The impact of neoadjuvant systemic therapy on the surgical management of soft tissue sarcoma

Burg, S.J.C. van der

Chapter 8

Magnetic seed localization is feasible for non-palpable melanoma, Merkel cell carcinoma, and soft tissue sarcoma lesions

Stijn J.C. van der Burg, A. Kuijpers, T. Baetens, Alexander C.J. van Akkooi, Sophie J.M. Reijers, Michel W.J.M. Wouters, Yvonne M. Schrage, Winan J. van Houdt

European Journal of Surgical Oncology. 2024 Oct;50(10):108485

Abstract

Background
Localization of non-palpable melanoma, Merkel cell carcinoma (MCC) and soft tissue sarcoma (STS) lesions can be difficult due to size, location, and obesity of patients or fibrosis due to previous treatments. Magnetic seed localization (MSL) is a common method to localize non-palpable breast lesions, but the feasibility of MSL for non-palpable melanoma, MCC and STS lesions has not yet been described.

Methods
In this retrospective single center cohort study, all consecutive patients between January 2021 and October 2023 who had a resection of a non-palpable melanoma, MCC or STS lesion guided by Sirius Pintuition, a MSL technique, were included. The primary endpoint was successful lesion localization during surgery and the secondary endpoints were seed migration, negative resection margins, and complications.

Results
Seventy-nine seeds were placed for 76 lesions, which were resected during 68 surgeries in 61 patients. All lesions (100%) were localized and resected. Median time of surgery was 44 minutes. No seed migration was observed. A negative resection margin was achieved for 60 (78.9%) lesions. Clavien Dindo grade ≥ 2 complications occurred in 7.4%.

Conclusion
Magnetic seed localization with Sirius Pintuition is feasible for both non-palpable melanoma, MCC, and STS lesions.

Introduction

Melanoma is a type of skin cancer which frequently metastasizes loco-regionally, either cutaneous or subcutaneous, as in-transit metastases, or to the draining lymph nodes (1). Soft tissue sarcoma (STS) is rare type of cancer that originates from mesenchymal tissue anywhere in the body and can recur locally or metastasize to several anatomical locations (2). Merkel cell carcinoma (MCC) is a very rare skin cancer which behaves similarly to melanoma (3). For these three entities, a surgical resection of recurrences/metastases can sometimes be challenging if the lesion is non-palpable due to small size, a difficult anatomic location, reduced palpability due to prior treatment, or in obese patients. To improve the localization of non-palpable lesions, various techniques have been developed.

The majority of localization techniques are developed and used for non-palpable breast cancer lesions. Wire-guided localization (WGL) is the first commonly used localization technique first described in 1965 (4). Since 1999, radioactive seed localization (RSL) using iodine-125 (125I) seeds is used as an alternative, especially in the Netherlands (5). Both WGL and RSL are still widely used because there is no proven inferiority of either of these methods (4). Radio-guided occult lesion localization (ROLL) is another alternative, where technetium-99m (Tc-99m) labelled albumin particles are injected into the lesions (6). Two less frequently used techniques are ultrasound-guided radar reflector localization and radiofrequency identification tags (4).

In 2012, a non-radioactive wireless alternative called magnetic seed localization (MSL) was introduced in Europe (7). With MSL, a magnetic seed is deployed in the lesion guided by ultrasound, X-ray or computed tomography (CT) and a probe is used to locate the seed during surgery (4). Currently there are two magnetic seeds available in Europe, the Magseed (paramagnetic seed) and Sirius Pintuition for surgical marker navigation (SMN) (8, 9). For breast (cancer) lesions, the feasibility of MSL has been proven in multiple studies demonstrating 100% successful seed localization and lesion detection (4, 10). No studies reported MSL for resections of STS and only two studies reported MSL for lymph node localization in melanoma patients (11, 12).

Although there is a lack of evidence for the applicability of MSL for non-palpable melanoma, MCC, and STS lesions, we have used this localization method for these entities in our tertiary referral center. This study aims to evaluate the feasibility of MSL with Sirius Pintuition for non-palpable melanoma, MCC and STS lesions, with the primary endpoint being successful lesion localization during surgery and the secondary endpoints being seed migration, negative resection margins, and complication rate.

Methods

Patient population
For this study, all consecutive patients who underwent a MSL assisted resection with Sirius Pintuition for a suspected or proven melanoma, MCC or STS between January 2021 and October 2023 were included. There were no exclusion criteria. Melanoma, MCC or STS was considered proven after pathological confirmation by cytology or histology; and suspected based on imaging characteristics. Throughout this paper, no distinction is made between proven and suspected cases. All patients were discussed in multidisciplinary tumor boards to determine whether resection was the preferred treatment and whether MSL was necessary. The decision to use MSL was made based on a lesion being non-palpable during physical examination and the location of the lesion.

Magnetic seed localization
The magnetic seeds used in our center are from Sirius Medical Systems® (Sirius Pintuition Marker, 5x1.6 mm) and the technique is called Surgical Marker Navigation (Figure 1). 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) was used to localize suspected melanoma or MCC lesions (Figure 2), while imaging for STS localization varied between PET/CT, CT and magnetic resonance imaging (MRI). Seeds were positioned through 12 cm length 14G pre-loaded Pintuition needle (Figure 2) under ultrasound (US) or CT guidance, either centrally in a lesion or on either side of a lesion to mark an area. During surgery, seeds were localized using the Pintuition system, a probe-based detection system that provides audio and visual feedback of distance and direction towards the implanted seed (Figure 3). After resection of the marked lesion, the specimen was checked with the Pintuition probe for confirmation of extraction of the magnetic seed, before sending the tissue to pathology.

Figure 1. The Sirius Pintuition Marker (5x1.6 mm) by Sirius Medical Systems®

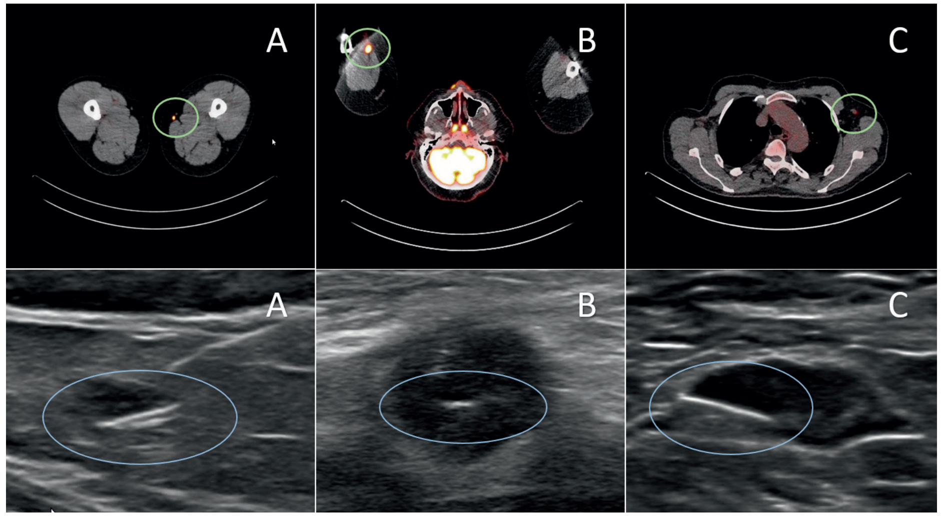

Figure 2. Upper row: 18 F-fluorodeoxyglucose (FDG)-avid lesions on a positron emission tomography/computed tomography (PET/CT). Lower row: Sirius Pintuition markers located in the lesion displayed on ultrasound. A: sub cutaneous melanoma. B: epitheloid sarcoma. C: Lymph node metastasis melanoma

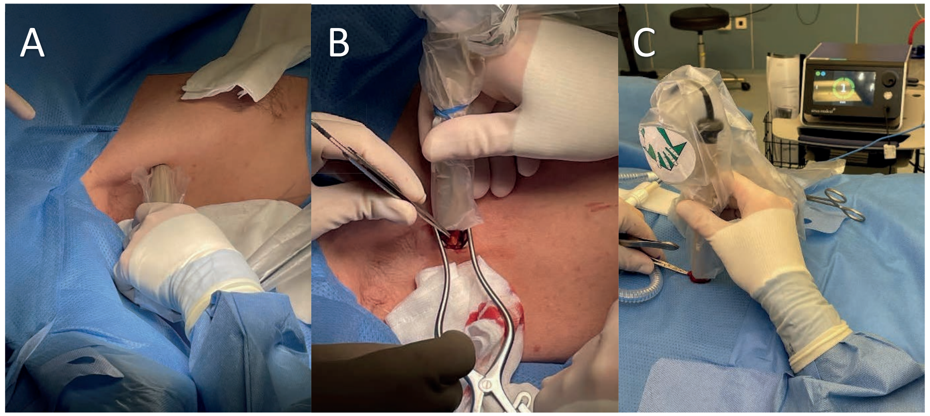

Figure 3. Localizing the magnetic seed before incision (A), during surgery (B) and after resection (C).

Study design

In this single cohort study, patient and lesion characteristics and surgery outcomes were collected retrospectively from electronic patients' files with approval from the Local Ethics Committee (IRB d23-324). Patient and lesion characteristics included age, gender, BMI, tumor type, stage of the disease, lesion size, location of lesion, and the administration of preoperative treatment. The primary endpoint, successful lesion localization, was defined as being able to localize the lesion guided by MSL. Secondary outcomes were seed migration, negative resection margins (13) and complication rate (Clavien dindo grade ≥2)(14). Seed migration was defined as clinical relevant displacement over time between implantation and surgery. Data on dislocation of the seed during surgery was collected as well.

Data analysis

The analysis was conducted using IBM SPSS 27.0 for Windows. Median values with interquartile ranges (IQR) were utilized as descriptive statistics because the data was non-normally distributed.

Results

Sixty-one patients operated between January 2021 and October 2023 were identified and included in this study. In this population, 79 seeds were deployed for 76 lesions that were resected in 68 surgeries (figure 4). Patient characteristics are displayed in Table 1. Melanoma lesions were diagnosed in 45 (73.8%), MCC lesions in two (3.8%), and STS in 11 (19.7%) patients. The other three patients were initially suspected to have a melanoma metastasis, but after resection and following pathologic examination it turned out to be rare types of STS (tenosynovial giant cell tumors in two patients and epithelioid hemangioendothelioma in one patient). These three incidental findings and the two patients with MCC lesions were treated similar to the melanoma patients, and will there for be discussed as melanoma lesions in this study.

Table 1. Patient characteristics

	n= 61	
Age	60	(49-75)
Gender		
Male	27	(44.3)
Female	34	(55.7)
BMI	28	(24-31)
Tumor type		
Melanoma	45	(73.8)
Merkel cell carcinoma	2	(3.8)
Soft tissue sarcoma[a]	11	(19.7)
Other[b]	3	(3.8)

Values are n (%) or median with inter quartile range. [a]Soft tissue sarcoma subtypes: Leiomyosarcoma (n= 1), Myxofibrosarcoma (n=1), Sarcoma not otherwise specified (n=4), Myxoid liposarcoma (n=2), Chondrosarcoma (n=1), Epitheloid sarcoma (n=2), [b] Tenosynovial Giant Cell Tumor (n= 2), Epithelioid hemangioendothelioma (n= 1).

All melanomas were diagnosed as metastatic non primary lesions while the STS were diagnosed as primary disease (14.3%), recurrent or residual disease (50.0%), or metastases (35.7%). The median size of the melanoma lesions was smaller than that of the STSs (11 mm vs. 30 mm). Of the melanoma lesions, 13 (21.0%) were pre-treated with systemic immune checkpoint inhibitors and three (4.8%) with intralesional injections of an oncolytic virus, talimogene laherparepvec (T-VEC). The STS lesions were pre-treated with radiotherapy in four (28.6%) patients, three patients (21.4%) were pre-treated

Table 2. Lesion characteristics, seed placement details, and perioperative outcomes

	Melanoma*		Soft tissue sarcoma	
	n		n	
Lesions	**62**		**14**	
Diameter (mm)	11	(7-18)	30	(18-50)
Type of lesion				
Lymph node	21	(33.9)	0	(0.0)
Subcutaneous	39	(62.9)	6	(42.9)
Intramuscular	2	(3.2)	7	(50.0)
Retroperitoneal	0	(0.0)	1	(7.1)
Stage of disease				
Primary disease	0	(0.0)	2	(14.3)
Local recurrence/residual disease	0	(0.0)	7	(50.0)
Metastases	62	(100.0)	5	(35.7)
Location				
Upper extremity	8	(13.1)	4	(28.6)
Lower extremity	37	(60.7)	5	(35.7)
Trunk	16	(26.2)	4	(28.6)
Abdomen	0	(0.0)	1	(7.1)
Preoperative treatment				
Yes	16	(25.8)	8	(57.1)
No	46	(74.2)	6	(42.9)
R0 resection				
Yes	49	(79.0)	11	(78.6)
No	13	(21.0)	3	(21.4)
Seeds	**64**		**15**	
Seed located ...				
In tumor	46	(71.9)	10	(66.7)
On border of tumor	10	(16.7)	4	(26.7)
Next to tumor	8	(12.5)	1	(6.7)
Seed migration				
No	64	(100)	15	(100)
Seed dislocation				
Yes	4	(6.1)	1	(7.7)
No	62	(93.9)	12	(92.3)
Operations	**56**		**12**	
Interval seed/surgery in days	9	(3-24)	14	(6-21)
Duration of surgery in minutes	40	(27-62)	56	(26-90)
Localization succeeded				
Yes	56	(100.0)	12	(100.0)
No	0	(0.0)	0	(0.0)
Complication Clavien-Dindo II				
Yes	4	(7.1)	1	(9.1)
No	52	(92.9)	11	(90.9)

Values are n (%) or median with inter quartile range. *Merkel cell carcinoma, epithelioid hemangioendothelioma and tenosynovial giant cell tumor included

with isolated limb perfusion and one lesion was treated with both radiotherapy and systemic chemotherapy. In 8 of the 13 melanoma lesions pre-treated with checkpoint inhibitors, the seed was deployed before the start of treatment. This was not the case in all other pre-treated lesions. Other lesion characteristics are displayed in Table 2. Ultrasound guidance was used to deploy the seed in 78 (98.7%) lesions. Only one lesion, a metastasis of a leiomyosarcoma in retroperitoneal fat, required computed tomography (CT) guidance for seed placement. The majority of seeds were located centrally within the tumor, 46 (71.9%) seeds for melanomas and 10 (66.7%) for STSs (Table 2). Localization of the seed on the border or outside the tumor was caused either by minimal movement of the seed after placement, the small tumor size, or if the tumor was in a difficult location. For three lesions, two seeds were located simultaneously: twice to indicate the lesions between two seeds (distance between seeds of 1.2 cm and 6.0 cm), and once because the first seed was placed 2 mm next to a lesion instead of centrally in the tumor.

During surgery, surgeons were able to successfully locate all (100%) lesions using MSL. Migration of the seed between placement and resection did not occur. Negative resection margins were achieved in 49 (79.0%) suspected melanomas and MCCs and 11 (78.6%) STSs. Surgery for suspected melanoma or MCC resulted in four complications (7.1%) and in one complication (9.1%) after resection of a STS. The complications were all wound infections after surgery and were treated with antibiotics and therefore scored as Clavien-Dindo grade 2. Dislocation of the seed during surgery (after localization of the lesion) occurred in 5 (6.2%) cases. These dislocations did not specifically happen shortly after implementation of MSL, but spread over the inclusion period. In 4 of those cases, the seed was deployed centrally in the lesion and in one case, just outside the lesion. Time between deployment and resection varied between two and 62 days for these 5 cases. A negative resection margin was achieved in only one of these 5 cases. All perioperative outcomes are displayed in Table 2.

Discussion

The aim of this study was to evaluate the feasibility of MSL for non-palpable melanoma, MCC and STS lesions. All lesions (100%) in this cohort were localized with MSL, resulting in 60 (78.9%) lesions resected with a negative resection margin. None of the seeds migrated before surgery, but 5 (6.2%) were dislocated during resection. The number of complications after these procedures was low and only consisted of wound infections after surgery treated with antibiotics.

Originally, MSL was mainly used for non-palpable breast lesions. In a study by Schermers et al., MSL was first described and used in breast lesions of 15 patients, resulting in 100% localization and resection of the lesions (5). In a study comparing MSL with WGL, 35 (100%) breast lesions were located and resected assisted by MSL which resulted in 79% negative resection margins (10). Studies with larger series of 300 and 1559 patients, using an alternative magnetic seed (Magseed; Endomagnetics Inc.), localized the breast lesions in 100% and 99.89%, respectively. Our data demonstrates that comparable outcomes can be achieved with the use of MSL for melanoma and, MCC and STS as for breast lesions (15, 16).

Since STS can occur at any anatomical location, localization is possibly difficult. Therefore, multiple localization methods have been described. Three studies with 8 to 15 included patients demonstrate that ^{125}I-radioactive seeds have comparable results as magnetic seeds (17-19). Lesions were localized in 100% of the patients and free resection margins were achieved in 80-90%. However, a downside of ^{125}I-radioactive seeds is that they cannot be left in the patient due to its radioactive properties in case of a cancelled resection. Also, strict protocols are necessary for the return of removed ^{125}I-radioactive seeds with repercussions in the event of seed loss. Another alternative method is radar reflector-guided resection, which also resulted in 100% lesion localization and 77% negative resection margins (20). Two small series of 6 and 7 patients describe radio-guided occult lesion localization (ROLL) for STS including our own recent paper, but no specific outcome measures are mentioned (21, 22). Besides, a similar downside of ROLL is the strict protocol regarding safety because of its radioactive particles. A downside of MSL is that the seed could cause MRI artefacts, restricting its applicability in a neoadjuvant settings when an MRI scan is necessary for restaging the tumor and no other alternative imaging technologies are suitable.

For melanoma lesions, less localization techniques are described because lesions are often cutaneous or subcutaneous and in most cases easily visible or palpable. On the other hand, improved scanning techniques, for example with PET-CT, lead more and more often to the detection of subclinical and non-palpable lesions. Some studies did focus on localization methods for lymph node metastases since it is sometimes harder to localize those. Both localization with ^{125}I-radioactive seeds as ROLL have been described in small cohorts of 10 to 15 patients (21, 23, 24) and again, localization and resection was successful in 100% of the lesions. The resection margins or migration rates were not mentioned in these studies.

Overall, in terms of localizing melanoma, MCC or STS lesions and achieving negative resection margins, MSL does not appear to be inferior nor superior to ROLL, ^{125}I-radioactive seeds, or the radar reflector technology. However, a major advantage of MSL is the absence of a timeslot for resecting the seed after placement. This makes MSL also very useful in case of neoadjuvant treatment. MSL is already used in this way for breast cancer with favorable results (25-27). For stage III melanoma, neoadjuvant immunotherapy might be standard of care treatment in the near future (28, 29). Based on the PRADO trial and the OPACIN-neo trials (30, 31), one might even discuss that further treatment after neoadjuvant treatment for stage III melanoma will be decided after examination of an index node. MSL with Sirius Pintuition is a feasible method for localizing and resecting the index lymph node (11). There are no breakthroughs yet with (neoadjuvant) immunotherapy for STS, but other treatment modalities can sometimes lead to significant downsizing as well. For example, myxoid liposarcoma often responds well and decreases in size after neoadjuvant radiotherapy (32), and localization of the remaining lesion might require a MSL as well.

The decision for implementation of a localization technique should be based on clinical results and specific features, but also cost effectiveness and patient experience have to be taken into account. Powell et all. used patient reported outcome measures to demonstrate the patient experience of MSL for breast lesions, which appeared to be well tolerated but is not studied yet for other non-palpable lesions (33). Lindenberg et all. compared the budget impact of MSL with RSL and WGL for non-palpable breast lesions (34). MSL appeared most cost-effective if 1) the price per seed would not exceed €178, if 2) the number of patients needing NACT with evaluation MRI would not increase because the seed is not compatible with MRI, or 3) MSL would result in better clinical results. Based on this analysis, MSL could be the most cost-effective localization method for melanoma, MCC and STS lesions, since the price is around this maximum, no MRI is necessary for melanoma and clinical results are comparable for the current patient population. However, prospective data regarding cost effectiveness and patient experience of MSL for melanoma, MCC and STS lesions are needed to be able to draw strong conclusions.

This study has limitations that should be acknowledged. First, its retrospective design may introduce a selection bias. Second, the sample size for STS lesions is relatively low. This study is also not a comparative study with other methods, which would require a prospective, multicenter trial to prove the effectiveness of MSL over other methods in melanoma, MCC and STS. Currently, the MELODY trial and the Ibra-net Breast Lesion Localization Study compare multiple localization methods for non-palpable breast lesions (35, 36). The results of these studies could assist in choosing the right localization tool for melanoma and sarcoma as well.

Conclusion

Magnetic seed localization with Sirius Pintuition for melanoma, Merkel cell carcinoma and soft tissue sarcoma is feasible with a 100% successful localization rate. No seed migration, low complication rates, and comparable negative resection margins with other localization methods were observed.

References

1. Elder DE, Bastian BC, Cree IA, Massi D, Scolyer RA. The 2018 World Health Organization Classification of Cutaneous, Mucosal, and Uveal Melanoma: Detailed Analysis of 9 Distinct Subtypes Defined by Their Evolutionary Pathway. Arch Pathol Lab Med. 2020;144(4):500-22.
2. Kunisada T, Nakata E, Fujiwara T, Hosono A, Takihira S, Kondo H, Ozaki T. Soft-tissue sarcoma in adolescents and young adults. Int J Clin Oncol. 2023;28(1):1-11.
3. Schmults CD, Blitzblau R, Aasi SZ, Alam M, Amini A, Bibee K, et al. NCCN Guidelines® Insights: Merkel Cell Carcinoma, Version 1.2024. J Natl Compr Canc Netw. 2024;22(1d):e240002.
4. Žatecký J, Kubala O, Jelínek P, Lerch M, Ihnát P, Peteja M, Brát R. Magnetic marker localisation in breast cancer surgery. Arch Med Sci. 2023;19(1):122-7.
5. Schermers B, van Riet YE, Schipper RJ, Vrancken Peeters MJ, Voogd AC, Nieuwenhuijzen GAP, et al. Nationwide registry study on trends in localization techniques and reoperation rates in non-palpable ductal carcinoma in situ and invasive breast cancer. Br J Surg. 2021;109(1):53-60.
6. Alamdaran SA, Farokh D, Haddad AS, Daghighi N, Modoodi E, Sadeghi R, et al. Assessment of Ultrasound / Radio-guided Occult Lesion Localization in Non-palpable Breast Lesions. Asia Ocean J Nucl Med Biol. 2018;6(1):10-4.
7. Endomagnetics becomes Endomag as business expands into new markets 2012 [Available from: https://www.endomag.com/en/blog/company/endomagnetics-becomes-endomag-as-business-expands-into-new-markets/.
8. Schermers B, van der Hage JA, Loo CE, Vrancken Peeters M, Winter-Warnars HAO, van Duijnhoven F, et al. Feasibility of magnetic marker localisation for non-palpable breast cancer. Breast. 2017;33:50-6.
9. Harvey JR, Lim Y, Murphy J, Howe M, Morris J, Goyal A, Maxwell AJ. Safety and feasibility of breast lesion localization using magnetic seeds (Magseed): a multi-centre, open-label cohort study. Breast Cancer Res Treat. 2018;169(3):531-6.
10. Struik GM, Schermers B, Mares I, Lont HE, Bradshaw JW, Ten Haken B, et al. Randomized controlled trial comparing magnetic marker localization (MaMaLoc) with wire-guided localization in the treatment of early-stage breast cancer. Breast J. 2021;27(8):638-50.
11. Schermers B, Franke V, Rozeman EA, van de Wiel BA, Bruining A, Wouters MW, et al. Surgical removal of the index node marked using magnetic seed localization to assess response to neoadjuvant immunotherapy in patients with stage III melanoma. Br J Surg. 2019;106(5):519-22.
12. Clement C, Schops L, Nevelsteen I, Thijssen S, Van Ongeval C, Keupers M, et al. Retrospective Cohort Study of Practical Applications of Paramagnetic Seed Localisation in Breast Carcinoma and Other Malignancies. Cancers (Basel). 2022;14(24).
13. Hermanek P, Wittekind C. The pathologist and the residual tumor (R) classification. Pathol Res Pract. 1994;190(2):115-23.
14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
15. Gera R, Tayeh S, Al-Reefy S, Mokbel K. Evolving Role of Magseed in Wireless Localization of Breast Lesions: Systematic Review and Pooled Analysis of 1,559 Procedures. Anticancer Res. 2020;40(4):1809-15.
16. Constantinidis F, Sakellariou S, Chang SL, Linder S, MacPherson B, Seth S, et al. Wireless localisation of breast lesions with MagSeed. A radiological perspective of 300 cases. Br J Radiol. 2022;95(1133):20211241.
17. Barranquero AG, Corral Moreno S, Martínez Lorca A, Hernández-Cosido L, Rioja Martín ME, Mena Mateo A, et al. Radioguided surgery of mesenchymal tumors with (125)I seeds. Rev Esp Med Nucl Imagen Mol (Engl Ed). 2023;42(5):296-301.
18. Barranquero AG, Corral Moreno S, Martínez Lorca A, Hernández-Cosido L, Rioja Martín ME, Mena Mateos A, et al. (125)I Radioactive Seed Localization vs. Conventional Surgery for the Treatment of Mesenchymal Tumours: A Propensity Score Matching Analysis. Langenbecks Arch Surg. 2023;408(1):161.
19. Garner HW, Bestic JM, Peterson JJ, Attia S, Wessell DE. Preoperative radioactive seed localization of nonpalpable soft tissue masses: an established localization technique with a new application. Skeletal Radiol. 2017;46(2):209-16.
20. Broman KK, Joyce D, Binitie O, Letson GD, Gonzalez RJ, Choi J, Mullinax JE. Intraoperative Localization Using an Implanted Radar Reflector Facilitates Resection of Non-Palpable Trunk and Extremity Sarcoma. Ann Surg Oncol. 2021;28(6):3366-74.
21. Reijers SJM, Mook FJ, Groen HC, Schrage Y, Stokkel MPM, Donswijk ML, van Houdt WJ. Radio-Guided Occult Lesion Localization With 99m Tc for the Localization of Nonpalpable Melanoma and Soft Tissue Sarcoma Lesions: A Feasibility Study. Clin Nucl Med. 2024;49(1):23-6.
22. Tyng CJ, Barbosa P, Bitencourt AGV, Amoedo MK, Almeida MFA, Lima ENP, Chojniak R. Computed tomography-guided preoperative localization of musculoskeletal lesions using the ROLL technique. Radiol Bras. 2018;51(3):147-50.
23. Hassing CMS, Tvedskov TF, Kroman N, Klausen TL, Drejøe JB, Tvedskov JF, et al. Radioactive seed localisation of non-palpable lymph nodes - A feasibility study. Eur J Surg Oncol. 2018;44(5):725-30.
24. Testori A, Rastrelli M, De Fiori E, Soteldo J, Della Vigna P, Trifirò G, et al. Radio-guided ultrasound lymph node localization: feasibility of a new technique for localizing and excising nonpalpable lymph nodes ultrasound suspicious for melanoma metastases. Melanoma Res. 2010;20(3):197-202.
25. Hartmann S, Banys-Paluchowski M, Stickeler E, de Boniface J, Gentilini OD, Kontos M, et al. Applicability of magnetic seeds for target lymph node biopsy after neoadjuvant chemotherapy in initially node-positive breast cancer patients: data from the AXSANA study. Breast Cancer Res Treat. 2023;202(3):497-504.
26. Martínez M, Jiménez S, Guzmán F, Fernández M, Arizaga E, Sanz C. Evaluation of Axillary Lymph Node Marking with Magseed® before and after Neoadjuvant Systemic Therapy in Breast Cancer Patients: MAGNET Study. Breast J. 2022;2022:6111907.
27. Reitsamer R, Peintinger F, Forsthuber E, Sir A. The applicability of Magseed® for targeted axillary dissection in breast cancer patients treated with neoadjuvant chemotherapy. Breast. 2021;57:113-7.
28. Long GV, Menzies AM, Scolyer RA. Neoadjuvant Checkpoint Immunotherapy and Melanoma: The Time Is Now. J Clin Oncol. 2023;41(17):3236-48.
29. Patel SP, Othus M, Chen Y, Wright GP, Jr., Yost KJ, Hyngstrom JR, et al. Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma. N Engl J Med. 2023;388(9):813-23.

8

30. Reijers ILM, Menzies AM, van Akkooi ACJ, Versluis JM, van den Heuvel NMJ, Saw RPM, et al. Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial. Nat Med. 2022;28(6):1178-88.
31. Rozeman EA, Menzies AM, van Akkooi ACJ, Adhikari C, Bierman C, van de Wiel BA, et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. Lancet Oncol. 2019;20(7):948-60.
32. Lansu J, Bovée J, Braam P, van Boven H, Flucke U, Bonenkamp JJ, et al. Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma: A Nonrandomized Controlled Trial. JAMA Oncol. 2021;7(1):e205865.
33. Powell M, Gate T, Kalake O, Ranjith C, Pennick MO. Magnetic Seed Localization (Magseed) for excision of impalpable breast lesions-The North Wales experience. Breast J. 2021;27(6):529-36.
34. Lindenberg M, van Beek A, Retèl V, van Duijnhoven F, van Harten W. Early budget impact analysis on magnetic seed localization for non-palpable breast cancer surgery. PLoS One. 2020;15(5):e0232690.
35. Banys-Paluchowski M, Kühn T, Masannat Y, Rubio I, de Boniface J, Ditsch N, et al. Localization Techniques for Non-Palpable Breast Lesions: Current Status, Knowledge Gaps, and Rationale for the MELODY Study (EUBREAST-4/iBRA-NET, NCT 05559411). Cancers (Basel). 2023;15(4).
36. Bromley HL, Dave R, Holcombe C, Potter S, Maxwell AJ, Kirwan C, et al. A Novel Mixed-Methods Platform Study Protocol for Investigating New Surgical Devices, with Embedded Shared Learning: Ibra-net Breast Lesion Localisation Study. Int J Surg Protoc. 2021;25(1):26-33.