

1 Article

2 Interstitial MR Lymphography with 3 Superparamagnetic Iron Oxide for Sentinel Lymph 4 Node Mapping of Clinically N0 Early Oral Cancer: A 5 Prospective Comparative Study with CT 6 Lymphography

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20 **Abstract:** The purpose of this prospective study was to evaluate the usefulness of interstitial
21 magnetic resonance lymphography (MRL) with superparamagnetic iron oxide (SPIO) in sentinel
22 lymph node (SLN) mapping of clinically N0 early oral cancer, and to conduct a comparative study
23 of this MRL with computed tomography lymphography (CTL). CTL and MRL was performed for
24 SLN mapping before surgery for 24 patients with clinically N0 early oral cancer. SLNs were
25 detected by CTL in 21 (87.5%) patients, and the total and mean number of SLN were 45 and 1.9,
26 respectively. All SLNs could be detected 2 min and 3.5-5 min after contrast medium injection. In all
27 patients, SLNs were detected by MRL at 10 min after SPIO injection, and the total and mean
28 number of SLN was 66 and 2.8, respectively. MRL at 30 min after the injection showed additional 2
29 secondary lymph nodes. Interstitial MRL with SPIO is safe and useful imaging for detection of
30 SLNs in clinically N0 early oral cancer, and the optimal imaging timing is 10 min after SPIO
31 injection.

32 **Keywords:** computed tomography lymphography; early oral cancer; magnetic resonance
33 lymphography; metastasis; sentinel lymph node; superparamagnetic iron oxide
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35

36 1. Introduction

37 Cervical lymph node metastasis is an important prognostic factor in oral cancer. Because occult
38 metastasis is found during observation after primary surgery in 20-30% of patients with N0 early
39 oral cancer [1], some studies recommend prophylactic neck dissection (ND). Nonetheless, 70-80% of
40 patients with early oral cancer who underwent ND may experience complications such as facial
41 nerve paralysis or shoulder dysfunction. Therefore, the concept of the sentinel lymph node (SLN),
42 which is the first lymph node to receive drainage from a primary tumor, has recently been applied in
43 detecting early lymph node metastasis in oral cancer patients [1-12], and SLN biopsy (SLNB) has
44 been performed to be less invasive than prophylactic ND. Although SLN detection using
45 radioisotope (RI) tracers is commonly performed [4,5,8-14], RI confers hazards to the patient and

46 staff and cannot be used in certain institutions due to restrictions regarding the handling and
 47 disposal of radioactive material [2,15]. Furthermore, SLN detection is difficult when the SLN is close
 48 to the site of RI injection, due to shine-through artifacts [2]. Another method for visualizing SLNs
 49 and lymphatics is computed tomography lymphography (CTL), which does not require special
 50 equipment and has recently been applied in melanoma, breast, esophageal, gastric and oral cancer
 51 [2,16-24]. However, CTL cannot be performed for patients with iodine allergy to iodinated contrast
 52 medium, and use of CT has radiation exposure as with RI. Therefore, other method with
 53 nonradioactive and non-allergenic tracers for SLN mapping is required [15]. Although interstitial
 54 magnetic resonance lymphography (MRL) with gadolinium or superparamagnetic iron oxide (SPIO)
 55 has recently been applied for SLN mapping of breast or esophageal cancer [15,25], there are few
 56 reports of interstitial MRL for SLN mapping of N0 early oral cancer [26,27]. The purpose of this
 57 prospective study was to evaluate the usefulness of interstitial MRL with SPIO in SLN mapping of
 58 clinically N0 early oral cancer, and to conduct a comparative study of this MRL with CTL.

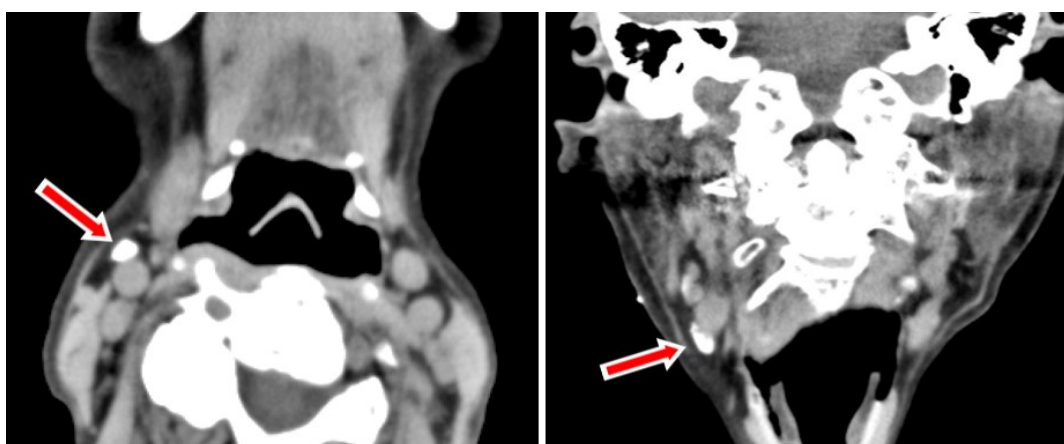
59 2. Results

60 There were 13 men and 11 women with a median age of 59 (range, 23-86) years. The most
 61 common primary tumor site was the tongue, and only 1 of all 24 patients had cancer of floor of the
 62 mouth. In total, 16 patients (66.7%) had clinical T1 and 8 patients (33.3%) had clinical T2.

63 SLNs were detected by CTL in 21 (87.5%) of the 24 patients (Figure 1). The number of SLNs was
 64 0 in 3 patients (12.5%), 1 in 6 patients (25.0%), 2 in 9 patients (37.5%), 3 in 4 patients (16.7%), 4 in 1
 65 patient (4.2%) and 5 in 1 patient (4.2%). The total number and mean number of SLNs were 45 and 1.9,
 66 respectively. All SLNs could be detected 2 min and 3.5-5 min after contrast medium (iopamidol)
 67 injection.

68 In all 24 patients (100%), SLNs were detected by MRL at 10 min after injection of ferucarbotran
 69 (Figure 2), and the total and mean number of SLNs was 66 and 2.8, respectively. MRL at 30 min after
 70 the injection showed additional 2 secondary lymph nodes. The number of SLNs was 1 in 5 patients
 71 (20.8%), 2 in 6 patients (25.0%), 3 in 7 patients (29.2%), 4 in 4 patients (16.7%), 5 in 1 patient (4.2%)
 72 and 7 in 1 patient (4.2%).

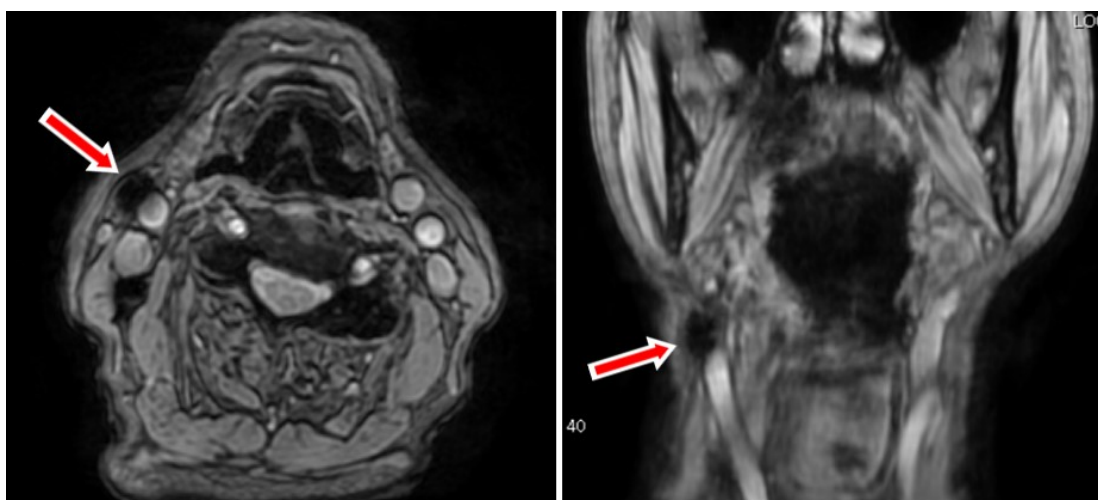
73 SLN location and number of MRL and CTL in N0 early oral cancer patients was showed in
 74 Table 1. In both imaging, SLNs without 1 SLN (level IB) on the contralateral side were located on the
 75 ipsilateral side. Although CTL showed 2 SLNs were lingual lymph node in 2 patients, MRL could
 76 not detect lingual lymph node for artifact of ferucarbotran injected into the primary site. Other 43 of
 77 45 SLNs enhanced by CTL could be detected by MRL.
 78



79
 80 Figure 1 CT lymphography

81 CT lymphography 2 min after iopamidol. A: Axial image, B: coronal image, Arrows indicate sentinel
 82 lymph node.

83



84

85 Figure 2 MR lymphography

86 MR lymphography in a spoiled T2* weighted sequence (Multiple Echo Recombined Gradient Echo)
 87 10 min after ferucarbotran. A: Axial image, B: coronal image, Arrows indicate sentinel lymph node.

88

89

90 Table 1 SLN location and number of MRL and CTL in oral cancer patients

SLN location	SLN number	
	MRL	CTL
IA	3	2
IB	31	21
IIA	31	19
IIB	1	1
Lingual lymph node	0	2

91

92 CTL, computed tomography lymphography; MRL, magnetic resonance lymphography; SLN,
 93 sentinel lymph node

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95

96 **3. Discussion**

97 Because occult cervical lymph node metastasis during observation after primary surgery is found
98 in 20-30% of patients with N0 early oral cancer and commonly occurs at level I to III, supraomohyoid
99 ND has been recommended [28,29]. However, minimally invasive surgery such as SLNB is required to
100 avoid the complications that can occur after ND, such as facial nerve paralysis. SLNB, which benefits
101 patients without lymph node metastasis by avoiding unnecessary lymph node dissection, has been
102 performed in the treatment of various cancers such as melanoma, breast, and gastric cancer [16-22].
103 SLNB using RI is standard procedure and has been recently applied in oral cancer [9,10,14]. However,
104 the main disadvantages of RI method are radiation exposure to patients and physicians, and short
105 half-life, availability, handling and disposal of RI [30]. It cannot be performed in hospitals that do not
106 have the required equipment and systems, thereby preventing its widespread use [1]. Therefore,
107 preoperative mapping of SLNs without RI is required for widespread application of SLNB and the
108 reliable detection of SLNs.

109 As an alternative method for preoperative visualization of SLNs and lymphatics, CTL without
110 requiring of special equipment can be performed at many hospitals with conventional CT scanners,
111 and has recently been applied in melanoma, breast, esophageal, and gastric cancer [16-21]. CTL has
112 clarified, with high resolution, the detailed arrangement of lymphatics along the route in various
113 malignant tumors when visualizing multiple lymph nodes. This then helped determine whether or not
114 these were secondary lymph nodes or lymph nodes from separate channels, thus facilitating more
115 accurate SLN identification [19]. Therefore, CTL without the shine-through effect is recommended for
116 the accurate identification of SLNs and for better topographical 3D orientation before SLNB [19], and
117 the reported detection rate of SLNs is 99% to 100% in breast cancer [O-Q]. However, the imaging
118 protocol for CTL is not clear [2,23,24], because there are few reports of SLN mapping using CTL for N0
119 early oral cancer. In a study of CTL for SLN mapping in patients with N0 early tongue cancer, Honda
120 et al. [2,24] injected 1.5 mL iopamidol (Iopamiron 370) into the peritumoral area. SLNs were detected
121 by CTL in 88.9-90.3% of patients. The number of SLNs was 0 in 9.7-11.1% of patients, 1 in 35.5-44.4% of
122 patients, 2 in 35.5-38.9% of patients, and 3 in 5.6-19.4% of patients (mean 1.6-1.8). In 28 patients, the
123 detection rates of SLNs at 1, 3, 5, 10 min after contrast injection were 7.1%, 53.6%, 17.9%, and 21.4%,
124 respectively [2]. Their studies required 4 separate CT scans for SLN mapping in tongue cancer
125 patients. In contrast, in our CTL study involving the injection of 2 mL of Iopamiron 300 into the
126 peritumoral area of early oral cancer patients, the SLN detection rate was 87.5% and the mean number
127 of SLNs was slightly higher 1.9 (range, 1-5). SLNs could be identified by 2 separate CT scans (2 min
128 and 3.5-5 min after contrast injection) and with lower radiation exposure. However, CTL cannot be
129 performed for oral cancer patients with iodine allergy to iodinated contrast medium.

130 Preoperative SLN mapping of N0 early oral cancer has commonly been performed using
131 lymphoscintigraphy and/or single-photon emission CT with CT (SPECT/CT), with a reported
132 identification rate of 95% to 100% [9,12,13], and the most common location of SLNs was level I to III
133 using RI [31]. Regarding the location of SLNs detected by CTL, Honda et al. [2] reported SLNs at level I
134 to III; in our study, SLNs were at level I to II and in the sublingual region. Although metastasis to the
135 lingual lymph nodes is one of the crucial events in determining survival outcome in cancer of the
136 tongue and floor of the mouth, few reports about the lingual lymph node are available because of its
137 small size and close location to the primary tumor [23]. In 2012, Saito et al. [23] first reported that CTL
138 revealed a lateral lingual lymph node as the SLN in a tongue cancer patient, and our study showed
139 SLNs which was detected in the sublingual region. The lingual lymph nodes are not always present
140 (incidence: 17.1% to 25.1%) [32-34], and lingual lymph node metastasis in oral cancer is rare [33,35-40]
141 with a reported incidence of 2.1% to 14.3% [32-34]. Owing to the close proximity to the primary tumor
142 and the frequency of extracapsular invasion, lingual lymph node metastasis can be misdiagnosed as
143 local recurrence [39]. Therefore, lingual lymph node metastasis may actually occur more frequently
144 than has previously been reported [39].

145 Recently, interstitial MRL has also been applied for SLN mapping of breast, esophageal, and head
146 and neck cancer [15,25,27,41-45]. The reported detection rate of SLN is 90.9-100% in breast cancer
147 [41,44]. However, there are few reports of interstitial MRL for N0 early oral cancer [26,27]. Gadolinium
148 or superparamagnetic iron oxide (SPIO) has been used as contrast medium of MRL [26,27,46], and
149 contrast medium drains through the lymphatics and accumulates in the SLN after the interstitial
150 injection. Loo et al [27] performed interstitial MRL with gadolinium for 7 oral cancer patients (5 tongue
151 and 2 buccal mucosa), and showed that optimal dose of gadolinium which was diluted with an equal
152 volume of sterile water and a small volume of 2% lidocaine (1:1:0.2-0.5 contrast:water:lidocaine) was
153 0.3-0.5 ml and optimal imaging time was 5-15 min after the interstitial injection. Although tongue
154 cancer patients had 4-8 SLNs (mean, 5.3) at level II-IV, SLN cannot be detected in 2 patients with
155 cancer of the buccal mucosa, and the detection rate of SLN was 71.4%. Bae et al [27] reported interstitial
156 MRL with gadolinium (0.3:1:0.2 contrast:water:lidocaine) for SLN mapping, and SLNs (mean, 1.7) were
157 detected at level I-III in all 26 oral cancer patients. Mizokami et al [26] performed a study on SLN
158 detection by interstitial MRL with SPIO and ^{99m}Tc-radiocolloid lymphoscintigraphy and SPECT/CT in
159 3 tongue cancer patients. MR images were acquired sequentially at 10 min, 30 min and 24 h after
160 injection of SPIO (ferucarbotran), and 1-3 SLNs were clearly visualized in the 10 min interstitial MRL
161 images and were completely concordant with those visualized by lymphoscintigraphy and SPECT/CT.
162 However, interstitial MRL 24h after SPIO injection showed additional 10 or more lymph nodes uptake
163 including secondary lymph nodes, probably due to the smaller particle size (approximately 45-60 nm)
164 and negative charge that may have resulted in increased phagocytosis [26]. Moreover, limitations of
165 this study were small number patients (3 patients) and different dosage of SPIO (0.1ml, 0.15 ml and
166 0.3ml). In our study, MRL at 10 min after injection of SPIO (0.4 ml) showed detection rate of SLNs was
167 100% in 24 oral cancer patients. Although the mean number of SLN was 2.8, the number was more
168 than number detected by CTL and was similar to number reported in RI imaging [5,10,12]. MRL at 30
169 min after the injection showed additional 2 secondary lymph nodes. From the above, the optimal
170 imaging timing of interstitial MRL for SLN mapping seemed to be 10 min after SPIO injection.
171 However, our MRL study showed lingual lymph nodes which enhanced by CTL could not be
172 visualized by shine-through artifacts, as RI imaging. Although the incidence and metastasis of lingual
173 lymph node in oral cancer patients are rare [35,32,33,36-40], the presence should be examined by
174 ultrasonography [49] before interstitial MRL because oral cancer patients with iodine allergy to
175 iodinated contrast medium cannot underwent CTL.

176 In interstitial MRL, gadolinium cannot help intraoperative detection of SLN during SLNB as RI
177 method. However, interstitial MRL with SPIO can provide preoperative mapping of SLN and SLNs
178 with SPIO can be detected a handheld magnetometer (SentiMag®, Endomagnetics Ltd, UK), in the
179 same way as the gamma probe is used for detection of isotope-containing nodes [15,30,47,48,50].
180 Several studies and review till now have shown non-inferiority of SPIO over RI method for SLN
181 detection in breast cancer [15,30,47,48,50]. This RI-free method does not have disadvantages of the
182 standard method and is promising as a safe and effective alternative in the absence of nuclear
183 medicine facilities [15]. However, MRL with SPIO for SLN mapping cannot be performed in
184 institutions without MRI or for patients with iron overload.

185 This prospective study has some limitations such as small number of patients, single center study,
186 and no comparison with RI imaging. Therefore, further prospective multicenter study with a larger
187 number of patients and comparison with RI imaging is required to assess usefulness of SLN mapping
188 using MRL with SPIO in clinically N0 early oral cancer.

189 4. Materials and Methods

190 4.1. Patients

191 Between January 2017 and May 2019, 24 early oral cancer patients without cervical lymph node
192 metastasis were enrolled in our study. All patients had primary cancer without prior surgery,
193 chemotherapy, and/or radiotherapy. The primary cancer and cervical lymph nodes before surgery
194 were assessed using 4 modalities: enhanced-computed tomography (CT), magnetic resonance

195 imaging (MRI), 18F-fluorodeoxyglucose positron emission tomography/computed tomography
196 (FDG-PET/CT), and ultrasonography (US). The criteria for a diagnosis of N0 oral cancer at our
197 institutions can be summarized as follows: (i) minimum axial diameter of the node < 10 mm and no
198 rim enhancement on enhanced CT; (ii) maximum standardized uptake < 2.5 on PET/CT; and (iii)
199 presence of hilar echoes on US. TNM staging was classified according to the Union for International
200 Cancer Control staging system (8th edition). This prospective study was approved by the
201 institutional review board of our university (B161201001) and was conducted according to the
202 Declaration of Helsinki. Written informed consent was obtained from all patients.

203

204 4.2. CTL

205 CTL was performed with a 128 multi-detector row CT scanner (Siemens SOMATOM Definition
206 AS+; Siemens Healthcare GmbH, Erlangen, Germany) to detect SLNs 2 day before resection of the
207 primary tumor and SLNB. Patients were placed in the supine position and CT scanning was
208 performed with the following parameters: tube voltage of 80 kVp, 400 mAs, helical thickness of 0.6
209 mm, field of view of 220 mm, and rotation time of 1.0 s. First, non-contrast CT images of the oral
210 cavity and neck were obtained. After local anesthesia, a total of 2.0 mL of iopamidol (Iopamiron 300;
211 Bayer Yakuhin Co., Ltd., Osaka, Japan) was injected submucosally into 4 points around the tumor
212 with a 27-gauge needle and the injected sites were massaged. CT scanning was performed in all
213 patients at 2, 3.5, and 5 min after administration of iopamidol. SLNs were identified as the first
214 enhancing lymph node in the lymphatic flow from the sites of injection of the contrast medium, and
215 the CT images with three-dimensional (3D) reconstruction were analyzed on the day of the
216 procedure. The 3D reconstruction was performed using the cinematic volume rendering technique
217 with syngo.via imaging software (Siemens Healthcare GmbH, Erlangen, Germany).

218

219 4.3. Interstitial MRL

220 MRL was performed with a 3 Tesla MRI system (Discovery MR750w; GE Healthcare, Chicago,
221 US) in the supine position the day before resection of the primary tumor and SLNB. Resovist®
222 (FUJIFILM RI Farma Co.,LTD., Kobayashi, Tokyo, Japan) was used as SPIO agent, and it contains
223 540 mg ferucarbotran per milliliter (27.9 mg iron/ml), containing of hydrophilic
224 carboxydextran-covered SPIO particles. Iron oxide nanoparticles are incorporated into macrophages
225 and other phagocytic cells, and have been used as “negative contrast agents”, i.e., their active uptake
226 by normal lymph nodes results in a homogeneous decrease in signal intensity on T2*-weighted
227 images. After local anesthesia, a total of 0.4 ml Resovist® (ferucarbotran) was injected submucosally
228 for four point around the tumor with a 27-gauge needle as same as CTL and the injected sites were
229 massaged. Imaging was performed 10 and 30 min after SPIO injection by some sequences; axial
230 MERGE (Multiple Echo Recombined Gradient Echo) which is developed by GE Healthcare and is a
231 spoiled T2*-weighted sequences and equipped the option of 3D acquisition., axial T1-weighted and
232 T2-weighted MR images of FS (FatSat). After MRL, we analyzed the MR images on the day of the
233 procedure, and LNs with SPIO uptake from direct lymphatic drainage of the injection site were
234 considered as SLNs.

235

236 4.4. Assessment

237 Detection rate, number and location of SLNs in CTL and MRL were evaluated. Furthermore,
238 optimal scanning/imaging timing in CTL and MRL was examined.

239 **5. Conclusions**

240 MRL with SPIO is safe and useful imaging for detection of SLNs in clinically N0 early oral
241 cancer, and the optimal imaging timing was 10 min after SPIO injection.

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243 T.I.; Formal Analysis, S.S.; Investigation, S.S. and J.B.; Resources, T.I.; Data Curation, J.B. and S.O.;
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