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SHORT COMMUNICATION

# Regional lymph node involvement in T1 papillary thyroid carcinoma: a bicentric prospective SPECT/CT study

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**Abstract**
*Purpose* Hybrid imaging combining single photon emission computed tomography (SPECT) with $^{131}$I and X-ray computed tomography (CT) performed at radioablation (RA) for thyroid carcinoma more accurately detects regional lymph node metastases (LNM) than does planar imaging. In this bicentric prospective study we used hybrid imaging in conjunction with histopathological examination to measure LNM frequency in a consecutive group of patients referred for RA due to stage T1 papillary thyroid carcinoma (PTC).
*Methods* At the Departments of Nuclear Medicine of the Ludwig Maximilian University of Munich and the Friedrich Alexander University of Erlangen-Nuremberg SPECT/spiral CT is routinely performed in all PTC subjects at the time of RA. Screening of our SPECT/CT databases for PTC patients with T1 histology produced 98 patients from Munich and 53 patients from Erlangen, including 96 of 151 patients with microcarcinoma. In 69 patients of the entire group, cervical lymph node dissection had been performed, whereas nodal staging in the remaining 82 subjects was based on SPECT/CT.
*Results* LNM incidence in the whole group was 26% [95% confidence interval (CI): 20–33%] versus 22% (95% CI: 15–31%) in the microcarcinoma subgroup. SPECT/CT was more accurate in 24.5% of our patients than planar imaging with regard to nodal staging.
*Conclusion* LNM occurs in one quarter of all patients with T1 PTC, and also in the subset with microcarcinoma. Performing $^{131}$I SPECT/CT, either with therapeutic or diagnostic radioactivities, directly after thyroidectomy should provide more accurate staging of T1 PTC, thus facilitating optimal therapeutic management.

**Keywords** Thyroid carcinoma · Microcarcinoma · SPECT/CT · Hybrid imaging

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## Introduction

Patients with differentiated thyroid carcinoma (DTC) are treated by thyroidectomy, usually followed by radioiodine ablation (RA) of thyroid remnants [1]. Tumours staged as T1 as defined by the classification of the Union Internationale Contre le Cancer/American Joint Committee on Cancer (UICC/AJCC) have an excellent prognosis [2]. However, in a minority of subjects with low-stage disease, DTC may persist and/or recur, despite thyroidectomy and RA [3]. The occurrence of cervical lymph node metastases (LNM) eluding primary treatment is a likely factor resulting in incomplete response to treatment. Nonetheless, cervical lymph node dissection is not generally recommended for

treatment of T1 tumours in the absence of clinical evidence for LNM. Consequently, there is a lack of prospective histopathological studies reporting the incidence of LNM incidence in PTC staged as T1.

Traditional imaging is unsuited for detecting LNM at the time of RA [4]. In particular, cervical ultrasound lacks sensitivity for reliable detection of LNMs smaller than 1 cm in diameter. Moreover, the specificity of ultrasound is compromised due to the occurrence of non-specifically enlarged lymph nodes after thyroidectomy. The sensitivity of planar scintigraphy usually performed after RA to diagnose LNM is also low since the LNMs that have accumulated radioactivity cannot be reliably distinguished from that in non-neoplastic remnant tissue. However, instruments combining $^{131}$I single photon emission computed tomography (SPECT) and CT have been recently proven to be significantly more accurate than planar imaging in detecting LNM [5–7]. The aim of the present study was to prospectively determine the frequency of LNM in PTC staged as T1 using this novel hybrid imaging technology.

## Materials and methods

We pooled patient data from the Department of Nuclear Medicine of the Friedrich Alexander University of Erlangen-Nuremberg (FAU) and the Department of Nuclear Medicine of the Ludwig Maximilian University of Munich (LMU). In both institutions, PTC patients are treated according to the guidelines of the European Association of Nuclear Medicine [1]. In particular, total thyroidectomy is followed by RA in all PTC patients with a tumour diameter greater than 1 cm. Patients with microcarcinoma presenting with clinical evidence of LNM or multifocal disease are treated similarly. Patients with seemingly uncomplicated microcarcinoma are advised to undergo RA in addition to total or near-total thyroidectomy, but are informed about the option of follow-up without radioiodine therapy. Roughly 80% of these subjects agree to undergo RA. Those patients with microcarcinoma in the absence of clinical evidence of LNM who undergo lobectomy or subtotal thyroidectomy are not offered follow-up RA.

Since January 2006 at the FAU and since May 2008 at the LMU, SPECT/CT has been added to the routine imaging protocol of all PTC treated with RA. We searched the two SPECT/CT databases using papillary differentiation, tumour stage T1 and performance of SPECT/CT at first RA as inclusion criteria. Patients with oncocytic tumours were excluded from the study. Based on these criteria, we identified 98 patients from the LMU and 53 patients from the FAU; 96 of 151 patients had microcarcinomas. The study protocol was approved by the Ethics Committees of the FAU and LMU. Table 1 summarizes the clinical and demographic data of the subjects. Mean age and distribution of gender did not differ significantly between FAU and LMU populations. Two of the subjects studied had a family history of DTC, and none of these patients was finally diagnosed as LNM positive. One subject had received radiation therapy for breast carcinoma and another subject for ependymoma. A review of the histopathological reports did not indicate in any subjects invasion of the thyroid capsule, vascular invasion or unfavourable histology, such as tall cell variant, columnar cell variant or diffusely sclerosing subtype.

**Table 1** Demographic and clinical data of the patients

| | LMU | FAU |
|---|---|---|
| Number of patients | 98 | 53 |
| Male | 31 | 20 |
| Female | 67 | 33 |
| Age (mean) | 49.2 | 49 |
| Age (range) | 21–76 | 13–76 |
| Range of $^{131}$I activity (GBq) | 1.801–3.974 | 2.940–5.300 |

*LMU* Ludwig Maximilian University of Munich, *FAU* Friedrich Alexander University of Erlangen-Nuremberg

In the entire group, whole-body scintigraphy (WBS) and subsequent SPECT/CT of the head and neck region were performed a mean of 3.2 days (2–4 days) after therapy. At the FAU, 16 of the data sets were obtained with a Symbia T2 and 37 with a Symbia T6 (Siemens Medical Solutions USA, Inc., Hoffman Estates, IL, USA), following the previously published procedure [5], which entailed a low-dose CT of the neck and upper thorax. The protocol used at the LMU for SPECT data acquisition and reconstruction was identical to that used at the FAU, but slightly different CT scanning parameters were used at the LMU, where the voltage was 130 kV, the mAs product 20–30 s using the CARE Dose 4D function, the rotation time 0.8 s and the collimation 2×4.0 mm. The CT data were reconstructed at LMU with a standard Feldkamp algorithm and the B30/60/80 s kernel.

As described and discussed in more detail previously [5], all radionuclide-positive foci in the planar as well as on the SPECT/CT images were classified either as malignant or benign. In patients staged histopathologically as N1, the N stage was naturally not altered according to the result obtained by SPECT/CT. Patients not found to harbour metastases by histopathological examination were upstaged by SPECT/CT if this modality yielded LNM. In patients who had not undergone lymph node dissection (Nx), only the results from nodal staging performed by SPECT/CT were used in the further analysis (Table 2).

The 95% confidence intervals (CIs) were calculated using the method recommended by Altman et al. [8]. The

**Table 2** Nodal staging of the patients

*sN1* nodal stage determined by SPECT/CT, *p/sN1* nodal stage determined by histopathological examination and SPECT/CT

| Histology | *n* | pN1 | % | Nx/N0>sN1 | % | p/sN1 | % |
|---|---|---|---|---|---|---|---|
| All pT1 | 151 | 14 | 9.3 | 25 | 17 | 39 | 26 |
| pT1≤1 cm (microcarcinoma) | 96 | 4 | 4.2 | 17 | 18 | 21 | 22 |
| pT1>1 cm | 55 | 10 | 18 | 8 | 15 | 18 | 33 |

significance of differences in frequencies between groups was evaluated using the chi-square test.

## Results

Figure 1 presents imaging findings in a representative patient with a microcarcinoma and LNM. Compared to SPECT/CT, planar imaging gave false-positive results in 15.9% and false-negative results in 8.6%. Thus, the accuracy of SPECT/CT for nodal staging of PTC at the time of radioablation was 24.5% higher compared to planar imaging with regard to nodal staging of PTC at radioablation. Figure 2 presents results of N staging as provided by histopathological examination and/or SPECT/CT.

In the whole group, LNM incidence was 26% (95% CI: 20–33%; Fig. 3). In cases of microcarcinoma, the LNM incidence was 22% (95% CI: 15–31%; Fig. 3). There was a non-significant 11% difference between LNM frequency in microcarcinomas and larger T1 tumours (95% CI: −3.5 to 26%; chi-square=2.15, $p>0.05$). There was no significant difference in LNM frequency between FAU and LMU in the whole group or in any of the subgroups.

## Discussion

In 24.5% of our series of 151 T1 PTC patients, SPECT/CT led to a revision of the nodal stage compared to planar imaging. This confirms data from three previous studies also conducted at the time of RA, albeit in considerably smaller and more heterogeneous patient groups than in the present study [5–7]. Defining the nodal stage is decisive for determining the overall prognosis of PTC patients [1, 2].

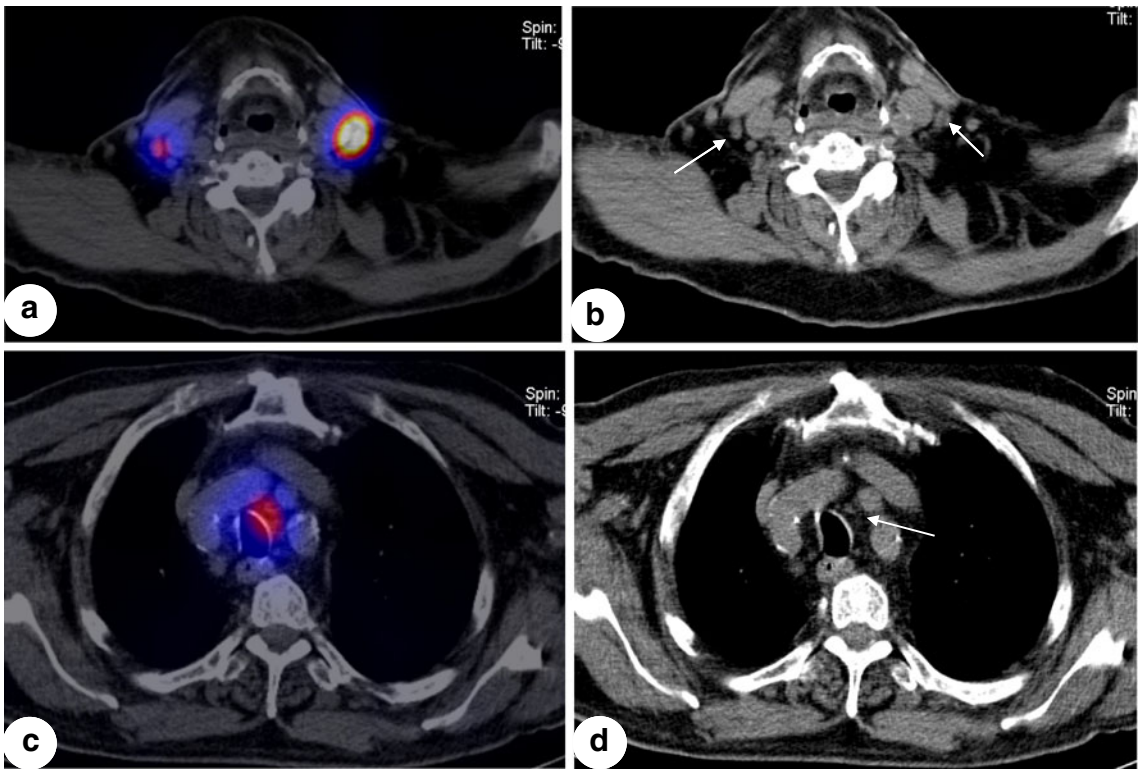


**Fig. 1** SPECT/CT images from a 74-year-old man with differentiated papillary thyroid carcinoma (pT1m, tumour diameters 0.3 cm and 0.7 cm), in whom LD had not been performed (Nx). SPECT/CT fusion images (**a** and **c**) and CT tomograms (**b** and **d**) demonstrate left and right LNM in level III as well as in the superior mediastinum (level VII)

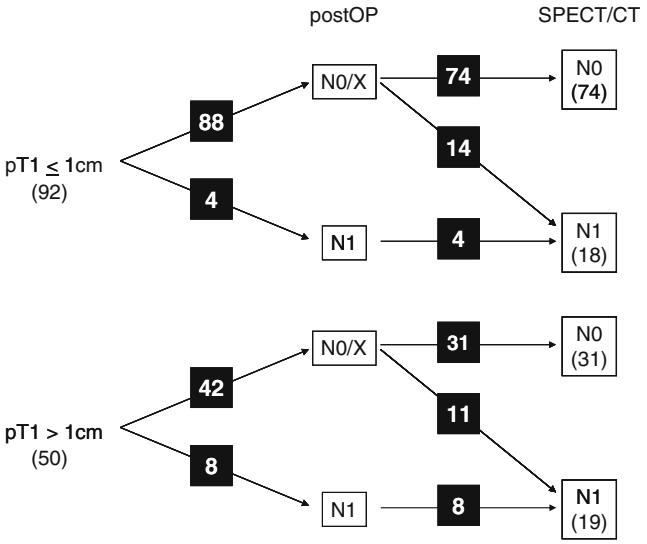


**Fig. 2** Postoperative N stage as well as N stage based on imaging in patients with a T1 PTC. The data are provided separately for pT1< 1 cm and pT1>1 cm. In 69 patients of the whole group, cervical lymph node dissection had been performed, and in the remaining 82 subjects nodal staging was based on SPECT/CT only

Our data therefore suggest the integration of SPECT/CT as a routine tool in the management of T1 PTC patients at RA in whom lymph node dissection was not performed.

Roughly one quarter of those patients with PTC staged as T1 in our prospectively studied series proved to have LNM. As noted above, there is little previous information about the frequency of cervical lymph node involvement in T1 PTC. All hitherto published studies on this topic are retrospective; in four published retrospective studies in a total of 1,495 patients, the LNM incidence ranged between 30.1 and 44.1% (mean 37%), mainly based upon histopathological examination of cervical lymph nodes [3, 9–11]. The mean incidence in these four reports lies above the 95% CI (29.1%) in the present SPECT/CT study. This discrepancy might be attributable to differences in the selection criteria of the patients studied. Furthermore, histopathological analysis in the earlier studies allowed detection of microscopic disease, which might be indiscernible to present imaging methods, at least when a sufficient number of lymph nodes were removed. Owing to the scheme of classification employed in this study, SPECT/CT classified all foci of radioiodine uptake localized in the central compartment as thyroid remnants; this may also account for the lower frequency of LNM identified in this work compared to the above-cited publications using histopathological examination as the means of detection.

The concept of papillary microcarcinoma was originally introduced to take into account the discovery upon autopsy of small PTC that had not become symptomatic during life. Two autopsy studies have nevertheless demonstrated that also between 1.0 and 35.6% of those tumours which had not resulted in symptoms during life may nonetheless already be accompanied by LNM (for a summary of the pertinent literature, see [3]). The incidence of LNM in microcarcinoma was also found in three previous retrospective studies to be higher than in our prospective study, ranging from 25 to 43% in a total of 456 cases [9–11]; this discrepancy is doubtless due to the reasons discussed above.

As yet, no publication has directly compared the accuracy of SPECT/CT with regard to nodal staging to that of histopathological examination of specimens from cervical lymph node dissection. Nevertheless, our attribution of radioiodine-positive foci outside the thyroid bed to LNM seems a highly plausible and parsimonious claim, as discussed in Schmidt et al. [5]. Our study pools data from two centres, in order to compensate for potential regional variations in tumour biology and patient management, although generalization to other patient populations should be made with caution.

The main novelty in our study resides in our original approach of combining a traditional way of demonstrating LNM, i.e. histopathological examination, with results from a novel imaging technology, i.e. SPECT/CT. Clearly, lymph node dissection of both the central and the lateral cervical lymph node compartments as well as of the upper mediastinum represents the gold standard of LNM diagnosis. However, this procedure is fraught with significant morbidity and costs, such that its routine use in low-risk PTC seems questionable. We contend that $^{131}$I SPECT/CT may emerge as the scientific and clinical gold standard of LNM detection in patients suffering from T1 PTC, especially those with microcarcinoma.

## Conclusion

Given the non-negligible incidence of LNM in patients with T1 PTC, most particularly in those cases with microcarcinoma, improved detection is critical. $^{131}$I SPECT/CT performed directly after thyroidectomy using either therapeutic or diagnostic radioiodine activities allows for more accurate staging of T1 PTC, thus affording more appropriate therapeutic management.

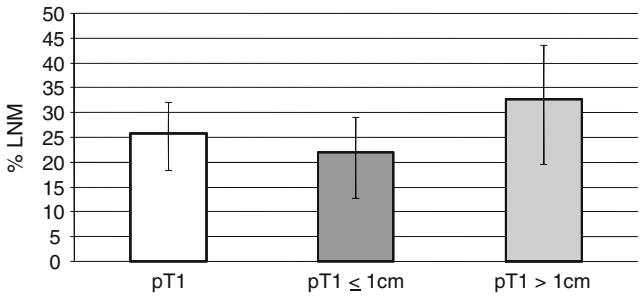


**Fig. 3** Frequency (%) of LNM in patients with pT1 tumours, given separately for pT1<1 cm and pT1>1 cm. *Error bars* are 95% CIs

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