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Meta-analysis

Magnetic nanoparticle technique versus radioisotope technique in detection of sentinel lymph node in early breast cancer: a systematic review and meta-analysis

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ABSTRACT

Sentinel lymph node biopsy is the standard technique to stage the axilla in early breast cancer. The gold standard is the dual technique of radioisotope and blue dye injection. The drawbacks of dual technique include handling and disposal of radioactive material. Equally reliable, user and patient friendly, magnetic tracer super paramagnetic iron oxide, was compared with the radioisotope tracer in detection of Sentinel lymph node in a clinically node negative axilla in early breast cancer in this meta-analysis, with emphasis on the utility and safety of both techniques. PubMed, Medline were searched from April 2015 to October 2019. 1395 patients' data was included from seven homogenous studies in this meta-analysis. A statistical analysis was performed using STATA 16.1 version for sentinel lymph node detection rate using standard technique, magnetic tracer technique and both techniques. Ratio of successes and failures of the outcomes was measured and analysed. A paired two sample 'Z' test was performed to compare between the standard technique and magnetic tracer techniques. The standardised mean difference of ratio of success rate between two techniques was; 1.013334 with a p value of 0.3136.The standardised mean difference of ratio of failure rate between two techniques was 1.016667, with a p value of 0.3132. Success and failure rate showed statistically no significant difference between the two techniques. This two-way analysis with paired two sample 'Z' test confirms that neither standard technique nor magnetic tracer techniques are superior or inferior to each other.

Keywords: Breast neoplasm, Sentinel lymph node, Super paramagnetic iron oxide, Sienna, SentiMAG, Radio isotope Tc99

INTRODUCTION

Sentinel lymph node biopsy (SLNB) is the standard technique to stage the axilla in early breast cancer. The gold standard for SLNB is the dual technique, consisting of technetium nano colloid and blue dye for the staging of clinically and radiological node-negative axilla in early-stage breast cancer. Introduced in the 1990's, SLNB has the advantage over axillary lymph node dissection, as it offers lower morbidity, less chance of lymphedema and shoulder related issues. Multiple randomised clinical trials have shown a detection rate of more than 97% and low false negative rate of approximately 5% (1, 2, 3, and 4) with the dual technique. The main drawbacks of the standard method of dual technique include handling and disposal of radioactive material, as well as the legislation regulating usage of radioisotope tracer, limited access of Technetium-99m along with its short half-life of 6 hours (5, 6), which limits its use to a day before or on the day of surgery. Some studies (7) showed an allergic reaction (1.6%) to the 1% blue dye (isosulfan blue). The blue dye also obscures the operating field and methylene blue can

cause DNA damage and tissue necrosis.[1,2] Due to these disadvantages, there is a need for a non-radioactive, equally reliable, user and patient friendly technique. Some groups have suggested that 'super paramagnetic iron oxide' (SPIO) nanoparticles like sienna+, magtrace (Sienna XP) and resovist could offer great services over the standard technique (SLNB). Various clinical studies have compared the radioisotope tracer to magnetic tracer in detection of sentinel lymph node (SLN) in a clinically node negative axilla in early breast cancer.[1,2,5,8-16] Results have indicated non inferiority of magnetic tracer over radioisotope method in SLN detection, retrieval, false negative rate and malignant SLN pick up rate. Some of the main merits of magnetic tracer technique includes non-radioactive, easy to handle, easy to store and a long shelf life. These advantages can make magnetic tracer technique more beneficial in diagnostic and therapeutic in breast, as well as other body system pathologies such as melanoma, prostate cancer.

Aim

In current study, a meta-analysis was carried out to assess and compare the utility and safety of magnetic technique, using SPIO and magnetic probe with standard dual technique of radioisotope tracer and blue dye in detection of SLNB in clinically node negative axilla in early breast cancer. The primary end point of the study was SLN detection rate, SLN retrieval rate, malignancy rate in detected SLNs, while the secondary end point was to compare breast conservation rates with magnetic tracer technique and with standard technique.

METHODS

Literature search and eligibility

The following databases were searched; PubMed, Medline, Clinical key and Clinical Trials.gov. Studies were included from April 2015 to October 2019.

Search strategy

Search terms that were used were; 'breast neoplasia', 'sentinel lymph node biopsy', 'super paramagnetic iron oxide'. Medical subject headings (Mesh) terms were; 'breast neoplasia', 'sentinel lymph node biopsy', 'nanoparticle' 'magnetic', 'sentimag'.

Inclusion criteria

Inclusion criteria for current study were; randomised prospective case control trials comparing standard versus magnetic tracer technique with similar sample size and female patients above the age of 18, with biopsy proven ductal carcinoma in situ, invasive breast cancer with clinical and radiology proven node negative axilla were included in this study.

Exclusion criteria

Studies that were including any of the following, were excluded from literature search; pregnant or lactating patients, proven axillary metastasis. hypersensitivity to isosulfan blue dye or reaction to blue dye, intolerance or hypersensitivity to iron or dextran compounds, iron overload disease and previous radiotherapy to breast or axilla and pacemaker or implantable devices in chest.

Based on inclusion and exclusion criteria only 7 studies have met the criteria for further statistical analysis as shown in PRISMA flow chart (figure 1). The data was pooled from these 7 studies with required variables as shown in (Table 1).

RESULTS

A total of 1395 patients data was included from 7 homogenous studies in this meta-analysis. Standardised mean age of patients was 60.43 years. The mean BMI of included patients was 25.84 old. A statistical analysis was performed for SLN detection rate using standard technique, magnetic tracer technique and dual techniques among all included studies.

Summary statistics

Standardised mean of success ratio of standard technique was 94.06, with standard deviation of 3.15 and variance of 9.95. Standardised mean of success ratio of magnetic tracer technique was 95.07, with standard deviation of 1.76 and variance of 3.11. Standardised mean of success ratio of both techniques was 93.16, with standard deviation of 3.80and variance of 14.46. Standardised mean of failure ratio of standard technique was 5.94, with standard deviation of 3.15 and variance of 9.96. Standardised mean of failure ratio of magnetic tracer technique was 4.92, with standard deviation of 3.15 and variance of 1.72. Standardised mean of failure ratio of both techniques was 6.76, with standard deviation of 3.88 and variance of 15.13.

Analytical statistics

A paired two sample 'Z' test was performed to compare between the standard technique and magnetic tracer techniques with results. The standardised mean difference of ratio of success rate between standard technique and magnetic tracer techniques was; 1.013334 with a p value of 0.3136, which is statistically not a significant difference. The standardised mean difference of ratio of failure rate between standard technique and magnetic tracer techniques was 1.016667, with a p value of 0.3132 which is statistically not a significant difference. This two-way analysis with paired two sample 'Z' test confirms that neither standard technique nor magnetic tracer techniques are superior or inferior to each other.

Table 1: Tumor characteristics with breast conserving surgery (BCS) and mastectomy rates along with statistics.

Study	Total patients	Average age of patient (years)	BMI (KG/M2)	DCIS	T1	T2	T3	T4	N0	N1	N2 - N3	Mastectomy	BCS	Total, SD for mastectomy	Total, SD for BCS	Total, mean for mastectomy	Total, mean for BCS
Taruno (Japan)	210	57	21.95	37	94	75	3	1	174	36	0	176	34	74.44	67.68	73.74	61.91
Alvarado (USA)	146	61.1	29	13	82	33	7	-	344	25	0	0	146	101.53	101.39	67.28	80.55
Karakat-sanis (Sweden)	338	64.2	26.5	30	111	47	8	-	491	56	-	108	231	158.70	161.72	127.97	140.27
Nordic (Sweden)	206	61.7	25.4	10	126	56	7	-	152	47	7	52	154	65.54	70.08	68.19	77.46
Houpeau (France)	115	-	-	-	98	10	-	-	168	46	0	5	103	65.04	60.85	63.14	77.14
Ghilli (Italy)	203	61	25	11	137	36	4	0	323	57	0	3	190	100.77	103.6	71.66	87.25
Pinero-Medroua (Spain)	181	56	27.2	-	180	0	0	0	245	76	0	50	130	87.70	88.81	74.10	81.38
Total	1395	62	25.8	101	828	257	29	1	1897	343	7	394	988	-	-	-	-

Standard deviation (SD), body mass index (BMI), ductal carcinoma in situ (DCIS), Tumour (T), Node (N)

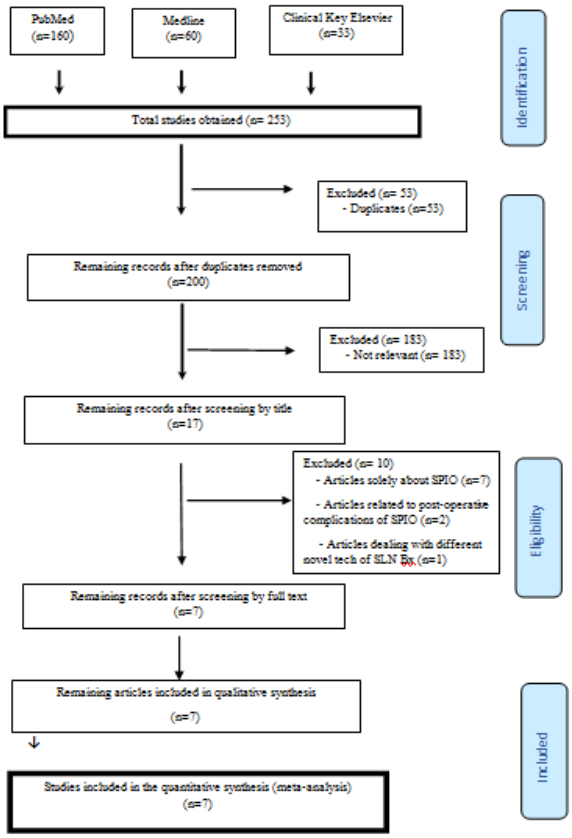

Figure 1: Prisma flow chart.

A Forest plot was also constructed to assess the difference in the outcomes, such as mastectomy rates versus breast conservative surgeries, while using magnetic tracer technique as shown in (Figure 2). The Random effects model showed that the Hodges's 'g' value as 0.08, favouring breast conservation surgery group (controls). The heterogeneity testing among included studies showed 'I2' statistic value of 30.14%, which is an acceptable or low heterogeneity.

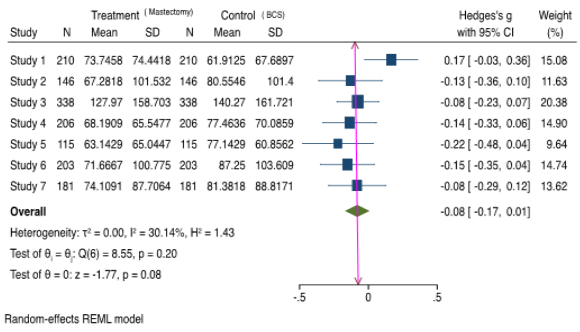

Figure 2: Forest plot showing Mastectomy rates versus breast conserving surgery (BCS). Random effects model that Hodges's g value -0.08 favouring BCS group. Heterogeneity testing among included studies showed value of 30.14% which is acceptable to low heterogeneity.

DISCUSSION

Standard technique of radioisotope and blue dye is gold standard in lymphatic mapping and sentinel lymph node detection. This dual technique consists of technetium nano colloid and blue dye for staging of clinically and radiologically node-negative axilla in early breast cancer. Introduced in the 1990s, SLNB has the advantage over axillary lymph node dissection, as it offers lower morbidity, less chance of lymphedema and shoulder related issues. Despite their well proven utility, there are disadvantages associated with the application of dual method. For example, the handling and disposal of radioactive material, the legislation regulating the usage of radioisotope tracer, limited access of Technetium-99m, along with its short half-life of 6 hours, limits its use to a day before or on the day of surgery.[5,6] Some studies showed allergic reactions (1.6%) to the 1% blue dye (isosulfan blue).[7] The blue dye also obscures the operating field and Methylene blue can cause DNA damage and tissue necrosis.[1,2] So, these disadvantages raised interest in alternate mapping agents, showing non inferiority and the same standard of clinical utility to the standard dual method in SLNB detection. In this respect, super paramagnetic iron oxide (SPIO) nanoparticles such as Sienna+, Magtrace (Sienna XP) and Resovist have shown promising results.

Firstly, in all the seven included studies following end points were compared; sentinel lymph node biopsy detection rate per patient, SLNB detection rate per node, total number of SLN with average retrieval rate per technique and malignant lymph nodes detected by both techniques, along with missed SLN by both techniques.[1,2,6,8,13-15]

The primary end points of meta-analysis were to calculate sentinel lymph node detection rate per patient was found as 96.2% for both techniques. It was 97.7% for standard technique and 97.1% for magnetic tracer technique, respectively. Sentinel lymph node detection rate per node for both techniques revealed success rate of 88.9%, for standard technique it was 92.06% and for magnetic tracer technique it was 94.27%.

In current meta-analysis, the detection rate of positive SLN per patient were also calculated and rate was found to be 15.5%. The count of 350 positive lymph nodes was detected in 334 patients, with total number of lymph nodes retrieved being 2247. The ratio of success rate of both techniques in detection of positive SLN per patient came out as 92.4%. The standard technique success rate was 92.43% and magnetic tracer technique success rate was 93.86%. The average SLN retrieved per patient was 1.76. The average SLN detected per patient by standard technique was 1.70 and the magnetic tracer technique was 1.68.

Table 2: Sentinel lymph node identification per patient in participating studies.

Studies	Pinero-Madrona N (%)	Ghilli N (%)	Houpeau N (%)	Nordic N (%)	Karakatsanis N (%)	Alvarado N (%)	Taruno N (%)	Total N (%)
Per patient SLN identified (N)	181	193	108	206	338	146	210	1382
Both techniques	177 (97.8)	187 (96.9)	102 (94.4)	196 (95.1)	343 (96.5) LN=159+184*	144 (98.6)	199 (94.76)	1359 (96.2)
Standard technique	178 (98.3)	191 (99.0)	103 (95.4)	200 (97.1)	155/159 (97.4)	144/146 (99.3)	206/210 (98.1)	1189 (97.7)
Magnetic technique	177 (97.8)	189 (97.9)	105 (97.2)	201 (97.5)	175/183 (95.6)	145/146 (99.3)	199/210 (94.8)	1200 (97.1)
Neither technique (N)	3	6	4	1	5-9/7	1	4	26

*Karakatsanis study used two arms one control and other with Magnetic tracer, distribution of patients in either arm of the study.

Table 3: Sentinel lymph node identification per node in participating studies.

Studies	Pinero-Madrona N (%)	Ghilli N (%)	Houpeau N (%)	Nordic N (%)	Karakatsanis N (%)	Alvarado N (%)	Taruno N (%)	Total
Per node SLN identified (N)	321	380	214	206	547	369	210	2247
Both techniques	260 (81.0)	344 (90.5)	188 (87.9)	180 (87.8)	502 (91.8)	326 (88.3)	199 (94.8)	1999
Standard technique	17 (86.3)	16 94.7)	5 (90.2)	15 (94.7)	(90.30)	19 (93.5)	7 (98.1)	1847
Magnetic technique	32 (91.0) 292/321	20 (95.8)	20 (97.2)	23 (98.5)	(93.5)	22 (94.3)	(94.8)	1845
Neither technique (N)	12	0	1	3	44	2	4	67

Secondly, adverse events were recorded in all participating studies relating to sentinel lymph node biopsy. All seven studies reported brown skin staining post injection of magnetic tracer, which showed variation of time in different studies to subside or disappear or decrease in size. Alvarado et al, reported breast discoloration in 24 patients (16.3%) and bruising in 10 (6.8%) patients.[1] As did Karakatsanis et al in two of his studies included in the meta-analysis, reported.[2,6] In his study 39.9% patients presented with skin discoloration. Staining was still present after 15 months in 36.1% patients. Patients with breast conserving surgery were predominantly involved with breast staining (97%). Patients receiving retro-areolar or peri areolar tracer injections were also found to be more prone to get skin discoloration, around 58 out of 73 patients. 15 out of 73 had peri tumoral injection of magnetic tracer and had less staining immediately post-surgery and shorter duration of breast staining. Only 3% of patients complained that they were affected by staining. Ghilli et al reported brown staining of breast in 71 out of 150 (around 47%) patients.[14] Out of 71 patients 51 (around 71%) had no regression of staining. Houpeau et al also reported brown pigmentation of breast in 22 out of 108 patients.[15] The longest follow up of patients concerning skin discoloration was 36 months.[2]

Thirdly, radioactivity is an issue with standard technique.[17] Miner et al demonstrated that almost all of the specimens removed after sentinel node biopsy contained considerable radioactive material after surgery.[18]

Lastly, our results showed that ratio of success rate of both techniques (standardised mean is around 93 with less standard deviation (3.80) and less variance (14.46). Similarly, again the ratio of success rate of standard technique showed a smaller standard deviation (3.15) and less variance (9.95). The summery statistics of ratio of success rate of magnetic tracer technique showed low variance (3.11) and low standard deviation (1.76). This explains that data is less deviated around mean and therefore the data is normally distributed. This also shows that data is less skewed with ratio of success rate of both techniques. So, any further analytical statistics we do with this data is reliable.

Table 4: Positive sentinel lymph nodes in studies of meta-analysis.

Studies	Pinero-Madrona N (%)	Ghilli N (%)	Houpeau N (%)	Nordic N (%)	Karakatsanis N (%)	Alvarado N (%)	Taruno N (%)
Positive SLN per patient	60 (33.2)	57 (28.9)	46 (42.6)	54 (26.2)	56 (17.08) (26+30)	25 (17.1)	36 (17.1)
Both techniques	52 (86.6)	54 (94.7)	43 (93.4)	52 (96.2)	56 (17.08)	24 (96.0)	92.8
Standard technique	1 (88.3)	2 (98.1)	0 (93.4)	1 (98.1)	30 (80.7)	24 (96.0)	92.4
Magnetic technique	3 (91.6)	1 (96.4)	2 (97.8)	0 (96.2)	26 (85.1)	24 (96.0)	93.9
Neither technique (N)	4	0	1	1	0	1	1.6

Further, we performed analytical statistics (because the distribution of the data is normal distribution). We used two sample 'Z' tests between ratio of success rate of both techniques versus ratio of success rate of standard technique and found that standardised mean difference was exceptionally low (-0.89). Similarly, when we did two sample 'Z' tests between ratio of success rate of standard technique and ratio of success rate of magnetic tracer technique again, it was found that there was no significant difference between these two techniques. Two sample 'Z' tests between ratio of failures rate of both techniques and ratio of failures rate of standard techniques did not show any significant difference (z=0.28, p=0.38). When 'Z' tests were performed between ratio of failures rate of standard technique and ratio of failures rate of magnetic tracer technique, it did not show any significant difference (z=0.48, p=0.31) and implied magnetic tracer technique is non inferior over standard technique.

Key summary

The two sample 'Z' test results showed neither superiority, nor inferiority of magnetic tracer technique over standard technique. Also, mastectomy rates remain low while using a magnetic tracer technique. This will reinforce the fact that the magnetic tracer technique is safe and effective method for SLN detection.

The last two meta-analyses on the comparison of two methods of standard dual technique versus magnetic tracer technique in detection of sentinel lymph node (SLN) in breast cancer patient was carried out in 2016.[15,19] There have been no further meta-analysis, and very few studies published post 2016, which compare these techniques specifically. In most of the studies prior to MONOS study in 2017 by Karakatsanis et al patients acted as their own control, receiving both the tracers, for non-inferiority comparison.[2] A point was raised regarding synergy bias, despite the non-inferiority of SPIO over standard technique in SLNB, shown in the previous studies carried out on the subjects. MONOS study used synchronous patient cohort, with standard dual technique as control arm.[2] Blinding was not possible for surgeons or patients, due to the nature of intervention. The results of the study showed SPIO tracer non-inferiority to standard technique and SPIO tracer could be used as alternate to radioisotope tracer+/- blue dye, in detection of SLN's in breast cancer. A similar meta-analysis conducted by Teshome et al in 2016, assumed statistically that the two techniques of SLNB were independent of each other but both techniques were used simultaneously on same patients, which nullify the assumption.[16]

Limitations

In the present meta-analysis, out of seven studies, only MONOS study used two cohorts, of patients. One as control and other as study group. Comparison between the magnetic technique and radioisotope technique, when the injection sites are similar, possibility of an interventional bias rises, as the operator cannot ignore the presence of blue dye during SLN identification. Another issue which could be raised is the presence of gamma probe and magnetic probe, making the procedure more difficult by trying to handle them simultaneously on the same patients instead of two separate cohorts. The MONOS study of 2017 by Karakatsanis et al a cohort of 338 patients, was the only study in the meta-analysis in which SPIO was studied as sole tracer of SLNB.[2] The control arm was the radioisotope tracer with or without blue dye and study arm was SPIO Sienna plus 2 ml diluted with 3 ml of xylocaine 10 mg/ml. This was the only study among the studies using sienna plus to dilute it with 1% xylocaine.

CONCLUSION

Further studies needed to be carried out on skin discoloration caused by magnetic tracer method, studies regarding dose, route of administration, timing of injection, and site of injection. The role of breast MRI in relation to magnetic tracer and ductal carcinomain situ (DCIS) and impalpable breast lesions to replace wire

localisation is encouraging and further research in this field is required. Furthermore, there is a need to compare other mapping agents for sentinel lymph node biopsy in breast cancer, like indo cyanine green (ICG), contrast enhanced ultrasound (CEUS), along with different types of SPIO tracers should be investigated and further research on the subject is warranted. 'New light cordless magnetic probe' experimented by Taruno et al, should also be studied for further evaluation. As there is scope for improvement in the current sentimag probe considering that the magnetic tracer technique is gaining popularity, due to ease of availability, being user friendly and short learning curve.

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