FDG PET of Recurrent or Metastatic ^{131}I-Negative Papillary Thyroid Carcinoma

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This study reports on the use of FDG PET in the follow-up of papillary thyroid cancer patients with negative findings on ^{131}I total body scans and elevated levels of thyroglobulin after total thyroidectomy. **Methods:** Eleven asymptomatic patients with previous papillary thyroid cancer, total thyroidectomy, ^{131}I ablation, and treatment of all known metastases had negative findings on ^{131}I total body scans after therapy but persisting elevations of thyroglobulin when not receiving thyroid hormone. All imaging before PET failed to show persisting tumor. FDG PET was performed on all patients while receiving full thyroid hormone replacement, except for the repeated scan of 1 patient (patient 6). After the PET scan, all patients were referred for supplementary CT, sonography, or biopsy of lesions in the neck. **Results:** All 11 patients showed FDG uptake in the neck or upper mediastinum—in the initial scan in 10 and in a repeated scan in 1. Sonographically guided biopsy confirmed malignancy in 6, was nondiagnostic in 2, and showed normal findings in 1. In 2 patients, the sonographic results were normal and no biopsy was attempted. FDG imaging redirected the treatment of 7 patients, resulting in surgery and external beam radiotherapy in 3, surgery in 1, and external beam radiotherapy in 2. One patient declined further recommended surgery. The other 4 patients remain under observation. Surgical histopathology confirmed thyroid tumor in all 4 surgically treated patients. Retrospective review of the original histopathology slides showed no preponderance of aggressive histology. **Conclusion:** FDG PET is able to guide further evaluation of thyroid cancer patients who have elevated thyroglobulin levels and normal findings on ^{131}I whole-body scanning.

Key Words: thyroid cancer; FDG PET; ^{131}I

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Both serum thyroglobulin and ^{131}I whole-body scans have established roles in detecting recurrence of thyroid cancer and localizing metastases from differentiated thyroid cancer after total thyroidectomy (*1–3*). In most cases, this combination of tests adequately defines the presence and extent of disease and serves also to prognosticate the response to ^{131}I therapy.

Both follicular and papillary carcinomas may lack, or lose over time, the ability to trap iodine while still retaining the ability to secrete thyroglobulin (*4*). Meta-analysis of 7 published studies has shown that approximately three quarters of recurrences and metastases from well-differentiated adenocarcinoma are capable of concentrating ^{131}I (*5*). This figure leaves a quarter of patients who have recurrent or metastatic disease and constitute a therapeutic dilemma, because they will usually have elevated thyroglobulin levels but no identifiable focus of disease on a diagnostic ^{131}I scan. In this subset, ^{131}I treatment may be effective for both diagnostic and therapeutic purposes as judged by demonstration of ^{131}I concentration in lesions on whole-body scans after therapy and by the subsequent reduction of thyroglobulin (*6*).

Within the set of patients with negative findings on ^{131}I diagnostic scans is a still smaller subset with suspected disease activity but negative findings on ^{131}I scans after therapy. Although ^{131}I may still be effective in treatment of disease with such a low level of uptake that it is not seen on a diagnostic scan, effectiveness is difficult to envision when even the post-therapy findings are negative. The clinical task in such patients is to identify the focus of disease activity so that surgery or external beam radiotherapy can be appropriately directed. Morphologic imaging modalities such as sonography, CT, and MRI may be effective in localizing lesions that have failed to concentrate ^{131}I, especially in the case of local recurrences or in the evaluation of suggestive remote sites, but these modalities are not practical for whole-body evaluation. Further, they often cannot be used to distinguish active disease from the fibrotic residue of previously treated disease. Several nonspecific radiopharmaceuticals, such as ^{201}Tl, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrafosmin, and ^{111}In-octreotide, have some usefulness in the identification of disease sites when ^{131}I fails and thyroglobulin levels are elevated (*7–10*). With all these approaches, positive findings are useful but negative results are less than fully reassuring when thyroglobulin is elevated.

Several studies have shown that FDG PET can identify locally recurrent disease and distant metastases (*11–13*). However, the most effective role of FDG PET in the treatment of thyroid cancer has not yet been well defined. The purpose of this report is to show the usefulness of FDG PET in that small subset of thyroid cancer patients who have elevated thyroglobulin levels and whose tumors do not

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demonstrably concentrate ^{131}I, even on post-therapy ^{131}I whole-body scans.

MATERIALS AND METHODS

In a practice with more than 300 thyroid cancer patients, 11 asymptomatic patients with papillary carcinoma were identified who had previously undergone nearly total thyroidectomies and subsequent ablation of remnants with ^{131}I and who had persistently elevated thyroglobulin levels when not receiving thyroid hormone replacement. Thyroid hormone replacement at a thyroid-stimulating hormone (TSH)–suppressive dosage partially or completely suppressed thyroglobulin in all 11 patients. Serum thyroglobulin was measured using the OptiQuant coated tube immunoradiometric assay (Kronus, San Clemente, CA). Figure 1 is an algorithmic outline of our treatment of thyroid carcinoma and of how the 11 patients were selected. The individual patient characteristics are summarized in Table 1.

Because of concern about the elevation of thyroglobulin when patients were not receiving thyroid hormone, all 11 patients had received at least 1 treatment with ^{131}I (3.7–7.4 GBq) no sooner than 6 mo after the ablation of remnants with ^{131}I. Before ^{131}I therapy, all patients stopped thyroxine replacement for 6 wk and followed a low-iodine diet for the last 2 wk. All these patients had negative whole-body findings 10 days after ^{131}I therapy, which was given 2 d after the diagnostic dose (up to 3700 MBq) and on the day of diagnostic scanning. All imaging was performed using a γ camera with a medium-energy collimator. All patients had an elevated thyroglobulin level when not receiving thyroid replacement and at the time of imaging.

The initial supplementary work-up, after the normal post-therapy whole-body findings, included sonography of the neck and CT of the neck and chest. In no patient did sonography or CT before PET reveal lesions suggestive of active disease. The patients were then referred for FDG PET. With 1 exception (patient 6), PET was performed while patients were receiving full thyroid hormone replacement. Imaging was performed 40 min after injection of 185 MBq FDG in fasting patients. The scanner was a CTI ECAT ART with an axial field of view of 15 cm, an aperture of 60 cm, and a resolution of 6 mm in all planes. Data were obtained in 15-cm sections with an acquisition time of 8 min. The total scanning time was approximately 1 h. No attenuation correction was applied.

After undergoing PET, the 10 patients with positive findings

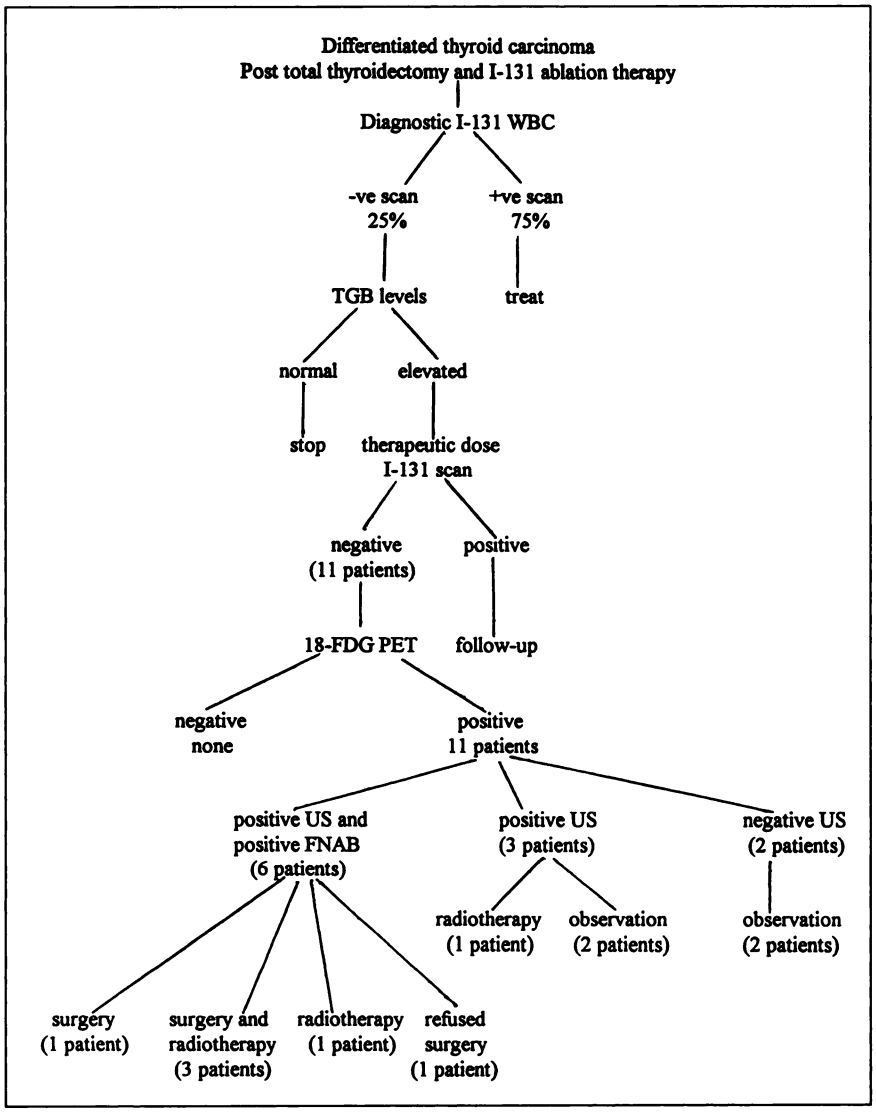

FIGURE 1. Algorithmic demonstration of our management of thyroid carcinoma.

TABLE 1
Patient Characteristics

Patient no.	Age (y)	Sex	Tg off T_4 (mg/L)	TSH off T_4 (mIU/L)	Tg on T_4 (mg/L)	TSH on T_4 (mIU/L)	Histology of thyroid carcinoma	Primary tumor	Regional nodes	Metastasis	Stage
1	27	F	41	150	5.1	0.1	Follicular variant of papillary	T2b	N1b	M0	I
2	60	F	11,778	150	177	0.7	Follicular variant of papillary	T4b	N1b	M0	III
3	45	M	29	>100	<1	<0.005	Tall cell variant of papillary	T4a	N1b	M0	III
4	66	F	132	48	<1	<0.005	Papillary	T2a	N1b	M0	III
5	37	F	93	>100	3.9	0.011	Papillary	T2a	N1b	M0	I
6	42	F	NA	NA	27.5 6 mo later, 38.0	0.129 1.4	Papillary	T1b	N1b	M0	I
7	36	F	72	>100	16.9	0.024	Papillary	T2b	N1b	M0	I
8	38	M	25	>150	8	<0.05	Papillary	T4b	N1b	M0	III
9	19	F	47	>100	<1	<0.005	Follicular variant of papillary	T4a	N1a	M1	IV
10	38	F	437	77	4.8	<0.011	Papillary	T2b	N1a	M0	I
11	40	F	51	>100	<1	0.008	Papillary	T1b	N1a	M0	I

Tg = thyroglobulin; T4 = L-thyroxine; TSH = thyroid-stimulating hormone; NA = not available.
Tg reference range for thyroidectomized patients is <5.0 mg/L.

were referred for repeated sonography and CT, including guided biopsy of any accessible lesions. Patient 6 had normal PET findings and, therefore, no immediate further work-up. However, 16 mo later, her thyroglobulin level rose further and a second PET scan was obtained 3 wk after she had stopped taking thyroid hormone.

The pathology reports for all patients were reviewed. The original specimens could be retrieved for 7 of the 10 patients with initial positive PET findings, and these specimens were reviewed by an independent pathologist to determine whether any unusual histologic features were present in these non–iodine-concentrating tumors. Thyroid cancer was staged according to the tumor node metastasis (TNM) classification designated by the American Joint Committee on Cancer (*14*). Six patients had stage I disease; 4, stage III; and 1, stage IV.

RESULTS

The results of the investigation, subsequent therapy, and follow-up are summarized in Table 2. The PET scans showed FDG localization in the neck or upper mediastinum in 11 patients, in the thyroid bed in 9, and in regional lymph nodes in 7. Sonographic and CT examinations were repeated with the radiologist aware of PET findings, and corresponding lesions were found in 9 of the 11 patients. Some of the lesions had previously been described as scar tissue. Sonographically guided fine-needle aspiration biopsy (FNAB) was attempted in the 9 patients and revealed malignancy in 6 patients, retrieved nondiagnostic material in 2, and retrieved normal cells in 1. An illustrative PET scan featuring patient 2 is shown in Figure 2.

The re-evaluation of patients after PET has led to changes of management in 6 patients. Four patients underwent additional surgery, with histologic confirmation of disease in all. Three patients underwent subsequent external beam radiotherapy. Two patients were treated with radiotherapy alone because their lesions were not amenable to surgical excision. A seventh patient (patient 6) declined further surgery despite advancing and now clinically evident disease. The surgical procedures were performed on the basis of the FNAB and the sonographic findings when these confirmed the PET findings. The remaining 4 patients with initially positive PET findings and either normal sonographic findings or benign cytology by FNAB continue under observation. Aside from the PET findings, disease activity has not been confirmed in any of these patients.

Patient 6, whose first PET scan showed normal findings, underwent a second PET examination 16 mo later that showed abnormal findings after withdrawal of thyroid hormone for 3 wk. The second scan revealed disease in the submandibular region and in the thyroid bed, subsequently confirmed by sonography and FNAB. The 2 PET scans are shown in Figure 3.

Review of the pathologic findings for all patients showed only 1 patient (patient 3) to have an aggressive tall cell variant of papillary carcinoma. All other specimens were typical of differentiated papillary carcinoma. Thus, no histologically unique characterization was seen among these ^{131}I-negative cancers.

DISCUSSION

FDG uptake in metastases of differentiated thyroid carcinoma was first described by Joensuu and Ahonen (*11*). They reported 3 patients with multiple metastases that accumulated FDG but not ^{131}I. Since then, several studies have compared FDG, ^{131}I, ^{99m}Tc-sestamibi, and ^{201}Tl uptake. Feine et al. (*12*) studied 41 patients, of whom 26 had scans negative for ^{131}I uptake. Of these 26, 19 had scans positive for FDG uptake. Unfortunately, the ^{131}I dose used varied

TABLE 2
Imaging, Pathology, Treatment, and Follow-Up Evaluation

Patient no.	FDG PET	CT	Sonography	FNAB	Treatment	Surgical Histopathology	FU Tg on T_4 (mg/L)	FU TSH on T_4 (mIU/L)	FU FDG PET	FU Sonography	FU CT
1	Thyroid bed	Tissue inf to L thyroid lobe, bilat CLN	Complex mass inf to L thyroid lobe	Nondiagnostic	Neck and sup mediast ext rad	NA	3.9	0.113	NA	Resolution of L thyroid mass, bilat CLN	NA
2	Two foci L ant mediast	Tissue L to trachea	Complex mass L to trachea	Malignant cells	Neck and sup mediast ext rad	NA	16.3	0.09	Minimal activity in mediast	Resolution of L tissue small R CLN	Residual tissue L neck
3	Thyroid bed, sup mediast	Residual thyroid tissue	Complex mass L suprasternal	Malignant cells	Ant mediast LN diss, neck and sup mediast ext rad	Four of 6 LN met pap extra-nodal invasion	<1.0	0.019	Resolution of sup mediast, new focus in sup mediast, thyroid bed	Normal	Significant reduction in residual thyroid tissue
4	Thyroid bed, L neck	Tissue L neck	Three L CLN	Malignant cells	L neck diss, neck and sup mediast ext rad	Four of 4 LN met pap	<1.0	0.005	NA	Normal	NA
5	Thyroid bed, ant and post mediast	R supraclavicular LN	Two R CLN	Malignant cells	R neck diss, neck and sup mediast ext rad	Two of 3 LN met pap	<1.0	0.005	NA	Resolution of R LN; small L CLN	NA
6	First scan normal, 16 mo later: thyroid bed, R submand LN	MRI scan normal	R CLN + submand LN	Malignant cells	Patient refuses surgery						
7	Thyroid bed	Soft-tissue density in neck	Complex mass R neck, bilat CLN	Malignant cells	R neck diss	Three of 3 LN met pap	NA	NA	NA	NA	NA
8	Thyroid bed	Normal	Normal	Not done	Observation						
9	Thyroid bed	Lung nodules	Normal	Not done	Observation						
10	Thyroid bed, R neck	Two R CLN	Two R CLN	Nondiagnostic	Observation						
11	R neck	R neck	R neck LN	Normal cells	Observation						

FNAB = fine-needle aspiration biopsy; FU = follow-up; Tg = thyroglobulin; T_4 = L-thyroxine; inf = inferior; bilat = bilateral; sup = superior; mediast = mediastinum; ext = external; rad = radiation; NA = not available; CLN = cervical lymph nodes; ant = anterior; LN = lymph node; diss = dissection; met = metastatic; pap = papillary; post = posterior; submand = submandibular.

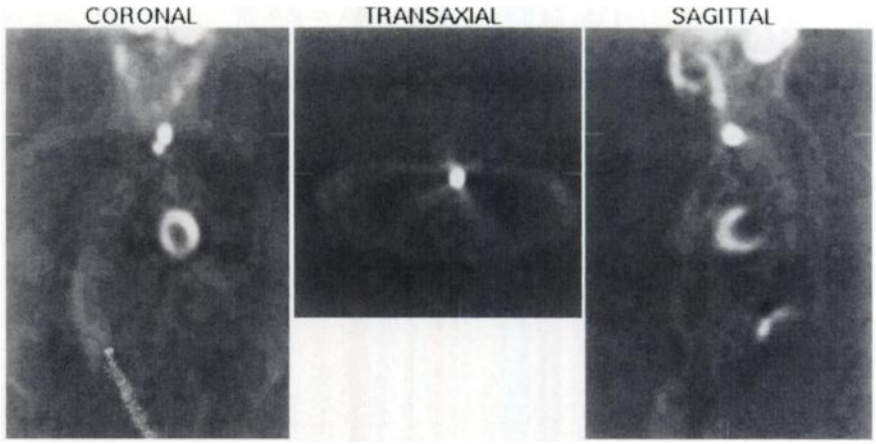

FIGURE 2. PET scan showing 2 foci of FDG concentration in left anterior mediastinum (patient 2).

widely, from 100 MBq to 6 GBq, and the number of ^{131}I-negative scans would likely have been fewer if all patients had received therapeutic doses. Dietlein et al. (*13*) studied 58 patients, of whom 28 had active disease. Of these 28, 11 had ^{131}I-negative scans and 7 had FDG-positive scans. The lowest ^{131}I dosage was 1.1 GBq, which may account for the lower incidence of scans negative for ^{131}I uptake compared with the findings of Feine et al.

^{131}I whole-body scans and thyroglobulin elevations are concordant for the detection of disease activity in 80%–85% of patients (*15*). A normal thyroglobulin level with positive scan findings is rare in the absence of antithyroglobulin antibodies. The converse, i.e., an elevated thyroglobulin level with negative ^{131}I whole-body findings, represents a relatively small but clinically difficult cohort. Our patients were drawn from this small subset of thyroid cancer patients. Without the evidence provided by PET, and in the absence of diagnostic findings on sonography, CT, or MRI, none of our patients would have been considered for therapy other than TSH-suppressive hormone replacement. Thus, PET had a demonstrable usefulness for the evaluation of these most difficult patients. Of these 11 patients, PET findings caused us to change the treatment of 7. The remaining 4 patients continue to be carefully followed up.

The discordance between ^{131}I and FDG tumor uptake has been attributed to differences in the extent of cellular differentiation, because glucose transport is increased in poorly differentiated tumors that have lost their ability to concentrate iodine (*16*). Some investigators have suggested that FDG uptake may correlate with the aggressiveness and, possibly, the prognosis of the tumor (*12*). We could not find any such correlation, because only 1 of the 11 patients had tall cell variant histology, and that variant has a 10% incidence in papillary thyroid cancer overall (*17*). With the exception of patient 3, our patients have not had evidence of aggressive disease. We also could not find a correlation between FDG uptake and the TNM stage of thyroid cancer. Of the 7 patients with confirmation of disease, 4 had stage I disease and 3 had stage III.

FDG uptake in the thyroid bed was a common finding and seen in 9 patients, but in only 1 patient (patient 1) did sonography reveal at the site a mass that could undergo biopsy. Increased glucose metabolism in the thyroid bed has been described and assumed to be related either to remnant thyroid tissue or to radiothyroiditis (*16*). In this regard, all our patients had undergone ablation more than 6–12 mo previously with a typical dose of 5.5 GBq. The probability of residual thyroid tissue or residual inflammation at the time of PET seems remote. Physiologic uptake with the potential for a false-positive interpretation may also arise from uptake by the sternocleidomastoid, scalene, serratus anterior, or longus coli muscles, and in some cases no explanation could be found (*18*). If the patient were to talk, cough, or clear the throat while the level of circulating FDG is still high, laryngeal uptake would be plausible. From our experience and the observations of others (*19*), we recommended that

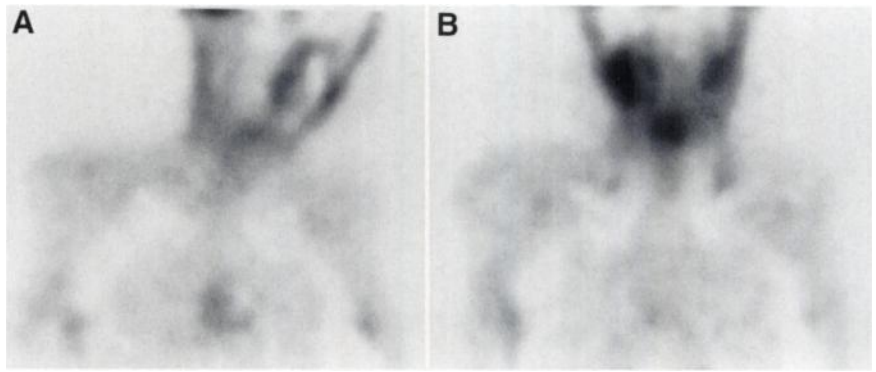

FIGURE 3. (A) Initial PET scan shows normal findings. (B) Repeated scan after 16 mo shows FDG concentration in submandibular region and in thyroid bed (patient 6).

the patient be kept at rest in a quiet, comfortable environment before the time of injection and throughout imaging. Thus far, we have not treated FDG uptake in the thyroid bed without supporting confirmation of disease, and we continue to follow these patients.

All PET scans but 1 were performed while the patients were receiving full thyroid hormone replacement. In the solitary case of patient 6, who had normal PET findings while receiving thyroid hormone, the follow-up findings when the patient was not receiving replacement were clearly positive, although the intervening time does not exclude interval growth of nodal metastases. A possibility is that the sensitivity of the FDG scan can be increased by prior discontinuation of thyroid hormone as suggested by Sisson et al. (*19*); however, PET findings were positive while the patients were receiving hormone replacement. Other authors, as well, did not observe any relationship between FDG uptake and TSH levels (*12,20*).

Wang et al. (*21*) recently reported on the performance of FDG PET in patients who had negative ^{131}I diagnostic findings irrespective of their thyroglobulin levels. These authors reported a positive predictive value of 92% when thyroglobulin levels were elevated and a negative predictive value of 93% when thyroglobulin levels were low. Our population was similar to their subset with elevated thyroglobulin levels, although we included only patients with negative findings after ^{131}I therapy. Wang et al. concluded that TSH levels at the time of PET are inconsequential, and we did not find any evidence to the contrary. Unlike us, Wang et al. also found a correlation between TNM staging and positive PET findings. In our 7 patients whose management was altered by PET, 4 had stage I disease and 3 had stage III. Further, in the 4 patients who continue under observation, 2 have stage I disease, 1 has stage III disease, and 1 has stage IV disease. We propose that the usefulness of functionally based PET should not be strongly correlated with the anatomically oriented TNM methodology in postoperative patients. The identification of disease with PET when ^{131}I whole-body findings are negative and thyroglobulin levels are elevated confirms the importance of the thyroglobulin assay as a reliable screen for recurrent thyroid cancer.

CONCLUSION

FDG PET led to the reevaluation of that small set of patients who had persistent elevation of thyroglobulin levels despite normal ^{131}I whole-body findings after a therapeutic dose. The result was identification of disease in 7 of 11 patients. The use of PET along with morphologically based imaging tests to identify sites capable of undergoing biopsy brought about treatment changes in most patients who had normal findings on ^{131}I whole-body scans after therapy.

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