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A complete magnetic sentinel lymph node biopsy procedure in oral cancer patients: A pilot study

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ABSTRACT

Objectives: To assess the feasibility and merits of a complete magnetic approach for a sentinel lymph node biopsy (SLNB) procedure in oral cancer patients.
Materials and methods: This study included ten oral cancer patients (stage cT1-T2N0M0) scheduled for elective neck dissection (END). Superparamagnetic iron oxide nanoparticles (SPIO) were administered peritumorally prior to surgery. A preoperative MRI was acquired to identify lymph nodes (LNs) with iron uptake. A magnetic detector was used to identify magnetic hotspots prior, during, and after the SLNB procedure. The resected sentinel LNs (SLNs) were evaluated using step-serial sectioning, and the neck dissection specimen was assessed by routine histopathological examination. A postoperative MRI was acquired to observe any residual iron.
Results: Of ten primary tumors, eight were located in the tongue, one floor-of-mouth (FOM), and one tongue-FOM transition. SPIO injections were experienced as painful by nine patients, two of whom developed a tongue swelling. In eight patients, magnetic SLNs were successfully detected and excised during the magnetic SLNB procedure. During the END procedure, additional magnetic SLNs were identified in three patients. Histopathology confirmed iron deposits in sinuses of excised SLNs. Three SLNs were harboring metastases, of which one was identified only during the END procedure. The END specimens revealed no further metastases.
Conclusion: A complete magnetic SLNB procedure was successfully performed in eight of ten patients (80% success rate), therefore the procedure seems feasible. Recommendations for further investigation are made including: use of anesthetics, magnetic tracer volume, planning preoperative MRI, comparison to conventional technique and follow-up.

Introduction

In oral cancer, the presence of cervical lymph node (LN) metastasis is one of the most important prognostic factors for treatment stratification. However, in 30% of early oral cancer (cT1/T2) cases, lymph node metastases are not clinically detected at presentation, and are instead labelled as so-called 'occult' metastases [1]. Currently, the main options to determine the lymphatic status in patients with a clinically negative neck involve an elective neck dissection (END) and a sentinel lymph node biopsy (SLNB) procedure. During END, all regional lymph nodes (LNs) are excised, but this is generally unnecessary, given the absence of metastases in 70% of patients [2]. An alternative to END is the SLNB procedure, in which only the sentinel lymph node (SLN – the first draining LN) is excised. In a standard SLNB procedure, radioisotopes are

Abbreviations: END, elective neck dissection; SPIO, superparamagnetic iron oxide nanoparticles; SLN, sentinel lymph node; FOM, floor-of-mouth; SLNB, sentinel lymph node biopsy; LN, lymph node; OSCC, oral squamous cell carcinoma; HEN, higher echelon node.

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peritumorally injected, allowing SLNs to be visualized on preoperative lymphoscintigraphy, and making them intraoperatively detectable using a gamma probe. A (therapeutic) neck dissection is performed only if the SLN is positive after detailed histopathological examination (including step-serial sectioning and immunohistochemistry). The advantages of SLNB over END include the absence of overtreatment, lower morbidity, and reduced costs. SLNB has been found to be as accurate as END in detecting occult LN metastasis (sensitivity 81% vs. 84%, and negative predictive value 93% vs 93%, respectively), except for floor-of-mouth (FOM) tumors (sensitivity 63% vs. 92%, and negative predictive value 90% vs. 97%, respectively) [3]. This might be caused by the "shine-through" phenomenon, wherein the injection site around the primary tumor produces a large hotspot on lymphoscintigraphy, which potentially hides SLNs [4]. Alternative tracers, imaging, and detection systems have been suggested to overcome the performance issues caused by this phenomenon in FOM tumors [5].

One of these alternative tracers is a magnetic tracer, which has the advantage that radioactive regulations do not apply (since there is no radiation exposure), and that its availability is not dependent on the complex process of radioisotope production and transport. Moreover, the resolution of MRI is superior to that of a gamma camera. Furthermore, a magnetic SLNB procedure in breast cancer is shown as non-inferior to radioactive procedure [6–8] and is recently widely accepted in clinical practice [9]. However, relatively little is known about suitability of a magnetic tracer for SLNB procedure in oral cancer. In two separate studies, preoperative identification of SLNs in oral cancer patients with magnetic tracer enhanced MRI corresponded with radioisotope tracer identification on lymphoscintigraphy [10,11]. Additionally, a recently reported study on 11 oral cancer patients demonstrated that magnetic SLNs could be intraoperatively identified with a magnetic probe after peritumoral magnetic tracer injections [12]. However, this study does not use preoperative MRI for identification of SLNs.

In this pilot study we investigated the feasibility and merits of a complete magnetic route for an SLNB procedure in oral cancer patients. We use superparamagnetic iron oxide nanoparticle (SPIOs) as a magnetic tracer. An MRI was used for preoperative SLN identification, and postoperatively to check on residual iron at the injection site; a magnetic probe was used for intraoperative detection of SLNs.

Materials and methods

Ten patients with oral squamous cell carcinoma (OSCC) were recruited in the period February 2018–December 2019 at Medisch Spectrum Twente (MST, Enschede, the Netherlands). All patients were clinically diagnosed with T1-T2N0M0 [13], and scheduled for resection of the primary tumor, and ipsilateral END (levels I–III). In one patient, level IV was also resected. In two patients with near midline tumors, contralateral levels I–II were also resected. At least one surgeon with experience in SLNB procedure participated in the surgical team. Specific tumor and patient characteristics are summarized in Table 1. Exclusion criteria were as follows: intolerance or hypersensitivity to iron or dextran compounds, Sienna+® or lidocaine; iron overload disease; non-palpable malignancies; an active implantable device in the upper body; pregnancy. Prior to entering the clinical trial, all patients provided oral and written informed consent. The study protocol is shown in Figure 1; it was conducted in accordance with the Helsinki Declaration, and approved by the local medical ethical committee (METC Twente, P17–23). The study was registered in the Netherlands Trial Register (ID: NL6656).

Tracer administration

Patients received a total volume of 0.4–0.8 ml undiluted Sienna+® containing 28 mg/ml iron (Endomagnetics Ltd., UK). The tracer was drawn from a single-use flacon via a sterile filter needle (BD™ Blunt Fill Needle with filter, 18G × 1.5 in. [1.2 mm × 40 mm]) and peritumorally administered in a maximum of four aliquots using a sterile injection needle (BD Microlance™ 3, 23G × 1 in. [0.6 mm × 25 mm]). The details of the injection volumes and timing are summarized in Table 1. Four of the first five patients experienced pain during tracer injection, so the last five received local anesthetics prior to SPIO injection; four received lidocaine spray (Xylocaine® spray (100 mg/ml), AstraZeneca Pty. Ltd., North Ride, Australia), and one received lidocaine injection (Ultracain® D-S Forte, 40 mg articaine hydrochloride; 0.01 mg/ml epinephrine). A visual analogue scale (VAS: 1–10, no pain – severe pain) was used to score the pain experienced during tracer injection for last five patients.

Preoperative and postoperative MRI

Preoperative and postoperative MRI were acquired for each patient using 1.5 T MRI system (Ingenia, Philips Medical Systems, Best, the Netherlands) with a dedicated head coil. The following MRI sequences were acquired in transversal plane: T1-weighted (T1w) 3D fast field echo (T_R/T_E = 25/4.6 ms, flip angle 30°, pixel size 0.75 mm × 0.75 mm × 1.6 mm) and T2-weighted (T2w) fast field echo (T_R/T_E = 1700/18.41 ms, flip angle 18°, pixel size 0.62 mm × 0.62 mm × 3 mm). The preoperative MRI was acquired shortly after tracer injection (range: 21–101 min; Table 1) and used for visual guidance during surgery. The follow-up MRI was acquired 4–6 weeks after surgery (limiting transient effects of surgical intervention, and prior to potential radiation therapy) to assess potential residual iron at the injection site on a binary scale. For

Table 1
Patient and procedure characteristics.

Patient number	Tumor location	Tumor stage (8th TNM)	Use of local anesthetics	Total Sienna+® volume (ml)	Number of aliquots	Interval (hh:mm)	
						Injection – MRI	**Injection – SLNB**
1	T	cT2	No	0.8	4	00:24	15:57
2	FOM	cT2	No	0.4	3	00:21	20:46
3	T	cT1	No	0.8	4	00:22	16:31
4	T-FOM	cT2	No	0.64[a]	3	00:27	03:07[b]
5	T	cT2	No	0.8	4	00:58	16:53
6	T	cT2	Yes	0.8	4	00:24	21:14
7	T	cT1	Yes	0.8	4	00:38	21:07
8	T	cT1	Yes	0.4	4	01:41	05:17[b]
9	T	cT2	Yes	0.4	4	01:20	18:07
10	T	cT1	Yes	0.4	4	01:09	04:06[b]

Tumor location: T = tongue, FOM = floor-of-mouth. Sienna+® was undiluted (28 mg iron/ml). Intervals are from injection to preoperative MRI, and from injection to start sentinel lymph node biopsy (SLNB).

[a] Due to pain, patient received 3 instead of 4 aliquots.

[b] Protocol deviation, tracer injection and MRI at day of surgery.

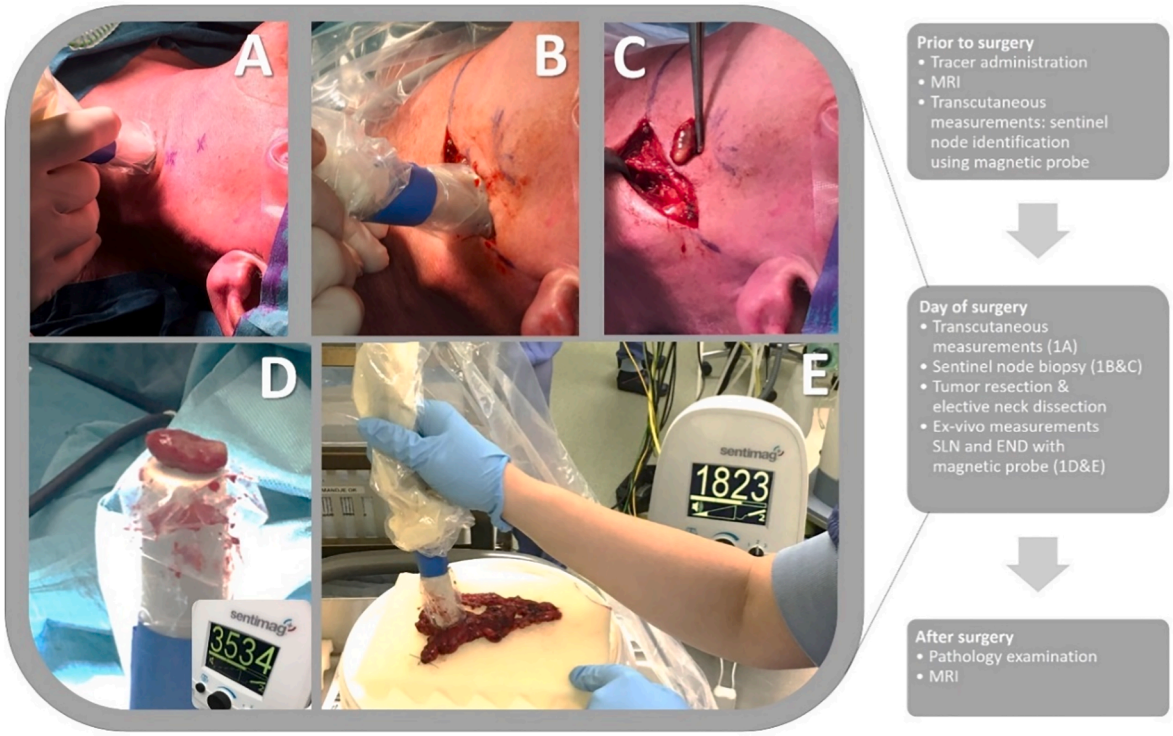

Figure 1. Left: Intraoperative measurements with the Sentimag®: (A) Transcutaneous to identify magnetic hotspots, see skin marks; (B) in vivo to identify SLN; (C) SLN is identified and excised; (D) ex vivo of the excised SLN; (E) ex vivo identification of magnetic hotspots in neck dissection specimen. Right: schematic overview of study protocol.

both MRIs, the number of LNs containing magnetic tracer per level I–III, was assessed by a radiologist experienced in head and neck oncology (JH). A hotspot on preoperative MRI was considered as SLN on the basis of iron susceptibility extent, and the LN position relative to the tumor location (first hotspot in any direction from the primary tumor). There was no limit on the number of LNs with iron uptake, and the neck level was considered not relevant. If a hotspot was clearly behind a SLN, this one was considered as second echelon node. However, if there was doubt, this hotspot was also considered as SLN [14].

Measurements using handheld detector, and surgical procedure

A magnetic handheld probe (Sentimag®, Endomagnetics, Ltd., UK) was used to detect the magnetic signal (counts) originating from SPIO, during five discrete stages, as shown in Figure 1: (1) for detection of transcutaneous magnetic hotspots on the day of the SPIO injection; (2) immediately prior to surgery; (3) to give direction during the SLNB procedure; (4) for ex vivo measurement of SLNs; and (5) for ex vivo detection of magnetic hotspots in the END specimen. Magnetic counts (corresponding to sensitivity level − 2) and corresponding lymph node levels were recorded. Before each measurement, the probe was balanced according to manufacturer's recommendations. Locations of transcutaneous magnetic hotspots were marked on the skin to guide detection of SLN(s), and subsequently used to define END incision line. SLNB procedure was performed through a key-hole incision on the END incision line. LNs intraoperatively detected by the probe were harvested and considered as SLN when ex vivo confirmed magnetically active. Magnetically active, brown-colored lymph nodes identified during the END procedure were also resected and labeled as SLNs. Each SLN was individually stored in a container filled with formaldehyde prior to pathology assessment. Plastic instruments were used throughout identification and resection of LNs, to prevent disturbance of the Sentimag® signal by metal instruments.

Histopathology

The SLNs were assessed for the presence of metastases and iron (step-serial sectioning, five levels with 200 μm interval) based on hematoxylin and eosin (H&E) stain. Immunohistochemistry (CK AE1/3) was applied when routine screening did not show metastases. The END specimen was evaluated according to standard pathology practice. LNs were assessed for the presence of metastases, and the number of LNs in each level was recorded.

Data analysis

For each LN level, the number of magnetic hotspots and LNs was documented. All hotspots or LNs between two levels were recorded as the lower of the two levels (e.g. an LN in level II–III was recorded as level II). We provide the percentage of SLNs and LNs per neck level, and a number of magnetic hotspots detected in neck dissection specimen. The preoperative SLN identification rate is defined as the proportion of patients where at least one magnetic hotspot was identified using a magnetometer. The intraoperative SLN identification rate is defined as the proportion of patients in which at least one SLN is detected in vivo and ex vivo confirmed by magnetometer. On patient level, sensitivity and specificity are calculated for metastatic status in magnetic SLN with END specimen as ground truth.

Results

The majority of suitable patients were willing to participate. Reasons not to participate included emotional and/or physical burdens, and the lack of clear benefit for the individual. Patients had an average age of 65.5 years (range, 43–77), and the male:female ratio was 7:3. A complete magnetic SLNB procedure was successfully performed in eight out of ten patients, amounting in 80% success rate. Regarding the metastatic status of LNs an accuracy of 90% is reported. In three patients metastases

were found in a magnetic LN (one was identified during END procedure, sensitivity of 67%). No metastases were found in END specimen resulting in specificity of 100%.

Tracer administration

Nine patients experienced pain due to the injection of magnetic tracer (Table 2), with VAS scores of 7–9 for the lidocaine spray group, and 5 for the individual with the lidocaine injection. Two serious adverse events were reported, both involving tongue swelling. One patient (patient 5) was given 50 mg dexamethasone to stop the swelling.

Preoperative and postoperative MRI

In all patients, magnetic uptake in LNs was observed on preoperative MRI (example shown in Figure 2). Four patients exhibited a bilateral lymphatic drainage, while six patients exhibited only ipsilateral lymphatic drainage. In total 87 LNs with iron uptake (74 ipsilateral and 13 contralateral) were identified in levels I–III (see Table 2). I.e., an average of 8.7 LNs (range, 5–16) per patient, with 14 LNs considered as SLN. For all patients, postoperative MRI showed residual iron at the injection site (Figure 2F), with 45 ipsilateral and 29 contralateral LNs with iron uptake identified in levels I–III (Table 2).

Measurements using handheld detector, and surgical procedure

In nine patients, magnetic hotspots were identified during at least one of the transcutaneous measurement stages (at day of injection, or during the surgery immediately before the SLNB procedure; for six patients, hotspots were identified during both, preoperative identification rate: 90%) (Table 2). From these nine patients, a total of 28 LNs were harvested, of which 26 (from eight patients) were considered SLNs (intraoperative identification rate: 80%). Of these SLNs, 21 (81%, from eight patients) were detected during the SLNB procedure, and five (from three patients) were additionally detected during the END procedure. Only one SLN was detected on the contralateral side. For two patients no perioperative magnetic counts were reported. In one patient excised LNs did not show an ex vivo distinctive signal and in the other no clear hotspots were preoperatively identified, consequently only END was performed. The resulting ten END specimens totaled 30 magnetic hotspots during ex vivo measurements using Sentimag®.

Histology

Of the 26 SLNs (resected from eight patients), one SLN was pathologically assessed as two distinct LNs, and two were found not to be LNs (fat tissue and salivary gland tissue), resulting in 25 SLNs in total. From these, three contained metastases (one SLN was identified during the END procedure). No metastases were found in the two LNs without distinctive magnetic signal ex vivo, although small iron deposits were observed in H&E-stained sections. In all but three SLNs, iron deposits were visible. Figure 3 shows an SLN with metastasis and visible iron deposit (H&E staining and Perls Prussian Blue). Histopathological assessment of the neck dissection specimen resulted in a total of 161 identified LNs, none of which contained metastases. The percentage of ipsilateral LNs (SLN and non-SLN) resected from levels I–IV is shown in Figure 4. Ipsilateral level II contains most LNs (39.3%) and SLNs (6.9%). The three SLNs harboring metastases were found in this level.

Discussion

This single-center pilot study evaluated the feasibility and merits of a magnetic approach for an SLNB procedure in oral cancer patients. Prior to the pilot, we expected patients to experience little or no pain from the use of Sienna+®, based upon manufacturer's instructions and previous experience with breast cancer patients in our center. However, transient excessive pain was experienced by four out of five not anesthetized patients. Therefore, the last five patients were administered local anesthetics and a decreased amount of tracer. The single patient receiving the lidocaine injection reported lower pain perception than the patients receiving lidocaine spray, which warrants further investigation to optimize patient comfort. Reduction of tracer volume did not lead to a reduction of pain, suggesting that pain may occur due to an interaction of Sienna+® with tissue. Pain after peritumoral injections of a radioactive tracer is well known for sulfur colloid, but seems rarely occur after injections of nanocolloid. A local inflammatory response due to tracer

Table 2
Study results.

	Preoperative				Perioperative				Postoperative				
	Pain (VAS)	**Hotspots MRI**		**In vivo (d1/d2)**	**Excised LN**	**Magnetic counts**	**Hotspots ENDs**	**Magnetic counts**	**Pathology**			**Hotspots MRI**	
Pt		ipsi	contra						SLN	metastasis in SLN	total LNs	ipsi	contra
1	Yes (na)	6	0	2/2	5[a]	600–5640	3	1300	6[b]	0	29	3	1
2	No (na)	4	4	3/0	2	na	2	318–1523	0	0	20	3	1
3	Yes (na)	14	0	2/2	4[a]	3580–8400	3[c]	300–9500	4	0	32	3	4
4	Yes (na)	6	2	na/0	0	na	2	500–2000	0	0	17	9	0
5	Yes (na)	11	5	4/2	6[a]	900–11900[d]	3	400–3000	6	1	19	4	6
6	Yes (9)	8	2	0/1	2	1360–5230	4	724–5148	2	0	11	2	3
7	Yes (7)	5	0	3/2	2	267–2548	4	581–3000	1	0	11	12	4
8	Yes (8)	7	0	1/1	1	6200	2	80–160	1	0	4	6	4
9	Yes (8)	7	0	3/2	5	970–8600	2	1300–1500	4	1	20	1	1
10	Yes (5)	6	0	0/2	1	3700	5	650–1400	1	1	25	2	5
total		74	13	18/14	28		30		25	3	188	45	29

Notes and abbreviations: Pt = patient, VAS = visual analogue scale for pain (1–10), hotspots MRI: identified magnetic hotspots level I–III, ipsi = ipsilateral, contra = contralateral, d1 = transcutaneous measurement with Sentimag® on the injection day, just before or after MRI, d2 = transcutaneous measurement at start of surgery, excised LN = lymph nodes excised based on magnetic signal, magnetic counts = range of magnetic counts measured ex vivo, hotspots ENDs: amount of magnetic hotspots from elective neck dissection specimen. Postoperative; SLN: sentinel lymph node, total LN: includes all identified lymph nodes (including SLNs). LNs of ENDs did not harbor metastasis.

[a] Additional magnetic SLNs were detected during the END procedure.

[b] One sample contained two small lymph nodes.

[c] Lymph node chain with counts: 5000.

[d] Converted to sensitivity level − 2, Sentimag®.

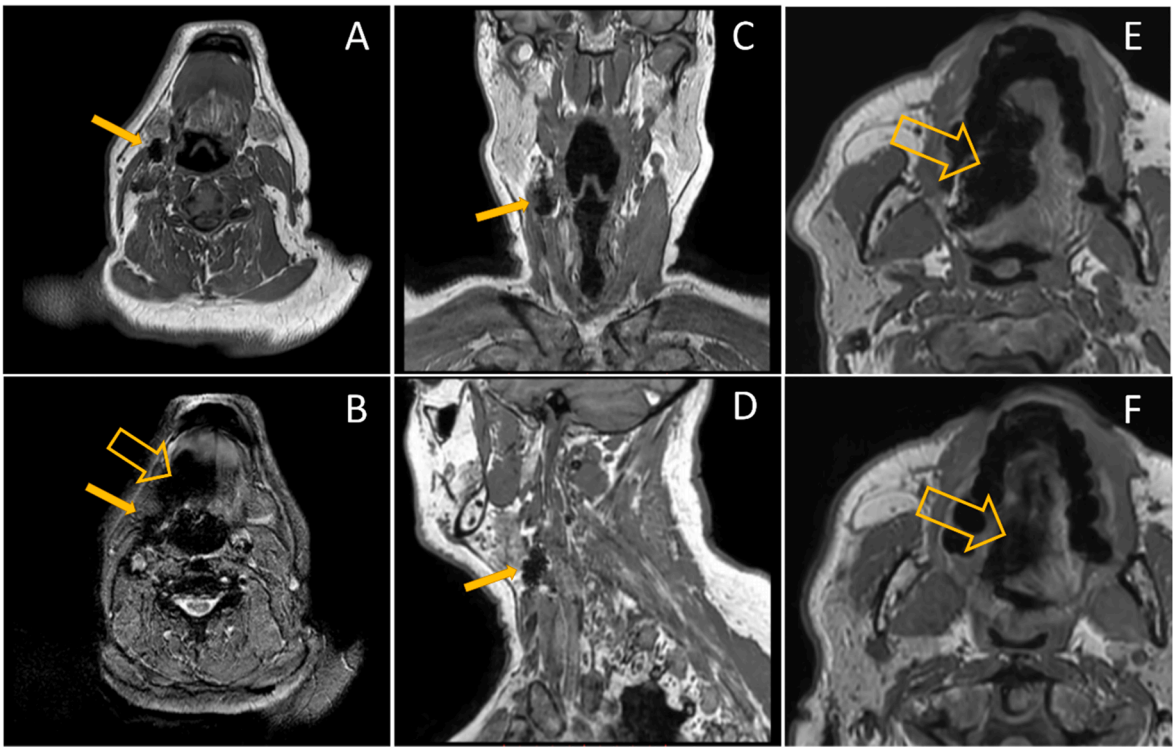

Figure 2. MRI data post magnetic tracer injection (A-E) and post-surgery (F). Solid yellow arrows show SLN (magnetic tracer uptake) in level IIa, right side (A-D). Open yellow arrows show tracer injection sites (B, E and F). (A) T1-weighted MRI (transversal plane); (B) T2-weighted MRI (transversal plane). The open yellow arrow points at the injection site, tumor at right side of tongue; (C) coronal reconstruction of Figure 2A; (D) sagittal reconstruction of Figure 2A; (E) preoperative MRI, the arrow points at the injection site (tumor at right side of tongue); (F) postoperative MRI at location represented in Figure 2E, the arrow points at the residual magnetic tracer.

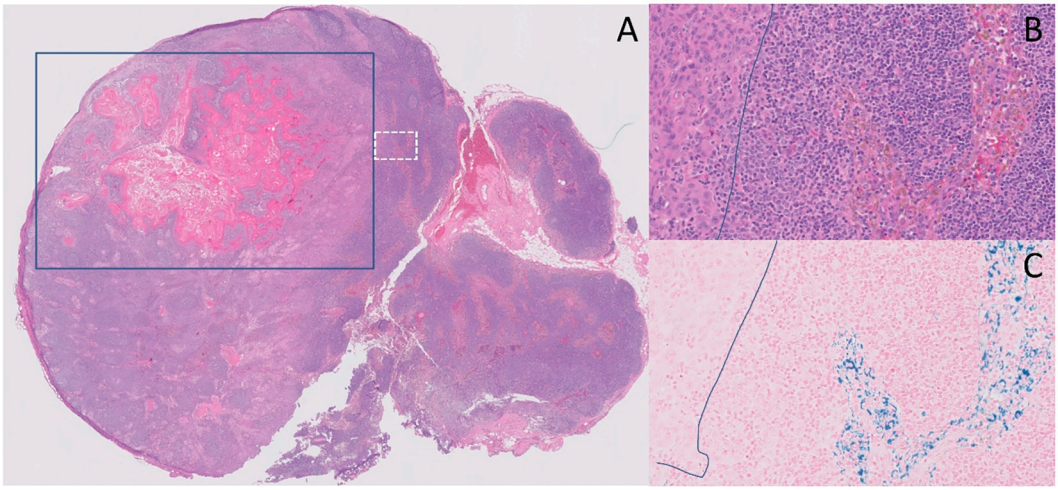

Figure 3. Sentinel lymph node with metastasis and visible iron deposits. (A) Sentinel lymph node coupe with hematoxilin & eosin (H&E). Within blue box, metastasis is represented by pink colored tissue. The white dotted box is enlarged in 3B and 3C; (B) high-power of white-dotted box in 3A. Metastasis is visible to the left of blue line, and brown-colored iron deposits in macrophages are visible to the right; (C) high-power of white-dotted box in 3A. Iron deposits were highlighted by Perls Prussian Blue, for this one example.

injection occurred in 20% of the patients, in line with an earlier case study [12]. Based on our experience, a 3-hour patient observation is recommended after tracer injection to mitigate possible adverse reactions.

Regarding preoperative SPIO-enhanced MR lymphography, a previous study has shown that SPIO may migrate to higher echelon nodes (HENs) over time [10]. Whereas conventional lymphoscintigraphy uses early and late enhancement static images to differentiate SLNs from HENs [14], our study uses only one static image. Regardless of carefully chosen timing, the number of magnetic hotspots identified in this study is higher than averages reported earlier [10]. Magnetic SLNB procedure in prostate cancer motives a relatively large numbers of SLNs by a high sensitivity of MR to small iron deposits [15]. Consequently, in line with guidelines for radiocolloid lymphoscintigraphy [14], SPIO-enhanced MR lymphography could be acquired earlier post injection to identify SLNs. To facilitate a clear definition of SLN, our study utilizes iron

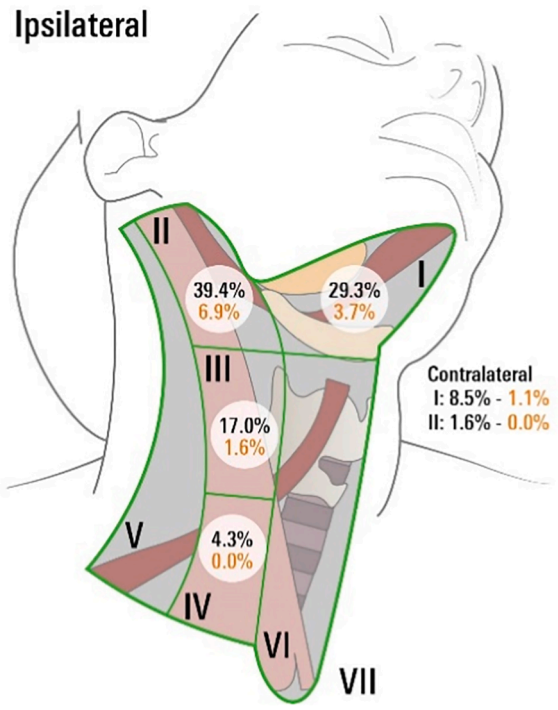

Figure 4. Distribution of all lymph nodes (black text) and magnetic sentinel nodes (orange text), as a subset of all lymph nodes, per resected level of ipsilateral side.

susceptibility and location of the LN relative to the tumor to label a LN with iron uptake as a potential SLN. Literature also advocates visualization of lymphatic vessels as alternative option to identify SLN [5]. Consequently, an accurate identification of SLNs by SPIO-enhanced MR lymphography benefits the SLNB procedure by allowing the identification of deeper-situated SLNs, which may be missed by using the Sentimag® probe alone.

Average number of resected SLNs is in line with earlier studies including magnetic SLNB case study [12], and the number of SLNs resected during a radioactive SLNB [4,16]. However, there is a discrepancy between the number of hotspots identified in SPIO-enhanced MR lymphography and number of resected SLNs. The same trend was observed earlier during prostate and breast SLNB procedure and was attributed to lower magnetic sensitivity of Sentimag® probe and the diamagnetic signal caused by human body [15,17].

Additionally, the lower sensitivity for magnetic SLNB procedure compared to a radioactive procedure [3] might be caused by relative inexperience of the investigators in handling a magnetic probe. Since the metastatic SLN that was not detected during the SLNB procedure was found magnetically active during END procedure. The use of plastic instruments requires adaptation in the clinical workflow. An excessive balancing protocol prior to each SLN detection was time-consuming and requires awareness of manganese fillings in molars, which was the case in one patient. In agreement with a previous study [12], we found that the Sentimag® probe diameter is slightly too large for an SLNB procedure in the neck.

Postoperative MRI showed residual iron uptake at the injection site, and in a number of enhanced LNs. However, these images were acquired with iron-sensitive sequences, and are therefore overestimates. Recent breast cancer follow-up studies have raised concern that long-lasting artefacts can hamper diagnostic MRI [18,19]. Therefore, there is a corresponding need to ascertain the extent to which similar artefacts affect clinical assessment in oral cancer patients during follow-up.

Conclusion

This pilot evaluated the feasibility and merits of a complete magnetic route for an SLNB procedure in oral cancer patients. The same magnetic tracer may be used for visualization of SLNs on preoperative MRI and for intraoperative detection of SLNs using a magnetometer. Some adaptations to the presented protocol are suggested, and the following recommendations are made for further research: (1) the use of lidocaine injection to optimize patient comfort; (2) the administration of 0.4 ml of magnetic tracer, which is still detectable, and is expected to have less residual iron on postoperative MRI; (3) injection and preoperative MRI on the day of surgery instead of a day before, limiting iron uptake by higher echelons, and allowing closer observation of patients for local inflammatory responses to the magnetic tracer; (4) comparison of magnetic tracer to radioisotopes for the identification of SLNs; and (5) a consistent follow-up scheme on residual magnetic tracer on MRI.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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