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The introduction of Magtrace® lymphatic tracer for axillary sentinel node biopsy for breast cancer in a rural Scottish district general hospital: initial experience, perspectives, outcomes and learning curves

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Abstract

Background

Magtrace® is a supraparamagnetic iron lymphatic tracer that has had increasing use in sentinel node biopsy (SNB) for breast cancer and has theoretical logistical benefits in centres where nanocolloid use may be associated with such issues. We describe our initial experience with the introduction of Magtrace® into our routine practice by dual localisation with nanocolloid, comparing performance and concordance.

Methods

This was prospective study of the first patients undergoing axillary SNB using Magtrace® in a single centre. These patients had dual localisation with nanocolloid and Magtrace®. Subjective global assessments of Magtrace® and nanocolloid performance as well as objective signal strength and anatomical concordance were compared across multiple timepoints in the operative journey.

Results

A total of 30 consecutive patients underwent SNB within the timeframe of this study. While there were no failed SNB, 8 issues were reported including 4 issues of perceived imperfect localisation on global assessment. No patient had a failed or abandoned SNB, and only one case had a potential challenge in subsequent management after histopathological examination of the retrieved nodes. The majority of these issues occurred in the first half of the study period. There was overall weak to moderate positive correlation between Magtrace® and nanocolloid signals of the retrieved sentinel nodes (ρ= 0.392,p=0.043).

Conclusions

This study suggests that introducing Magtrace was feasible and safe in the context of a rural breast cancer service. A possible strategy to ameliorate the learning curve associated with these procedures is the routine dual localisation in the initial phases of performing Magtrace localisation.

Microabstract

Magtrace® is a supraparamagnetic iron lymphatic tracer that has had increasing use in sentinel node biopsy (SNB) for breast cancer. We describe our initial experience with the introduction of Magtrace® into our routine practice by dual localisation with nanocolloid, comparing performance and concordance. We report this as a safe way of introducing its use and ameliorating the learning curve associated with this new technique.

Keywords

Breast cancer; sentinel node biopsy; lymphatic tracer

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Introduction

Sentinel node biopsy (SNB) localisation techniques in breast cancer surgery have evolved over time. Initial reports of SNB using blue dye had a sentinel node identification rate of 66%, with surgeon expertise but this improved to up to 97% in latter reports from the same centre (1). The need for blind dissection with blue dye led to the development of technetium-99m labelled nanocolloid tracer and a handheld gamma probe; these when used together with blue dye was consistent with sentinel lymph node identification rates of more than 90% in large studies, leading to routine adoption of this technique and recommendation as best practice (2-3).

These localisation techniques however continue to have limitations. Apart from the need for blind dissection when used alone, blue dye has been associated with a low but possible risk of anaphylaxis and tissue necrosis and skin staining (3-4). Nanocolloid use avoids blind dissection but may have resource and logistical implications due to the need of a nuclear medicine service in its administration.

There is accumulating evidence that Magtrace®, a superparamagnetic iron oxide nanoparticle base lymphatic tracer, provides an alternative tracer material with comparable accuracy rates as the aforementioned traditional agents (5-6).

The use of Magtrace may be of most benefit to centres and settings with limited or difficult access to a nuclear medicine service; national guidelines in the UK (NICE) indeed now recommend Magtrace® use in SNB localisation in such hospitals (7).

Methods

Local service and geographical context

Dumfries and Galloway Royal Infirmary (DGRI) is situated in a relatively rural setting in south-west Scotland about 100-120km southwards of Edinburgh and Glasgow. The health service has unique service dimensions; while it serves a relatively low population of 150000, it covers a relatively wide geographical area (~6500 km^2) (8). DGRI provides a comprehensive secondary care service for patients with breast disease with around 120 new breast cancer cases per year and 80-90 breast cancer operations each year. There are therefore well-established shared services with neighbouring regional health authorities (healthboards) to be able to deliver a comprehensive breast surgery service. Relevant to this study, nuclear medicine services are shared with and outsourced to a neighbouring health authority with visiting nuclear medicine radiographers travelling from their base hospital about 100 km away to administer nanocolloid tracer.

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While this was a well-established partnership, there are significant human resource, logistical and service provision challenges with potential concomitant financial and ecological and patient risks with the use of nanocolloid localisation (NL) for SNB.

For the local clinical service this led to relatively inflexible scheduling of operative sessions in which sentinel node biopsies could be performed (limited to one day per week, and in the afternoons). There was unique vulnerability to adverse weather, traffic and staff shortage events, all of which have potential risks for delaying patient surgery. The need for a visiting radiographer team additionally attracted a financial, human resource and ecological impact.

Study design

Due to these challenges, a clinical decision was made by the multidisciplinary breast surgery service to introduce the use of Magtrace® localisation (ML) in SNB in breast cancer surgery coiniciding with the few months leading up to the natural end of the service contract for the administration of nanocolloid by the nuclear medicine service of the neighbouring healthboard.

Before the introduction of ML, our centre routinely used single agent localisation for SNB with nanocolloid and dual agent localisation with nanocolloid and blue dye in SNB or sentinel node sampling (SNS) in neoadjuvant breast surgery resections.

It was decided that there would be a run-in period during the introduction of Magtrace® where all cases requiring SNB or SNS would undergo routine dual localisation (DL), followed eventually by single localisations (ML) or when dual localisation are indicated, with Magtrace® and blue-dye.

The experience and outcomes of these sentinel node biopsies were prospectively audited during this introduction period for a total of 6 months. Inclusion criteria was any patient undergoing SNB or SNS for breast cancer. Patients in whom Magtrace® had not been used were excluded.

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Surgical procedures

Patients underwent either mastectomy or wide local excision (WLE), alongside SNB. If used, nanocolloid was administered as per standard practice. In all cases, Magtrace® was administered at induction of anaesthetic at the lateral edge of the ipsilateral areola into the subdermal plane. The injection site was then massaged in a circular motion for 5 minutes by the operating surgeon. In mastectomies, SNB or SNS is routinely carried out via the mastectomy wound. In WLE, SNB and SNS are carried out through a separate axillary wound or the WLE wound itself depending on the site and proximity of the WLE wound in relation to the axilla. A cut-off of a minimum of 10% of the sentinel node with the maximum signal strength was used to determine if any additional nodes should be retrieved.

The operations were performed by 2 consultant/attending surgeons and one trainee/resident surgeon. As mentioned, prior to the introduction of ML, it was routine practice for both consultant surgeons to perform single agent NL in SNBs in non-neoadjuvant cases and routine dual localisation with nanocolloid and blue-dye. The trainee surgeon had prior experience of performing of SNBs with nanocolloid either in the context of single localisation or dual localisation with blue dye in the 6 months before the start of this study.

Data collection and assessments

Data was prospectively collected using a standardised proforma. Collected data included routinely recorded patient and procedure characteristics.

Both surgeon-assessed and objective assessments of the use of ML either alone or in dual localisations with NL were made at a variety of time-points in the patients' surgical journey (Table 1).

Objective assessments were made at three time-points; pre-incisionally from the magnitude of the axillary signal and the magnitude of the signals of the delivered lymph node and the confirmation of lymph node tissue at histopathology examination. Subjective operating surgeon assessments were performed at two time points during the patients' surgical journey, anatomic concordance of the signal and the presence of a focal signal pre-incisionally and assessment of quality of localisation and anatomic concordance during the axillary dissection. In dual localisation cases, where both signals are present comparisons are made between the two agents at all four time-points.

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The correlation between Magtrace® and nanocolloid signal values in DL cases delivered lymph nodes was analysed.

Anatomic concordance was rated by the operative surgeon as absolute (maximum signal from both probes in the exact same spot), close (maximum signal from both probes in the same general area), or none (maximal signal in different areas).

Additionally, any specific additional issues including global assessments related to the use of these techniques were prospectively recorded.

Statistical analysis

The strength and direction of correlation between signal magnitude of ML and NL delivered lymph nodes in DL cases was assessed by the Spearman rank correlation coefficient. Differences between groups were analysed for significance using χ^2 or Fishers exact tests. $p < 0.05$ was considered significant.

All statistical analyses were performed using SPSS Version 29 (IBM, Armonk, Ny, USA).

Ethics

Full ethical review was not required as this study was observational in nature with no experimental interventions and used routinely collected patient and procedural data. The project was registered the Research and Development Office, NHS Dumfries and Galloway.

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Results

A total of 30 patients were included in this study of a total of 33 patients who underwent SNB or SNS within the whole study period. Of these, 3 cases were excluded as Magtrace® was not used. Magtrace® was used as a single method of localisation in 8 cases (Figure 1).

The patient and procedural characteristics are described in Table 2. All patients had a breast procedure performed concurrently. In terms of the breast procedure, a total of 24 underwent WLE and 6 underwent mastectomies. In the WLE group, 16 patients had palpable tumours while 8 had Magseed® localisation of their breast tumour. A total of 9 patients had undergone neo-adjuvant chemotherapy.

The operating surgeon performing the SNB was a consultant or trainee in 16 and 10 cases, respectively. In 4 cases both trainee and surgeon performed the SNB jointly.

A total of 60 nodes were harvested with 39 nodes harvested from dual localisation. A mean of 2 nodes were harvested per patient.

Assessment of quality of localisation

There was a total of 8 cases with reported issues across the whole cohort and the whole assessment spectrum (Table 1).

There was one case in which there was no detectable nanocolloid signal throughout the whole case despite administration. There was a sufficient tracer signal in this case. On the contrary, there were no cases with an absent Magtrace ® signal throughout the whole study. There were no failed SNBs in this cohort.

At the pre-incision stage, there were no issues identified in the 8 ML cases and there were no cases where there was a disparity between pre-incision anatomical location of the strongest signal and the final harvested site. In DL cases, there was one case where there was no pre-incisional signal; in this case there was subsequently a relevant signal on axillary dissection. There was absolute or close concordance between both tracers at the pre-incisional stage in the other 21 cases.

In terms of global assessments of the quality of localisation, there 4 cases with perceived issues. There was only one ML case where the tracer signal 1 case where there were generally high tracer signals with no palpable nodal tissue. In DL cases, there were 3 cases where there were perceived issues, comprising two cases where localisation was perceived by the operating surgeon to be globally imperfect and 1 case where there were generally weak Magtrace® signals.

In terms of assessment of anatomical concordance between ML and NL in the dual localisations, only 1 case had poor concordance between NL and ML. In this particular case there was absolute concordance on the 1st node but there was a discordance in the dissection and retrieval of the 2nd node.

In terms of retrieved lymph node signal assessment, only one DL case had discordant Magtrace and nanocolloid signals. This particular node had high Magtrace signals but a low but present nanocolloid signal. There were no perceived localisation issues in this particular case.

At histopathology assessment of retrieved SNB/SNS samples, only one case involving an SNS of 4 nodes where two samples (the 3rd and 4th consecutive node) were found to be non-nodal tissue.

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Signal concordance between ML and NL in dual localisations

A total of 27 nodes had paired data for both Magtrace and nanocolloid signal dual-localisation cases appear to be positively correlated (weak to moderate) with a Spearman rank correlation coefficient ρ=0.392 (p=0.043).

Relationships of localisation issues with potentially challenging procedural factors

Table 3 shows the relationship between possible patient and procedural factors which may pose challenges to the SNB procedure and the reported issues in cases during our study period. There were no significant differences in the proportions of these possible explanatory variables between cases with and without reported issues.

The distribution of the issues were then visualised within a Venn diagram to explore in detail whether the cases with issues were possibly clustered around cases with multiple possible factors which may be associated with difficulty (Figure 4). The cases visually appear to be clustered around trainee delivered operations, neoadjuvant cases, and those with concomitant Magseed® localisation of the breast tumour. One issue H occurred in a case without any of these variables and one case F occurred in a case where the same incision was used for both the wide local excision and SNB. 4/8 issues occurred in cases with more than one patient/procedural variable possibly associated with challenges to a successful SNB.

Learning curve analysis of the introduction of ML

Comparing cases between the start of the study up to the midpoint, and cases between and inclusive of the midpoint to the end of the study, 7/16 versus 1/14 cases had reported issues (p= 0.039). The majority of cases where issues were reported occurred in the first half of the study period, with only 1 case with reported issues in the second half of the study period. Figure 3 shows plots these issues against the timeline of the study period.

Service provision benefits

The introduction of ML SNB has allowed us to avoid reliance on the main logistical factor of relying on external visiting staff from a neighbouring healthboard's nuclear medicine department. This has allowed us to schedule sentinel node biopsies across two operating days per week as opposed to just one of our two scheduled operating days per week.

Prior to the introduction of ML, patients often had to come in early on the day of their operation to have their nanocolloid tracer administered and this necessitated our operating to be scheduled in the afternoon to allow for travel time for both the nuclear medicines technician with travel distances of about 100 km and the patient also potentially having long journeys to get to our unit. Intraoperative tracer administration has also allowed us flexibility in scheduling the time of operation on our scheduled operating day.

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Discussion

This study's findings support the feasibility and safety of introducing ML as a novel axillary SNB localisation technique in breast cancer in a relatively rural health setting. The study's strengths lie in the prospective detailed documentation of surgeons' perspectives of quality of localisations, associated issues and difficulties and detailed signal data of the first consecutive cases of ML, in addition to routinely collected outcome data, and patient and procedural characteristics.

The study also uniquely allowed assessment and correlation of ML and NL in a subset of these cases allowing within-case subjective and objective comparisons to be assessed. The majority of current available evidence assessed differences in these localisation methods between cohorts of patients undergoing single localisation with either technique. Our results show that concordance is moderate to strong between the Magtrace® and nanocolloid signals of the retrieved sentinel nodes.

We found only a weak to moderate albeit positive correlation between the Magtrace® and nanocolloid signals of the retrieved nodes. While the positive direction of the correlation is expected and confirms the concordance between both tracers, the significance and interpretation of the magnitude of the correlation is less clear and may require further study.

Evidence regarding the feasibility, and safety of Magtrace localisation is building. The SentiMAG multicentre trial, demonstrated that Magtrace® was a feasible technique for SNB localisation and non-inferior to traditional methods (5). Magtrace® has already been shown to be non-inferior to nanocolloid with similar rates of node identification and good concordance (9-10).

Our data shows that Magtrace localisation is safe. There were no failed SNBs in the whole cohort. None of the 8 cases with identified issues led to a failed or abandoned SNB. In one case the SNB led to a challenge in subsequent management, where in a planned axillary node sample the 3rd and 4th tissue biopsies with above-threshold tracer signal retrieved were found on histopathology to be non-nodal tissue. In this particular case, there were multiple patient and procedural characteristics which were potentially associated with difficult surgery including neoadjuvant therapy, previous axillary surgery, and concomitant Magseed® localisation of the breast tumour.

Our centre's experience provides a case example of the logistical benefits of ML use, with a reduction in the risk of patient surgical procedure delay or cancellation because of non-clinical factors such as weather, staff shortage and motor traffic. This has also allowed us increased flexibility in terms of operation session scheduling mainly from removing the

reliance on nuclear medicines staff from an external centre but also the intraoperative administration of the tracer. There is a significant paucity of evidence on the benefits of ML in this context especially in a rural setting. Shams et al reports a shortened peri-operative care pathway with ML versus NL (11).

The influence of timing of tracer administration (pre-operative as opposed to intraoperative administration) on localisation quality is a similarly understudied area in ML. We performed intraoperative administration of Magtrace® in our whole cohort and continue to do so in our practice as this provides a significant logistical benefit and a proportion of our patients with long travel times may not find it acceptable to make an additional journey pre-operatively to have tracers administered a few days pre-operatively if intraoperative administration was sufficiently effective.

The UK Sentimag trial and SentiMAG Multicentre Trial both administered the tracer on induction of anaesthesia, similar to our cohort (5-6). Hersi et al reported that while a pre-operative administration was associated with a statistically significantly higher SLN detection rate versus intraoperative administration, this difference was not statistically significant when using a lower threshold for Magtrace® signal and taken as a whole, the difference in these rates were marginal and both administration timepoints were associated with very high detection rates in excess of 97% (12). These findings need to be validated in future studies.

Further the design of this study with detailed granular real-time surgeon's perspectives on quality of localisations may have led to an over-reporting of 'issues' compared to larger scale multi-centre studies. Specifically, 4 of the 8 issues reported were 'global' subjective assessments of the procedure by the surgeon.

This prospective collection of detailed surgeon perspective data and intraoperative issues and nodal yield data also allowed us to assess with granular detail the learning curves associated with Magtrace localisation in the introduction phase.

The mapping of issues across the timeline of introduction of Magtrace localisation is consistent with a learning curve effect with the majority of issues occurring within the first half of the introduction period. A clustering of these reported issues in trainee led localisation may also reflect a learning curve effect. Importantly, 7/8 of these issues occurred in the first half of the introduction phase with only 1 issue reported in the 2nd half of the phase. The global subjective assessments by the operating surgeon may also reflect a surrogate measure of the learning curve in terms of surgeon assessment of their own competence with the technique. Considering these global subjective assessments in isolation, the first half of the study period was associated with 4 issues indicating a subpar global assessment versus an absence of similar issues in the 2nd half of the study period. The literature suggests that

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surgeons become comfortable with magnetic based SNLB localisation after between 3 and 5 cases and our practice and findings are on the whole consistent with this (6).

The specific learning curves of experts (consultant/attending surgeons) versus novices (trainee/resident surgeons) may differ as well; while the SNB expert's learning curve with ML introduction may be confined to just the differences associated with the tracer itself, the novice may have a steeper learning curve associated with and larger cognitive load comprising not only the aforementioned tracer differences but also reaching full competence in the SNB technique itself as well.

From a subjective point of view, we found that the routine dual localisation with Magtrace® and nanocolloid which we routinely used was very useful in providing immediate feedback intraoperatively and providing reassurance of our SNB technique using Magtrace.

Neoadjuvant therapy is a known factor which may make node axillary localisation relatively less accurate and associated with a higher false negative rate compared to upfront surgery due to lymphatic channel alterations in the context of post-neoadjuvant fibrosis (13-14). In our cohort there were 9 (30%) neoadjuvant cases and while there was no statistically significant difference between the proportion of neoadjuvant cases within the procedures with reported issues versus those with no reported issues, there was a trend suggesting that neoadjuvant cases were associated with cases with reported issues (50% versus 22.7%, p= 0.195). The modest size of neoadjuvant patients limits further interpretation of these results with regards to the comparative learning curves between neoadjuvant and non-neoadjuvant cases.

Existing data in the literature for the use of ML in neoadjuvant patients are relatively more limited as this is a common exclusion criterion in clinical trials. Kurylcio et al report in a series of 74 neoadjuvant patients that ML was safe and feasible (15). Pelc et al similarly showed in a propensity score matched analysis that ML compared with NL was associated with a higher chance of obtaining at least a 3-node sample in the neoadjuvant setting (16). None of these studies however reported detailed learning curve data.

In our centre, after the study period, interrogation of our continuing audit of our clinical practice revealed no adverse events associated with sentinel node biopsy/sampling procedures in the 21 neoadjuvant patients in the 12 months after the end of our study period associated with the subsequent withdrawal of NL in this context.

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This study has some limitations. This is a single-centre case series of patients with a modest sample size but the prospective nature of the study, detailed granular data curation across multiple timepoints in the surgical journey and the use of routine dual localisation allowed us to assess in detail the introduction of Magtrace® in our centre. The use of subjective measures such as global assessments of quality of localisations may be confounded by learning curves and surgeon experience and personality but provides an important perspective in this study and maybe in itself a useful surrogate for the perceived learning curve and self-competence associated with this procedure.

Our study suggests that the introduction of Magtrace® localisation in SNB is feasible and safe in the introductory phase in a relatively rural healthcare setting, and an effective strategy may be performing routine dual localisation with a tracer that the centres surgeons are confident with when introducing ML. Within our local context, the use of a magnetic lymphatic tracer has had significant logistical benefits in terms of service provisions.

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Clinical Practice Points

- Magtrace®, a superparamagnetic iron oxide nanoparticle base lymphatic tracer, provides an alternative tracer material in sentinel node biopsies with comparable accuracy rates as the aforementioned traditional agents that is increasingly used in practice and may yield logistical benefits to select institutions.
- Real-world granular data on the associated learning curves on its initial introduction continue to be sparse.
- This paper provides reports the experiences and learning curves associated with its introduction within a relatively low resource setting.

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Author contributions

The study was conceptualised by CK, DM and MB. JW and CK wrote the first draft of the paper. CK, JW and NH curated the data. Data analysis was carried out by JW and CK. All the authors have reviewed the paper and given permission for the final draft to be published. JW and CK have full access to all the data and take responsibility for the integrity of the data and accuracy of data analysis. DM and MB provided supervision of the project. All authors edited the manuscript and approved of its contents.

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Declaration of competing interest

There was no specific funding for this study. DM has previously consulted for Endomag and National Institute of Clinical Excellence (NICE), UK. The other authors have no conflicts of interests to declare.

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Table 1. Assessments across the operative journey

Type of localisation	Type of assessment	Time-points			
		Pre-incision	Axillary dissection	Lymph node delivery	Pathology asssessment
Single localisation (ML)	Objective	Presence of signal through skin		Magnitude of lymph node signal	Confirmation of lymph node yield/tissue
	Subjective	Presence of a focal signal Disparity between skin and lymph node position	Quality of localisation Disparity between skin and lymph node position		
Dual localisation (DL)	Objective	Presence of signal through skin		Magnitude of lymph node signal	Confirmation of lymph node yield/tissue
	Subjective	Presence of a focal signal Concordance between NL and ML Disparity between skin and lymph node position	Quality of localisation Concordance between NL and ML Disparity between skin and lymph node position	Concordance between NL and ML	Concordance between NL and ML

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Table 2. Patient and disease characteristics.

Patient characteristics	**N (%) or median (range)**
Age	64 (36-88)
Neo-adjuvant systemic anti-cancer therapy	9 (30)
Procedure	
Wide local excision	24 (80)
Mastectomy	6 (20)

Localisation Method in WLE	
Magseed	8 (33.3)
Palpation	16 (66.7)
Operating surgeon	
Consultant only	16 (53.3)
Trainee only	10 (33.3)
Both	4 (13.3)
Previous axillary procedure/surgery on the ipsilateral side as SNB	1 (3.3)

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Table 3. Comparison of patient and procedural characteristics between cases with issues and without issues

Patient/Procedure characteristics	**Cases without issues N= 22**	**Cases with reported issues N= 8**	**p-value**
Wide local excision	17 (77.3)	7 (87.5)	1.0
Magseed localisation	5 (29.4)	3 (42.9)	0.647
Neo-adjuvant systemic anti-cancer therapy	5 (22.7)	4 (50)	0.195
Trainee led axillary dissection	5 (22.7)	4 (50)	0.195
Previous axillary surgery	0	1 (12.5)	0.267
SNB through wide local excision wound	7 (41.2)	2 (28.6)	0.669

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Figure 1. Patient inclusion flowchart

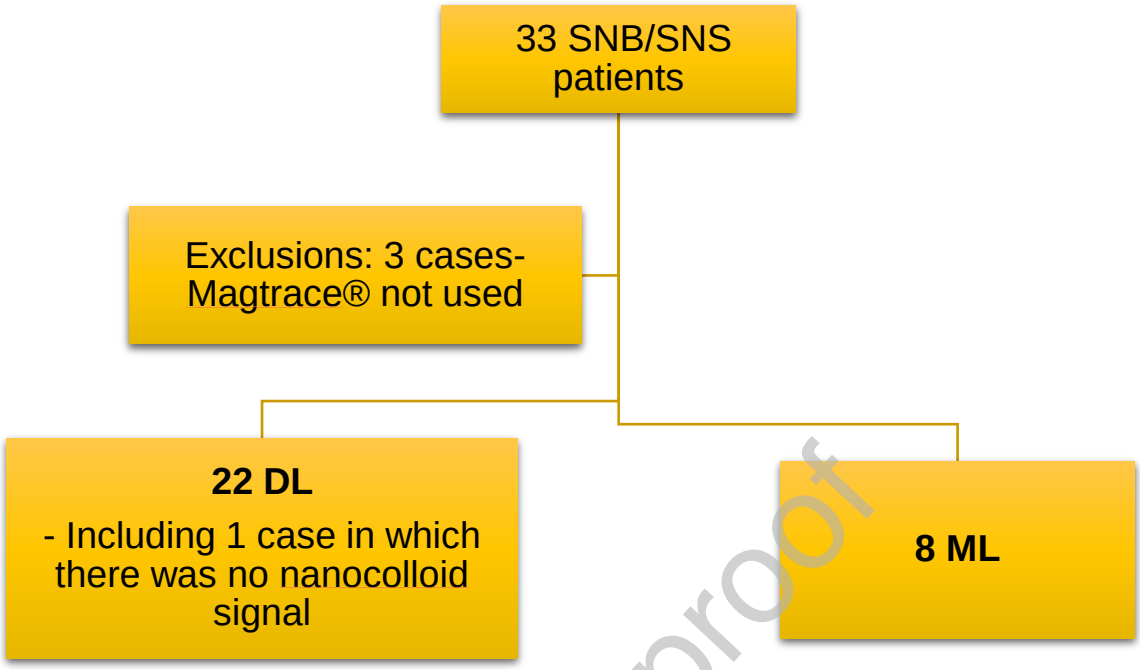

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Figure 2. Timeline of Issues and Problems. (□- Consultant led operation, ☐- Trainee led operation, ●- Joint consultant and trainee operation)

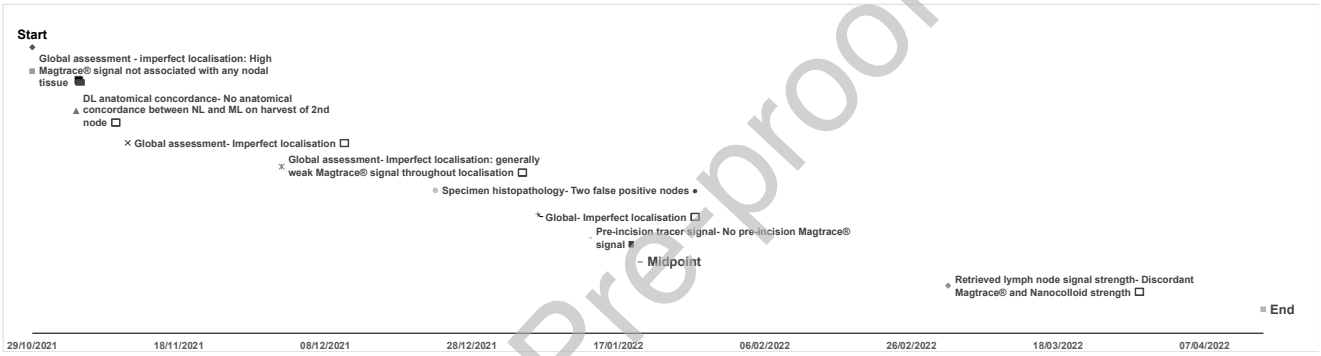

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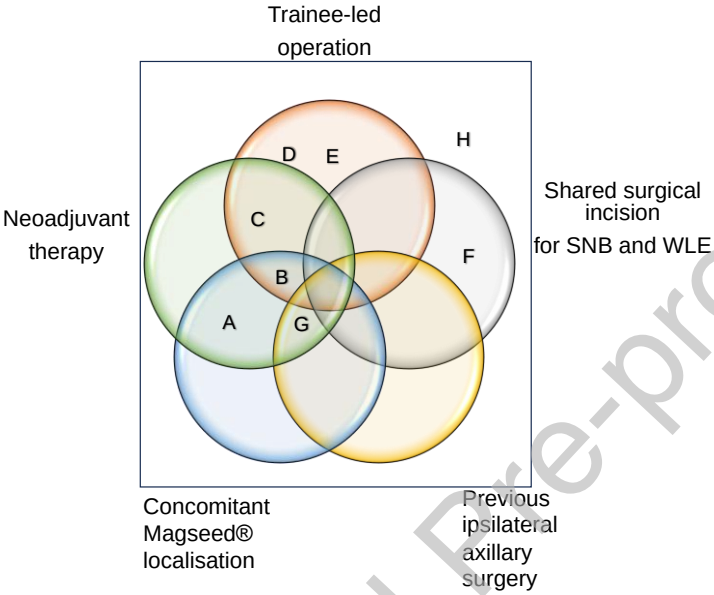
Figure 3. Venn diagram of cases and potentially challenging patient/operative characteristics.



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