The Breast 33 (2017) 50–56

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Feasibility of magnetic marker localisation for non-palpable breast cancer

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ARTICLE INFO

Article history:
Received 29 December 2016
Received in revised form
1 March 2017
Accepted 2 March 2017

Keywords:
Breast sparing surgery
Surgical localisation
Magnetism
Non-radioactive

ABSTRACT

Objectives: Accurate tumour localisation is essential for breast-conserving surgery of non-palpable tumours. Current localisation technologies are associated with disadvantages such as logistical challenges and migration issues (wire guided localisation) or legislative complexities and high administrative burden (radioactive localisation). We present MAgnetic MArker LOCalisation (MaMaLoc), a novel technology that aims to overcome these disadvantages using a magnetic marker and a magnetic detection probe. This feasibility study reports on the first experience with this new technology for breast cancer localisation.

Materials and methods: Fifteen patients with unifocal, non-palpable breast cancer were recruited. They received concurrent placement of the magnetic marker in addition to a radioactive iodine seed, which is standard of care in our clinic. In a subset of five patients, migration of the magnetic marker was studied. During surgery, a magnetic probe and gammaprobe were alternately used to localise the markers and guide surgery. The primary outcome parameter was successful transcutaneous identification of the magnetic marker. Additionally, data on radiologist and surgeon satisfaction were collected.

Results: Magnetic marker placement was successful in all cases. Radiologists could easily adapt to the technology in the clinical workflow. Migration of the magnetic marker was negligible. The primary endpoint of the study was met with an identification rate of 100%. Both radiologists and surgeons reflected that the technology was intuitive to use and that it was comparable to radioactive iodine seed localisation.

Conclusion: Magnetic marker localisation for non-palpable breast cancer is feasible and safe, and may be a viable non-radioactive alternative to current localisation technologies.

1. Introduction

Due to mammographic screening programmes and improved detection, breast cancer is increasingly diagnosed at an early stage when tumours are still small and frequently non-palpable. Non-palpable breast cancers make up for 33% (UK [1]) to 44% (Netherlands [2]) of all diagnosed breast cancer cases. For these tumours, breast-conserving surgery (BCS) is generally the treatment of choice. Complete removal of the tumour whilst minimizing resection of normal tissue is the cornerstone of a curative, breast-conserving approach that recognizes the value of cosmetic outcome for patient satisfaction [3,4] and quality of life [5]. To facilitate this, localisation technologies have become indispensable in everyday clinical practice.

Currently, the most common localisation technology is wire-guided localisation (WGL). In WGL, a radiologist implants a metal wire with an anchor tip in or near the lesion using image guidance. During surgery, the surgeon uses the wire to locate and remove the tissue around the tip. Unfortunately, WGL suffers from considerable disadvantages. First, the ideal wire insertion site for the radiologist is frequently distant from the ideal skin incision site for the surgeon, which can lead to extensive normal tissue dissection and/or higher irradicality rates [6,7]. Second, the wire may dislodge, migrate, fracture or even become transected during surgery, all

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http://dx.doi.org/10.1016/j.breast.2017.03.003
0960-9776/

resulting in a loss of guidance [8–10]. Third, the time between wire placement and surgery has to be minimized (typically one day at most), which stresses hospital planning and logistics [7,11]. Lastly, the wire protruding from the breast is generally considered more painful than alternative techniques [12].

Radioactive guided technologies such as radio-guided occult lesion localisation (ROLL) and radioactive seed localisation (RSL) were introduced as alternatives to WGL. In these technologies, the tumour is pre-operatively marked using a radioactive technetium-99 m solution (ROLL) or solid iodine-125 seed (RSL), which both can be located during surgery using a handheld gammaprobe. Drawbacks of ROLL are that the radioactive solution is invisible on mammography, hampering post-injection verification of the correct injection site [13]. Moreover, the use of a diffusing tracer as localisation signal reportedly leads to larger resection volumes [14,15].

RSL overcomes both WGL and ROLL's drawbacks by offering a radio-opaque, fixed signal point source for the surgeon to operate towards. Although RSL is discussed favourably in literature [16–18], it suffers from high regulatory barriers and administrative burden due to its radioactive nature. Furthermore, the need for a nuclear medicine department excludes most rural clinics. Consequently, clinical adoption is low. Almost 15 years after its introduction, RSL is used in only 18% of all localisation procedures in the Netherlands [2]. Although data are lacking, the use of RSL is expected to be even lower in other countries.

In a field in which three quarters of patients are still treated using a suboptimal technology, the development of new technologies is imperative. Recently, magnetic localisation using a solution of superparamagnetic iron oxide particles (SPIOs) and a handheld magnetic probe has emerged as a non-inferior alternative to radioactive technologies in sentinel lymph node biopsies (SLNBs) for breast cancer [19,20]. The advantage of using magnetism is to obviate the need for radioisotopes and their inherent challenges. Also, magnetism does not decay over time.

Magnetic occult lesion localisation in combination with SLNB localisation using a single intratumoral injection of magnetic SPIOs has also been reported in the literature (MagSNOLL) [21]. This technique is limited by the same drawbacks as ROLL: no possibility for post-injection verification of correct injection location and potential cross-talk between primary and SLNB lesions [21]. Therefore, our group set out to investigate the application of magnetism for primary lesion localisation, analogous to RSL rather than ROLL or MagSNOLL. A novel, radio-opaque, magnetic marker that can be implanted into the tumour was developed. This marker can be accurately detected using a handheld magnetic probe that functions like a gammaprobe.

Here, we report on the first clinical experience with the MaMaLoc technology: MAgnetic MArker LOCalisation for non-palpable breast cancer. The goal was to assess safety and feasibility of this novel technology in a small group of patients. We focussed on the ability to transcutaneously detect the magnetic marker during surgery, and secondarily on radiologist and surgeon satisfaction.

2. Method and materials

2.1. Magnetic detection

The MaMaLoc technology functions similar to RSL, but without the need for radioactivity. A magnetic probe (SentiMag, Endo-Magnetics Ltd., Cambridge, UK), similarly sized as conventional gammaprobes, emits a small (several mT) sinusoidal fluctuating magnetic field. The ferromagnetic MaMaLoc marker amplifies this magnetic field and this amplified magnetic field is again detected by the magnetic probe. The amount of amplification is relative to the distance between probe and marker. The amount of amplification is translated into a count value and fed back to the surgeon using a display and an audible tone that increases in pitch when nearing the marker. In preclinical, unpublished work the absolute distance over which the MaMaLoc marker can be detected was established at 35 mm, by creating response curves of the magnetic count relative to incrementally increasing distance [22]. A limitation of using a magnetic marker is that this precludes MRI response evaluation in a neo-adjuvant setting, in *ex vivo* work the image voids using a standard MR breast protocol were considerable at approximately 8 cm diameter [22].

Although both magnetic and radioactive detectors can provide roughly the same information and output, the physical principle of magnetism is fundamentally different from radiation. Therefore, the specific intraoperative handling of both probes differs as well. The magnetic probe requires calibration prior to and occasionally during surgery, which takes five to ten seconds and is controlled using a foot switch. This a direct consequence of using magnetometry, which does not specifically detect the MaMaLoc marker, but is also influenced by other magnetic signals such as the slightly magnetic body of the patient or metal objects near the probe. The latter also means surgeons should use non-magnetic polymer surgical tools to prevent signal disruption. In addition, temperature differences may slightly influence the magnetic probe and cause the signal to gradually drift away from zero (thermal drift). The detector attempts to filter away these slow and small incremental signal changes to compensate for thermal drift. Users can also manually correct for a drifted signal by re-calibrating the probe.

These differences also mean that applying the standard operating procedures of gammaprobe detection directly to the magnetic probe can lead to poor results. In general, magnetic detection is *less* sensitive to directional changes and far *more* sensitive to depth changes. In practice this means that to facilitate accurate detection using the magnetic probe, it is essential to *1)* keep the magnetic probe slightly in motion when performing a measurement; *2)* find the exact hotspot location by *pivoting* the probe rather than scanning it over the surface and *3)* to confirm the hotspot by gently palpating the tissue with the probe, to utilize the excellent depth sensitivity.

2.2. Procedure

Fifteen female patients with unifocal, non-palpable breast cancer that were scheduled for primary surgical treatment without neo-adjuvant chemotherapy were recruited in our institute and provided written informed consent. No exclusion based upon breast size or volume was applied. The ethical committee of the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital approved the study.

2.3. Radiology

All subjects received concurrent, ultrasound-guided placement of the radioactive iodine seed (Bard Medical, Covington, USA) that is the standard localisation technology in our institute, and the experimental magnetic MaMaLoc marker (3.5 × 1.5 mm, Fig. 1). The MaMaLoc marker was implanted in the same session, directly after the iodine seed using a custom 10 cm length, 14G applicator. The tumour depth was recorded as the distance between tumour edge and skin on ultrasound. Subsequently, standard two view mammographic imaging was performed to confirm correct placement of both markers. The shortest distance from skin to marker edge, as well as between both marker edges on the images was recorded. Additionally, breast thickness during mammography –