Lymph node metastases from head and neck squamous cell carcinoma: MR imaging with ultrasmall superparamagnetic iron oxide particles (Sinerem MR) – results of a phase-III multicenter clinical trial

Abstract The aim of this study was to compare the clinical usefulness of ultrasmall superparamagnetic iron oxide (USPIO) MR contrast media (Sinerem, Guerbet Laboratories, Aulnay-sous-Bois, France) with precontrast MRI in the diagnosis of metastatic lymph nodes in patients with head and neck squamous cell carcinoma, using histology as gold standard. Eighty-one previously untreated patients were enrolled in a multicenter phase-III clinical trial. All patients had a noncontrast MR, a Sinerem MR, and surgery within a period of 15 days. The MR exams were analyzed both on site and by two independent radiologists (centralized readers). Correlation between histology and imaging was done per lymph node groups, and per individual lymph nodes when the short axis was ≥10 mm. For individual lymph nodes, Sinerem MR showed a high sensitivity (≥88%) and specificity (≥77%). For lymph node groups, the sensitivity was ≥59% and specificity ≥81%. False-
positive results were partially due to inflammatory nodes; false-negative results from the presence of undetected micrometastases. Errors of interpretation were also related to motion and/or susceptibility artifacts and problems of zone assignment. Sinerem MR had a negative predictive value (NPV) ≥90% and a positive predictive value (PPV) ≥51%. The specificity and PPV of Sinerem MR were better than those of pre-contrast MR. Precontrast MR showed an unexpectedly high sensitivity and NPV which were not increased with Sinerem MR. The potential contribution of Sinerem MR still remains limited by technical problems regarding motion and susceptibility artifacts and spatial resolution. It is also noteworthy that logistical problems, which could reduce the practical value of Sinerem MR, will be minimized in the future since Sinerem MR alone performed as good as the combination of pre-contrast and Sinerem MR.

**Keywords** Magnetic resonance · Contrast enhancement · Lymphatic system · Neoplasms · Head and neck neoplasms

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### Introduction

Imaging plays an important role for lymph node survey in patients with head and neck carcinoma. Imaging can modify the clinical staging by showing additional cervical nodes, ipsi- or contralateral, by detecting clinically nonaccessible lymph nodes located at the retropharyngeal or paratracheal levels, or by showing invasion of critical structures such as the common and internal carotid arteries and skull base [1].

The performance of currently used techniques (CT, MR imaging, and US) remains, however, unsatisfactory. As a consequence, in cancer patients with high nodal metastatic risk, many clinicians only take into account positive imaging findings for their treatment planning. Elective neck dissection is routinely performed to ensure microscopic diagnosis of lymph node metastasis, leading to overtreatment and additional morbidity.

The information provided by MR imaging can be improved by the use of contrast agent designed for intravenous MR lymphography [2, 3, 4, 5, 6]. Ultrasmall superparamagnetic iron oxide (USPIO) particles with a long plasma circulation time are captured by macrophages within normally functioning lymph nodes. As a result, a reduction of signal intensity is observed in tissue in which the contrast agent accumulates, because of the T2 and susceptibility effect of iron oxide. The USPIO-enhanced animal studies showed a significant decrease of signal intensity in normal nodes, whereas the signal intensity of metastatic nodes did not change on T2-weighted images [2], or showed mixed enhancement patterns, depending on the dose of contrast agent and type of imaging sequence [4]. To our knowledge, USPIO particles have been used in a limited number of patients [6, 7, 8, 9, 10, 11]. Anzai et al. [7, 8] reported a series of 12 patients with head and neck cancer, yielding 95% sensitivity and 84% specificity. Bellin et al. [11] has used USPIO particles in a series of 30 patients with pelvic and urologic cancer. The sensitivity of USPIO-enhanced MR lymphography was 100% and the specificity was 80%.

Since these encouraging results were obtained only in a limited number of patients, a large phase-III multicenter clinical trial was designed whose main objective was to establish the sensitivity and specificity of USPIO-enhanced MR compared with precontrast MR.

Two secondary objectives were also studied:

1. To analyze the sensitivity and specificity of USPIO-enhanced MR in the subpopulation of patients having no clinical or radiologic evidence of lymph node (N0 patients)
2. To check if the data obtained with USPIO-enhanced MR alone were comparable with those resulting from the comparison of noncontrast MR and USPIO-enhanced MR

### Materials and methods

**Patients**

This study was a multi-institutional phase-III clinical trial and was supported in part by Guerbet Laboratories (Aulnay-sous-Bois, France). The study protocol was approved by the ethical committee at each of the seven clinical sites and informed consent was obtained from all patients.

Ninety patients (79 men and 11 women; age range 35–83 years, mean age 55.3 years) were enrolled in the study which presented the following criteria:

1. Proven head and neck squamous cell carcinoma of upper aerodigestive tract
2. Absence of previous chemotherapy, irradiation or surgical treatment in the head and neck area
3. Candidates for surgery and neck dissection within 15 days of contrast-enhanced MR imaging

Nine patients dropped out of the trial. In 7 cases surgery was not performed because of rapid tumor progression or patient’s refusal to be surgically treated. In 2 cases the administration of the contrast media was stopped because of adverse affects. In 1 patient a worsening of preexisting dyspnea and tachycardia occurred, and resolved without treatment; 1 patient presented dyspnea, cyanosis, and hypertension, and was controlled by appropriate medication. Minor adverse effects were observed in an additional 9 patients (10%), but the contrast media was completely administered.

Pre- and postcontrast MR exams and pathologic specimen were available in 81 patients (73 men and 8 women; age range 35–83 years, mean age 54.7 years). The primary sites were as follows: oropharynx (n=26); oral cavity (n=20); larynx (n=19); hypo-