CI indicates a higher precision of the OR [84]. In this study the odds ratio with the related 95 % CI was used to compare successful location for each location technique and the effect size for each considered study in the review. The odds ratio was reported for successful location only, because for the clip location techniques a few articles report this outcome.

A P value <0.05 was considered significant. All analyses were performed using Statistic Toolbox of Matlab R2007a (The Math-Works, Natick, MA, USA).

Results

A Pubmed search yielded 55 articles for key breast clip placement or location, 299 articles for wire location, 34 articles for CL, 36 articles for ROLL, 23 articles for seed location, and 35 articles for titanium, radiopaque, collagen clip location. Three-hundred and ninety-one articles were regarded as irrelevant and excluded because they did not correspond to the topic of interest. Ninety-one articles were read and evaluated on the basis of the inclusion and exclusion criteria defined in the "Methods" section. A total of 47 articles were included in this systematic review: 7 for the wire location technique, 5 for the ROLL technique, 13 comparing wire location with radioguided location, 3 for the CL technique, 2 comparing wire location with CL, and 17 for the clip location technique. No overtly duplicated article was found (Fig. 1).

In Fig. 2, in which several location techniques are compared, the sizes of the circles represent the number of lesions studied by each technique. The most frequently used location technique was WL (43 % of studies); ROLL was used in 17 % of articles, CL in 14 %, and clip location in 25 %.

Table 3 shows reported diagnostic success and clear margins, both as percentages, for wire location, radioguided location, and CL. The range of successful location for the WL technique was 65–100 % (53.9 ± 46.6 %) and the range for clear margins was 58–84 % (50.9 ± 29.2 %). The range of successful location for ROLL was 93–100 % (54.9 ± 50.5 %) and the range for clear margins was 60–100 % (78.4 ± 22.4 %). The range of successful location for CL was 79–99 % (90.8 ± 7.4 %) and the range for clear margins was 75–81 % (78.0 ± 4.3 %). Table 4 shows diagnostic success and clip migration less than 1 cm, both as percentages, for the clip location technique. The range of successful location was 80–100 % (95.4 ± 7.6 %) and the range for clip shift <1 cm was 56–100 % (66.7 ± 39.8 %).

High odds ratios indicate reduced risk of unsuccessful location using each method. High variability of the odds ratios and 95 % confidence intervals for the different studies reported reveal heterogeneity of successful location.

Discussion

Successful management of non-palpable lesions depends on accurate location, which is essential for achieving complete surgical excision with optimum cosmesis and

Table 3 Successful location and clear margins for the different location modalities, with odds ratios and CI for successful location

Ref.	Location technique	Number of lesions	Successful location (%)	Clear margin (%)	Odds ratio	95 % CI
Chadwick et al. [62]	WL	212	97.7	58.0	1713	488.8–6009.3
Allen et al. [63]	WL	182	79.0		14.4	8.7–23.8
Chen et al. [67]	WL	35	97.0		116	69.4–19245.8
Chu et al. [2]	WL	76	99.0	68.0	5625	345.4–91606.1
Ernst et al. [1]	WL	479	98.0		2199.6	907.1–5334.1
Landheer et al. [57]	WL	36	81.0	83.7	17.2	5.3–55.1
Ng et al. [58]	WL	59		42.1		0.1–51.2
Liberman et al. [4]	WL	103	65.0	44.0	3.4	1.9–6.1
Mariscal Martinez et al. [33]	WL	68		82.4		
Rao et al. [38]	WL	18		27.2		
Rose et al. [30]	WL	72	90.0	70.8	86.2	28.7–259.7
Thind et al. [68]	WL	70		60.0		
Ronka et al. [69]	WL	14	100.0	57.0	841	15.6–45324.6
Zgajnar et al. [70]	WL	92		44.0		
Medina-Franco et al. [35]	WL	8		62.5		
Gray et al. [71]	WL	46	100.0	53.0	8649	168–445172.9
Gray et al. [64]	WL	79	82.0	76.0	21.6	9.5–48.8
Nadeem et al. [37]	WL	65	97.7	58.0	4096	250.7–66916.2
Riedl et al. [72]	WL	427	99.1		11183	2778.6–45009.2
Moreno et al. [73]	WL	51		86.4		
Rampaul et al. [74]	WL	47		93.6		
Hughes et al. [75]	WL	79		54.0		
Aydogan [36]	ROLL	25		60.0		
Chu et al. [2]	ROLL	89		84.0		
Feggi et al. [83]	ROLL	73	100.0	94.0	21609	423.1–1103696.9
Gray et al. [71]	ROLL	51	100.0	75.0	10609	206.5–544945.5
Gray et al. [64]	ROLL	83	93.0	90.0	164.7	50.9–533.2
Ronka et al. [69]	ROLL	64	100.0	69.0	16641	325.2–851529.7
Smathers et al. [77]	ROLL	36	97.2	100.0	1225	73.7–20371.1
Mariscal Martinez et al. [33]	ROLL	66	100.0	89.4	17689	345.8–904744.2
Rao et al. [38]	ROLL	14		71.4		
Esserman [79]	ROLL	72	100.0	90.0	21025	411.6–1074065.5
Nadeem [37]	ROLL	65	100.0	83.0	17161	335.4–877935.2
Thind et al. [68]	ROLL	70		84.0		
Medina-Franco et al. [35]	ROLL	50	100.0	88.9	10201	198.5–524184.6
Zgajnar et al. [70]	ROLL	51		70.0		
Rampaul et al. [74]	ROLL	46		95.8		
Moreno et al. [73]	ROLL	57		93.4		
Hughes et al. [75]	ROLL	306		73.0		
Belloni et al. [76]	ROLL	288	97.6		1611.4	557.9–4654.2
Rose et al. [30]	CL	143	99.1	81.1	20164	1248.9–325544.9
Moss et al. [65]	CL	92	79.0	75.0	14.8	7.2–30.1
Arman et al. [66]	CL	16	94.0		225	12.8–3939.7
Mazy et al. [41]	CL	153	92.0		138.1	60–317.7
Riedl et al. 72]	CL	276	89.9		78.45	45.1–136.3

WL wire location, *ROLL* radioguided breast location, *CL* carbon location

Table 4 Successful location, clear margin, and clip shift for the clip-location system with odds ratio and CI for successful location

Ref.	Clip type	Number of lesions	Successful location (%)	Clear margin (%)	Clip shift <1 cm (%)	Odds ratio	95 % CI
Rosen et al. [22]	Collagen clip	31			84.0		
Parker et al. [78]	GelMark	113			97.0		
Esserman et al. [79]	GelMark	50			96.0		
Margolin et al. [80]	Hemoclip	109	100.0		98.0	47961	943.1–2438961
Chen et al. [54]	Inrad Stainless Steel	35	97.0	60.0		1156	69.4–19245.8
Liberman et al. [81]	MammoMark	95	91.0			91.3	34.6–241.1
Rosen et al. [22]	MammoMark	43			56.0		
Kass et al. [44]	MammoMark	165			88.5		
Dash et al. [32]	MicroMark	29			93.1		
Phillips et al. [61]	MicroMark	11	100.0			529.0	9.6 to 29007
Rosen et al. [22]	MicroMark	111	100.0		72.0	49729	978 to 2528464
Margolin et al. [80]	MicroMark	119	100.0		97.0	57121	1124.1 to 2902605
Coles et al. [82]	Titanium clip	30	80.0		>90	16	4.5 to 56.7
Oh et al. [7]	UltraClip Inrad	145		89.0			
Smathers et al. [77]	Vivant Medical	17			100.0		
Lehman et al. [59]		101			91.1		
Uematsu et al. [45]	MicroMark	204			72.0		

minimum morbidity. A variety of imaging techniques and labeling materials are available for location of non-palpable lesions.

Imaging guidance is performed by use of mammography (stereotactic biopsy) or sonography and less often by use of magnetic resonance imaging (MRI). In general terms, the choice of guidance tool depends on the characteristics of the lesion and on radiologist preference.

Core biopsy guided by stereotactic mammography is the most common technique used for investigation, location, and sampling of non-palpable suspicious mammographic lesions. Mammographic location methods differ in technical requirements, duration, and precision. Stereotaxis reduces the time from mammographic detection to treatment; it results in significant cost savings compared with open biopsy, and is an accurate and less invasive method [15]. However, because, to obtain the views, limited compression is necessary, perfectly orthogonal images cannot be obtained and, consequently, perfect location is not achievable [15]. Sonography is an important adjunct to mammography and clinical examination of breast lesions. Limitations include poor results for fatty breasts, inability to depict microcalcifications, and excessive scan and review time [16]. Ultrasound guidance is simple and safe, and is preferable to other methods whenever feasible [16–18]. MRI is a relatively new technique and few reports have been published. Disadvantages such as overlap of MRI features of malignant and benign lesions, high cost, and inability to resolve smaller masses and microcalcifications have been described [19]. MRI has been used to evaluate multicentricity or multifocality of breast cancer detected by other methods, locate mammographically occult cancer in women with axillary metastases, evaluate treatment response during neoadjuvant chemotherapy, and identify breast cancer in high-risk patients [20–22]. MRI can furnish important information that cannot be obtained by conventional mammography or physical examination and may detect cancer that is mammographically, ultrasonographically, and clinically occult [9, 23, 24]. Therefore, for lesions detected with MRI that cannot be visualized with other methods, MR-guided intervention is necessary if tissue diagnosis is required. MR-guided wire location followed by excision biopsy is still the mainstay of MR-guided intervention, although an increasing number of investigators use MR-guided vacuum-assisted core-needle biopsy of the breast to yield tissue for diagnosis [25]. Walf et al. reported that wire location of the lesion with MRI was efficient and reliable for non-palpable lesions only visible on MRI by use of a non-dedicated body coil [26].

Whatever the guidance tool used, the most diffuse and standardized modality of preoperative location of non-palpable lesions is WL. There are several well-described disadvantages of WL, however, for example wire incidental migration, kinking, and fracture [10, 27, 28]. Microscopic margins may be positive, requiring additional operations: 20–50 % of excisions are reported as incomplete [10]. Furthermore, because it is advised that hookwire location is performed on the same day as surgery to prevent migration, there may be logistical problems between the radiological, surgical, and nuclear medicine departments:

the surgeon is often unable to confirm the exact site of the lesion in the breast; scheduling conflicts between the surgeon and the radiologist can occur, resulting from the need to coordinate multiple procedures on the same day with different teams; and there is an inability to use wire location for the first start time in the morning without a significant delay in the operating room.

Several location techniques alternative to WL and a variety of markers have been described by different authors [29–33]. ROLL is a useful method for detection of nonpalpable lesions by injection of a nuclear tracer (99m Tc-labeled colloidal albumin) directly around the tumor. Excision of the primary tumor is guided by a hand-held gamma probe. A sentinel lymph-node excision biopsy can be performed at the same time, if needed [34–36]. ROLL is a fast, safe, and effective method for identifying and removing subclinical breast lesions. Compared with WL, the volume of breast parenchyma removed is smaller, there is better centering of the lesion within the surgical specimen, and the cosmetic results are better because skin incision and breast dissection are determined by the surgeon, irrespective of any wire positioning [37]. Another radioguided location procedure, termed breast seed location, uses a titanium capsule containing iodine 125 [38]. Radioactive seeds may be placed up to 3 days before surgical intervention, enabling the radiology and surgical schedules to remain independent, thereby increasing operating suite efficiency and optimizing the schedule of the mammographer and the surgeon. Studies using these seeds, as an alternative to WL, revealed significant reduction in re-excisions to obtain negative margins and elimination of need for specimen mammograms [10]. However, seeds have the disadvantages of requiring a location procedure on a separate occasion from the percutaneous needle biopsy and of requiring expensive and specialized radiopharmaceuticals.

Carbon location (CL) is another procedure, first reported in 1983 [39]. This technique involves placement of an inert carbon tract, which stains the tissue black in color, does not diffuse into the surrounding tissue, and can be used by the surgeon to locate the lesion days or weeks later. Insertion of the carbon track immediately after needle biopsy adds only 5 min to the procedure. It is used in some parts of the world [40, 41] but has not been widely reported and its effectiveness has not been compared with that of the hookwire [30]. Without CL, deployment of a titanium clip is required to enable subsequent mammographic location. In these circumstances, a carbon track is less expensive than a titanium clip, a post-procedure mammogram is unnecessary, because of the carbon map success, and an additional locating procedure is avoided. CL with stereotaxis is useful for lesions in which the mammographic abnormality is revealed in one projection only, rendering hookwire location virtually impossible. There are cases in which CL suffers from technical difficulties. Needle and syringe port blockage by carbon particles is not uncommon when the carbon is injected vertically, and this limits the utility of add-on stereotactic devices [30]. If the lesion is close to the chest wall, particularly in a large breast, there is a danger that a long carbon track will be difficult for the surgeon to follow and a hookwire may be preferable. For extensive or multifocal lesions several carbon tracks are difficult to follow. In the rare event a lesion is missed, it is usually relocated with hookwire, because the hematoma in the cavity can interfere with recognition of the carbon. CL has advantages and disadvantages for the pathologist. The main advantage is that the carbon track can be used to locate the lesion in the specimen. There is scope for CL to be used before total mastectomy, especially for large breasts or when mastectomy is being performed for synchronous or very small cancers. The disadvantages are that the carbon tracks resist slicing and the carbon can distort or obscure the lesion. To avoid this, the carbon should be injected only as far as the edge of the lesion [30].

Placement of marker clips can be used to indicate the biopsy site as part of image-guided breast procedures. The objective is to mark the tumor bed, thus enabling accurate needle location at the time of definitive surgery in the event of complete mammographic and sonographic resolution of the tumor [31, 32]. Markers are usually small stainless-steel clips prone to pinching a minute amount of breast tissue (e.g. MicroMark; Ethicon Endosurgery, Cincinnati, OH, USA). However, the clip may fail to hold on to the tissue or the clip may migrate to a different, undesired, location. New markers have been developed, for example clips included in pellets of a copolymer of resorbable polylactic acid and polyglycolic acid (Gel Mark, Gel Mark Ultra and Gel Mark UltraCor; SenoRx, Aliso Viejo, CA, USA) or titanium clips that are embedded centrally on a collagen plug (Mammomark; Artemis, Hayward, CA, USA) or a radiopaque titanium metal ring surrounding a bioabsorbable collagen cylinder (Vivant Medical Biopsy Marker; Vivant Medical, Mountain View, CA, USA), or a desiccated hydrogel embedded with either a stainless steel or titanium coil (Hydromark; Biopsy Sciences, Clearwater, FL, USA). For the first, clip migration has been described in case reports [21, 42]. The collagen plug marking device might be an effective alternative to existing marker clips [43]. After deployment of the marking device, the collagen expands as it absorbs fluid and stabilizes the marker within the cavity. Theoretically, this feature tends to place the metallic marker centrally in the biopsy cavity and makes the marker resistant to migration. Also there is a potential hemostatic benefit from the collagen because it promotes haemostasis [44]. However, there are several published data on the deployment accuracy of these clips (Table 4).

Rosen et al. [22] and Uematsu et al. [45] reported clip placement >1 cm in 28 % of the cases, as determined by comparing the coordinates of the clip and those of the original target on the stereotactic images. Burbank and Forcier [46] determined their initial clip placement accuracy (89–93 %) on the basis of the mask measurement system by using mammograms obtained before and after biopsy. There are many reported causes of clip migration. The clip is deployed at the end of the stereotactic biopsy, with the breast compressed in the cranio-caudal or lateral plane. However, when compression is released, the breast expands to its original shape and size and the clip can migrate in the direction of compression, which is along the direction of the needle track (*Z* axis). Other mechanisms of migration include: clip migration in the biopsy track, clip floating in a hematoma, clip displacement by a hematoma, change in clip site because of resorption of air at the biopsy cavity, and change in clip site after surgery, chemotherapy, or radiation therapy [47, 48]. Results suggest that the position of metallic clips placed during stereotactic core needle biopsy may differ substantially from the location of the biopsy site [1]. For a marker to be useful, it must remain close to the biopsy site. Studies of the accuracy of clip deployment show that 72–98 % of clips are <1 cm from the target [13, 22].

Conclusions

In conclusion, a variety of location techniques are currently used to assist the breast surgeon in achieving complete removal of the nodules/calcification clusters and achieving clear histological margins. Each modality has its advantages and disadvantages. The published literature basically lacks comparative analysis or meta-analysis of all the different breast lesion-location techniques by means of prospective randomized studies on a homogeneous population, and the high variability of odds ratio and 95 % confidence intervals in different reported studies shows the heterogeneity of successful location. Moreover, although the absence of comparative studies does not enable recommendation of one of the techniques discussed, certainly a promising technique, considering high mean successful location and clear margin, is clip location.

Acknowledgments The authors are grateful to Alessandra Trocino, librarian at the National Cancer Institute "G. Pascale" of Naples, Italy, for bibliographic assistance.

Conflict of interest The authors declare that they have no competing interests. The authors have no conflict of interest to be disclosed.

Author contribution RF works on literature search, statistical analysis and drafting of the manuscript incollaboration with AP. OC,VG and SF participated in the drafting the manuscript. MSparticipated in the design of the study and performed the statistical analysis. MD, QPand MDA conceived of the study, and participated in its design and coordination andhelped to draft the manuscript. All authors read and approved the final manuscript.

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