Sentinel Lymph Node Identification with Technetium-99m-Labeled Nanocolloid in Squamous Cell Cancer of the Vulva

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In patients with early-stage squamous cell cancer of the vulva, inguinofemoral lymphadenectomy is performed primarily as a diagnostic procedure. The morbidity of this procedure, however, is not negligible. The aim of this study was to evaluate the feasibility of minimally invasive detection of the sentinel inguinofemoral lymph node (SILN) and to investigate whether the histopathology of the SILNs is representative of that of the other non-SILNs. **Methods:** Patients with early-stage squamous cell cancer of the vulva, planned for resection of the primary tumor and uni- or bilateral inguinofemoral lymphadenectomy, were eligible for the study. Technetium-99m-labeled nanocolloid was injected intradermally at four locations around the tumor the day before operation. Images were recorded immediately and after 2.5 hr using a gamma camera. SILN locations were marked on the overlying groin skin. The next day, during general anesthesia, blue patent dye was injected intradermally at the same locations around the tumor. During the operation SILNs were identified at the place indicated using a handheld gamma-detection probe. It was noted if SILNs were found by the probe, by blue dye or by both techniques. After resection of the SILNs, a standard inguinofemoral lymphadenectomy was performed. The results of histopathology of the SILNs were compared with those of the non-SILNs. **Results:** The procedure was well tolerated by 10 of 11 patients. One patient, initially agreeing to participate, refused the injection of tracer because of fear of pain. In all 10 patients, identification of the SILNs was successful. The mean time for identification was 11 min. Identification of SILNs was primarily performed using the hand probe in all patients, whereas in 10 of 18 removed SILNs afferent lymph channels were also blue stained (56%). In 8 patients, pathologic examination showed no metastatic disease in both SILNs and non-SILNs, whereas in 2 patients metastases in the SILNs (one and two metastatic lymph nodes, respectively), as well as in other non-SILNs, were found. **Conclusion:** This study shows that identification of SILNs in squamous cell cancer of the vulva is feasible with preoperatively administered ^{99m}Tc-labeled nanocolloid. Intraoperatively administered blue dye was only useful for confirmation of identification with nanocolloid. To date, no false-negative SILNs have been found, but expansion of the study is necessary to determine the possible clinical application of this new diagnostic technique.

Key Words: lymphoscintigraphy; sentinel lymph node; vulvar cancer

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Vulvar cancer accounts for 3%–4% of all female malignancies and mainly affects older women. For many years the standard treatment for squamous cell cancer (SCC) of the vulva has been radical vulvectomy and en bloc bilateral inguinofemoral lymphadenectomy (*1*). Although overall survival figures for patients with early-stage disease are excellent with radical surgery, the morbity associated with this procedure is major. Primary wound healing is often difficult, and postoperative wound breakdown and infection commonly occur (up to 85%), frequently prolonging hospitalization (*2*). Over the long term, inguinofemoral lymphadenectomy is often followed by chronic lymphedema and cellulitis of the legs (30%–70%) (*2–4*). Various modifications have been used to decrease short- and long-term complications. Changes in treatment policy have been wide local excision or hemivulvectomy instead of radical vulvectomy and uni- or bilateral inguinofemoral lymphadenectomy via separate incisions instead of en bloc lymphadenectomy (*5,6*).

There is general agreement that inguinofemoral lymphadenectomy is indicated for patients who have clinically suspicious or pathologically proven metastatic nodes. In early-stage SCC of the vulva, however, inguinofemoral lymph node metastases occur in only 10%–26% of patients (*7*). As the large majority of these patients do not have nodal metastases and are unlikely to benefit from an inguinofemoral lymphadenectomy, the performance of this operation as a routine procedure is questionable. Preferably a noninvasive or minimally invasive method should be available to identify those patients who have inguinofemoral lymph node metastases. To date, no reliable noninvasive diagnostic methods have been reported. Clinical palpation and sonography are not capable of discriminating between metastastic and normal lymph nodes (*8*). No data exist for CT or MRI. A preliminary study using PET showed only moderate success in diagnosing metastastic inguinofemoral metastases in SCC of the vulva (*9*). In other malignancies, such as cutaneous melanoma and breast cancer, the minimally invasive technique of the sentinel lymph node (SLN) has been described. The SLN is defined as the first node in the lymphatic basin that receives primary lymphatic flow. The intention of identification and subsequent pathologic examination of the SLN is to provide full nodal staging with decreasing morbidity (*10–12*). In this study, the feasibility of identification of the SLN in the inguinofemoral region by perilesional injection of ^{99m}Tc-labeled nanocolloid and blue dye was investigated.

MATERIALS AND METHODS

Patients

Patients with primary SCC of the vulva were referred to Groningen University Hospital for treatment. Patients with T_1 or T_2 tumors [International Federation of Obstetrics and Gynecology staging; tumors <2 cm and >2 cm, respectively, not encroaching in urethra, vagina or anus with clinically negative inguinofemoral lymph nodes (*7*)] were eligible for the study. Approval for the study was given by the medical ethical committee of the Groningen University Hospital. Before entrance into the study, written informed consent was obtained from each patient.

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TABLE 1
Patient Characteristics

Patient	Tumor stage	Tumor site	Tumor diameter (cm)	Invasion depth (mm)	Lymphadenectomy
1	T_1N_0	Left labium maius	1.6	9.0	Bilateral
2	T_2N_0	Perineum	3.0	8.0	Bilateral
3	T_2N_0	Clitoris	3.4	4.0	Bilateral
4	T_2N_0	Clitoris	3.5	15.0	Bilateral
5	T_1N_0	Left labium maius	1.2	1.6	Bilateral
6	T_1N_0	Left labium maius	2.0	6.0	Unilateral
7	T_1N_0	Right labium maius	2.0	3.0	Bilateral
8	T_2N_1	Clitoris	2.5	3.0	Bilateral
9	T_2N_1	Clitoris	2.5	6.0	Bilateral
10	T_1N_0	Right labium maius	1.5	4.0	Unilateral

Sentinel Node Procedure

The day before operation, 0.2 ml 60-MBq ^{99m}Tc-labeled nanocolloid (Solco Nuclear, Birsfelden, Switzerland) with a particle size of <80 nm was injected circumferentially intradermally at four locations (each 0.05 ml 15 MBq ^{99m}Tc-labeled nanocolloid) around the primary tumor. Anterior images were obtained using a single-head gamma camera with a low-energy, high-resolution collimator. Immediately after injection, dynamic imaging was started with 30-sec frames during 30 min. An anterior and lateral static image was obtained after 2.5 hr. To facilitate interpretation transmission, scanning was performed simultaneously using the 120-keV gamma rays of a ^{57}Co flood source. The first appearing persistent focal accumulation was considered to be a sentinel node. Sometimes a direct connection from the injection site to the sentinel inguinofemoral lymph node (SILN) was visible. The site of the SILN was marked with a pencil on the overlying skin. On the following day, after induction of anesthesia, ~0.5–1.0 ml Patente blue-V (2.5% in aqueous solution containing 0.6% sodium chloride and 0.05% disodium hydrogen phosphate; Laboratoire Guerbet, Aulney-Sous-Bois, France) was injected intradermally at the same four locations around the primary tumor ~5–10 min before the surgical procedure. During operation, a handheld gamma-ray detection probe (Neoprobe, Neoprobe Corp., Dublin, OH) was used to confirm that lymphoscintigraphy marked the area of greatest activity in the groin. A small skin incision was made at the marked spot, and a sentinel node excision biopsy was performed using the handheld gamma-ray detector and dissection of blue-stained lymph vessels. Time spent on identification of the SILNs was measured. After removal of the SILN(s), the biopsy bed was re-examined for radioactivity, and if radioactivity was detected in >10% of the first excised lymph node, the dissection was continued in search of additional SILNs. The removed SILNs were sent to the pathologist separately. Subsequently, a routine inguinofemoral lymphadenectomy was performed in all patients.

Operative Procedure

Treatment consisted of excision of the primary tumor (wide local excision, hemivulvectomy or radical vulvectomy) in combination with uni- or bilateral inguinofemoral lymphadenectomy by separate incisions. The choice of surgery depended on the characteristics of the tumor (size, uni- or multifocality, medial or lateral). Bilateral inguinofemoral lymphadenectomy was always performed, except in patients with unilateral lesions. A unilateral tumor was defined as a lesion that did not cross the midline with the medial margin of the tumor more than 1 cm from midline structures (*13*). Separate incisions for lymphadenectomy were made parallel to the inguinal ligament, and then the node-bearing fat pad was removed. The extent of the dissection was the inguinal ligament cephalad, the adductor longus muscle medially and the sartorius muscle inferolaterally. After opening the cribiform fascia, all node-bearing fatty tissue medial from the femoral vein was removed as well. The vulvar excision varied with the location of the lesion. A radical wide local excision of the primary tumor with at least a margin of 1 cm normal skin around the lesion and to a depth of at least 1 cm below the lesion was performed.

Histopathology

The pathologist received SILNs and lymphadenectomy specimens separately. From the lymphadenectomy specimens, all lymph nodes were studied individually. One section per 0.5-cm diameter of the node was cut for hematoxylin and eosin staining.

RESULTS

Patient Characteristics

Between July 1996 and February 1997, 15 consecutive eligible patients were asked to participate in this pilot study. Four patients refused. The other 11 patients were planned for SILN procedure. One patient refused further participation just before the injection of the ^{99m}Tc-labeled nanocolloid because of fear of pain. Therefore, 10 evaluable patients were left. The median age of these patients was 68 yr (age range 46–85 yr). All patients had clinically negative inguinofemoral lymph nodes and no signs of distant metastases.

Patient characteristics are summarized in Table 1. In 2 of 5 patients with a T_1 tumor the lesion was regarded as unilateral. Five patients had a T_2 tumor, of which none was regarded as unilateral.

Operative Procedures

In 2 patients with a unilateral T_1 tumor, wide local excision with unilateral inguinofemoral lymphadenectomy was performed, whereas in 3 patients with a central T_1 tumor and in all patients with a T_2 tumor, wide local excision with bilateral lymphadenectomy was performed. Therefore, 10 patients underwent 18 inguinofemoral lymphadenectomies.

Sentinel Lymph Node Identification by Lymphoscintigraphy

Administration of ^{99m}Tc-labeled nanocolloid was well tolerated by all 10 patients. Table 1 lists the results of lymphoscintigraphy. In 3 patients with T_1 tumors (two lateral and one central, respectively), one unilateral SILN was found, and in 2 patients with T_1 tumors (one central and one lateral), two unilateral SILNs were found. In 4 patients with central T_2 tumors, one or two SILNs were present in each groin. One patient with a T_2 lesion on the left side of the clitoris had two SILNs in the left groin. In no patients were contralateral SILNs

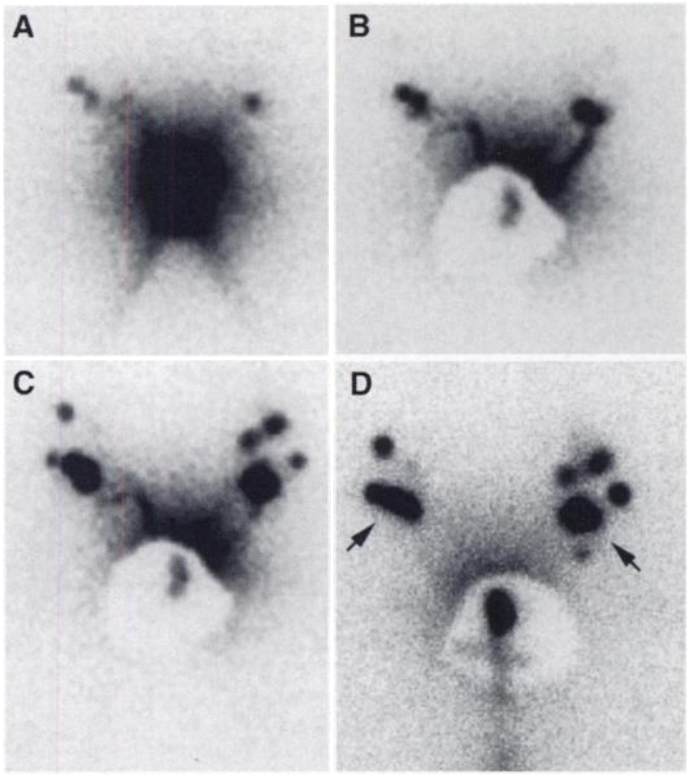

FIGURE 1. Lymphoscintigram of Patient 4 with a T_2 tumor on the right side of the clitoris. Graphs were selected from a dynamic series. A and B were recorded 5 and 10 min after administration of tracer, without (A) and with (B) shielding of the primary tumor. On the right side two sentinel nodes are shown and on the left side one sentinel node is shown. C and D were recorded 30 and 150 min after administration of tracer. Overflow to nonsentinel nodes is clearly visible on both sides. The arrows in D point to the nodes that were regarded as sentinel nodes.

recorded without ipsilateral SILNs. All SILNs were visualized by lymphoscintigraphy within 5 min after injection of ^{99m}Tc-labeled nanocolloid. Figure 1 shows an example of lymphoscintigraphy of a patient with a T_2 lesion on the left side of the clitoris.

Sentinel Lymph Node Identification at Operation

All sentinel node procedures were performed by the same physician. Table 2 lists the results of lymphoscintigraphy compared to the findings at operation. All SILNs, as shown by lymphoscintigraphy after 5 min, were identified at operation using the hand probe. In Patient 8, lymphoscintigraphy showed 2 SILNs with high radioactivity on the left side (also the side of the lesion on the clitoris) within 5 min and another 2 possible SILNs with low activity on the contralateral right side after 30 min. These 2 contralateral SILNs could not be identified at operation. Ten of 18 SILNs, as identified by radioactivity, were also found by blue-stained lymph vessels (56%). No SILNs were found guided by blue-stained lymph vessels only. The mean time to identification was 11 min (range 5–30 min). No complications associated with the SILN procedure were observed.

TABLE 3
Number of Metastases in Sentinel and Nonsentinel Nodes

	Left		Right	
Patient	SILNs*	Non-SILNs†	SILNs*	Non-SILNs†
1	0 (1)	0 (10)		0 (9)
2	0 (1)	0 (9)	0 (1)	0 (8)
3	0 (1)	0 (9)	0 (1)	0 (6)
4	0 (1)	0 (8)	0 (2)	0 (11)
5	0 (2)	0 (9)		0 (12)
6	0 (1)	0 (7)		
7		0 (12)	0 (1)	0 (9)
8	2 (2)	1 (9)		0 (9)
9	1 (2)	1 (11)		0 (7)
10			0 (2)	0 (2)

*The total number of SILNs is in parentheses.
†The total number of Non-SILNs is in parentheses.
SILNs = sentinel inguinofemoral lymph nodes.

Histopathology

Table 3 summarizes the results of histopathologic examination. In total, 18 inguinofemoral lymphadenectomies were performed (9 left; 9 right). The number of removed lymph nodes ranged from 4 to 13 per inguinofemoral region, with a mean of 10 lymph nodes. In 8 patients with no metastasis in the SILNs, all other nodes were also negative for tumor. Two patients had SILNs with metastasis at histopathologic examination. One patient with 2 SILNs with metastasis also had metastatic disease in 1 other node (of 9), whereas 1 patient had

TABLE 2
Results of Identification and Number of Sentinel Inguinofemoral Lymph Nodes (SILNs) Detected with Lymphoscintigraphy, Neoprobe and Blue Dye: Time for Identification at Operation

	SILNs identified by								Time for identification at operation (min)	
	Lymphoscintigraphy		Neoprobe		Blue dye		Operation			
Patient	L	R	L	R	L	R	L	R	L	R
1	1		1				1		30	
2	1	1	1	1	1	1	1	1	5	7
3	1	1	1	1	1		1	1	10	21
4	1	2	1	2	1	2	1	2	15	10/10
5	2		2		1		2		5/8	
6	1		1		1		1		10	
7		1		1		1		1		13
8	2	2	2				2		10/10	
9	2		2		1		2		5/5	
10		2		2				2		7/7
Total	11	9	11	7	6	4	11	7		

L = left; R = right.

1 SILN with and 1 had SILN without metastatic disease but also had metastastic disease in another node (of 11).

DISCUSSION

This study shows that SILN identification using ^{99m}Tc-labeled nanocolloid, administered perilesionally on the day before operation, is feasible in patients with vulvar cancer. A relatively large number of eligible patients (4 of 15) refused to participate in the study, which illustrates the anticipated burden (pain) by vulvar cancer patients of tracers administered without general anesthesia. However, the majority (10 of 11) of patients that consented to participate tolerated the procedure well.

SILN identification in patients with vulvar cancer has to date only been described by Levenback et al. (*14*). In 1994, they showed the feasibility of intraoperative lymphatic mapping by perilesional administration of Isosulfan blue in a series of 9 patients (*14*). In a second article, their experience with the same technique in an extended series (n = 21) was reported (*15*). A major advantage of the technique used by Levenback et al. compared to ours is that the whole procedure is performed intraoperatively under general anesthesia, thereby omitting the burden of painful perilesional injections. However, much larger datasets on techniques for identification of sentinel lymph nodes are available from other malignancies, such as cutaneous melanoma and breast cancer. These studies show that the combination of intraoperatively administered blue dye together with preoperatively performed lymphoscintigraphy with intraoperative gamma probe detection is superior to intraoperative blue dye alone with regard to the percentage of identified SLNs (*11,12*). Kapteijn et al. (*16*) recently compared the two techniques in patients with cutaneous melanoma and found identification of sentinel nodes with the combination technique in 99.5% but with blue dye alone in only 84%. Although our study primarily concerns the feasibility of the technique and numbers are still small, a similar trend in vulvar cancer can be found when our results are compared to those reported by Levenback et al. (*14,15*). Our combined technique facilitated identification of the SILN in 100% of patients and in 94% of dissected groins [Levenback et al. (*15*), 86% and 66%, respectively].

Stehman et al. (*17*) reported on the management of patients with T_1 SCC vulvar cancer with only superficial inguinofemoral lymphadenectomy and identified an unexpectedly high percentage of groin recurrences (7.4%). A possible explanation for this high number of groin failures may be that the SLNs were not in the removed superficial compartment or in an unexpectedly extreme lateral or medial position, as was occasionally observed in the series of intraoperative mapping by Levenback et al. (*15*). Until now, we did not observe SILNs in such positions, but it is quite clear that preoperative lymphoscintigraphy will greatly facilitate identification of such SILNs.

Another argument (especially in vulvar cancer, which is a rare gynecologic tumor) for application of the combined technique may be that, in general, identification of SLNs by the combined technique (with the intraoperative gamma probe as a guide during dissection) is technically easier to perform than identification with blue dye only. It is the experience of several authors that only after 20–30 patients does the blue dye technique become more effective in their hands [Koops HS, *personal observation*; Morton et al. (*10*)]. In a comment on this issue, McCarthy et al. (*18*) stated clearly that identification of a node as the sentinel node should preferably be based on both increased radioactivity and blue staining of the node and its afferent lymphatics.

Finally, a last important argument in favor of the combined technique in vulvar cancer is that preoperative lymphoscintigraphy showing ipsilateral SILNs will allow dissection of only one groin once the technique has been proven to be effective.

Recent studies in cutaneous melanomas and breast cancer show very low frequencies of false-negative SLNs (0%–4%) (*11,12*). In 21 vulvar cancer patients reported by Levenback et al. (*14,15*) and in 10 patients from our study, no false-negative SILNs have been found to date. We fully agree with Levenback et al. (*14,15*) that, although the results are encouraging, more data must be collected before meaningful statistical conclusions can be reached with regard to the predictive value of a negative SILN for the status of the entire groin. When our study is extended to 34 patients and no or only one false-negative SILN is found, the sensitivity of a negative SILN in our series can be calculated to be higher than 90% within 95% confidence intervals. For patients with a T_1 vulvar cancer with an estimated frequency of inguinofemoral lymph node metastases of 10%, application of the SILN technique with a sensitivity of more than 90% implies that, in 100 patients, a maximum of 1 metastasis will be missed. At present, we certainly do not advocate application of the SILN technique by individual institutions that do not participate in trials in which the safety of this new approach is evaluated.

To determine whether metastatic disease was present in the SLNs, routine histopathologic procedures were used. From studies of other malignancies (especially melanomas), it is now clear that by application of immunohistochemistry and/or PCR micrometastases can be detected that are not found by routine histopathology (*19*). At present, it is unresolved if application of similar techniques for detection of micrometastases of SCC will have clinical significance in the management of patients with vulvar cancer.

CONCLUSION

Identification of the SILN in patients with SCC of the vulva with ^{99m}Tc-labeled nanocolloid and blue dye is feasible and superior to SILN identification by blue dye only. To date, the histopathology of SILNs appears to be representative for the other lymph nodes. It is hoped that further development of this technique will spare patients with a negative SILN full inguinofemoral lymph node dissection and, thus, associated short- and long-term morbidity.

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Fluorine-18-FDG Detection of Laryngeal Cancer Postradiotherapy Using Dual-Head Coincidence Imaging

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The aim of this study was to investigate whether, in patients treated for laryngeal carcinoma, a differentiation was possible between local recurrence or local control using a dual-head SPECT camera with PET capability. **Methods:** Eleven male patients (age range 51–71 yr; mean age 62 yr) who had previously undergone radiotherapy for laryngeal carcinoma were studied using 5 mCi (185 MBq) ^{18}F-fluorodeoxyglucose (FDG). The mean interval between initial treatment and ^{18}F-FDG PET was 21.9 mo (range 6–65 mo). Six patients had histologically proven local recurrence and five patients showed local control clinically. The mean follow-up in the local control group was 5.2 mo. **Results:** Fluorine-18-FDG PET scans were positive in all six local relapses. Histopathological examination of the laryngectomy specimen revealed a mean tumor size of 2.6 cm (range 1.4–5.0 cm). In one patient, false-positive uptake was seen in an inflammatory lymph node. Fluorine-18-FDG PET scans were negative in all five patients with local control. **Conclusion:** It is possible to differentiate between local recurrence and local control in patients previously treated for laryngeal carcinoma with a dual-head SPECT scanner with PET capability.

Key Words: PET; SPECT; laryngeal carcinoma; local recurrence; fluorine-18-fluorodeoxyglucose

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With an incidence of about 600 cases per year, laryngeal carcinomas represent 2% of the newly diagnosed cancers in the Netherlands (*1*). Modern treatment of these tumors consists of high-dose radiation therapy, either as a single therapy or in combination with surgical intervention. These procedures may cause a variety of acute and late post-treatment changes such as edema, fibrosis and scarring (*2*). In these patients, recurrent disease, which can occur in as many as 50% of patients with advanced primary disease (*3*), may be difficult to distinguish from post-treatment reactions. CT or MRI frequently do not accurately predict disease recurrence (*4,5*). In addition, post-treatment biopsies may reveal false-negative results and should be performed with caution, since the capacity of the irradiated tissue to recover is diminished.

Tumor imaging with ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) has yielded promising results for detecting a variety of primary tumors (*6–9*). The mechanism of FDG uptake is well documented and is based on the increased glycolysis that is associated with malignancy compared with most normal tissues (*10,11*). However, because of the high cost and limited availability of dedicated PET scanners, alternative methods of imaging the 511-keV photons of positron emitters have been sought. With a dual-head SPECT scanner with a coincidence module, PET scanning with FDG is possible.

The aim of this study was to investigate if a differentiation could be made in patients being treated for laryngeal carcinoma between malignant and benign lesions using a dual-head SPECT scanner with a coincidence module.

MATERIALS AND METHODS

Patients

Eleven male patients (mean age 62 yr) who had previously undergone radiotherapy for laryngeal carcinoma underwent ^{18}F-FDG PET. Six patients had proven recurrent disease with a mean interval of 20 mo (range 6–65 mo) after initial treatment. Direct laryngoscopy and biopsy under general anesthesia were performed 13 times in these patients with an interval between biopsy and ^{18}F-FDG PET of at least 4 wk. Three out of six patients underwent a contrast-enhanced CT study (two glottic and one supraglottic laryngeal carcinoma). Five patients without clinical suspicion of tumor recurrence were used as control subjects. In this group, the average time from the completion of the initial treatment was 23.8 mo (range 12–45 mo). Mean follow-up after ^{18}F-FDG PET was 5.2 mo. Diabetes mellitus was an exclusion criterion. All six patients with proven recurrent disease underwent laryngectomy. Age, primary site, primary tumor, regional nodes and metastasis (TNM)-stage, previous treatment, time since last treatment and pathologic findings of the laryngectomy specimens are summarized in Table 1.

Imaging Study

All patients were studied after fasting overnight. Preceding the PET studies, the patients' plasma glucose levels were measured with a standard clinical test. At 60 min after the intravenous administration of 5 mCi (185 MBq) ^{18}F-FDG imaging of the neck was performed using a dual-head SPECT scanner with a coincidence module (Vertex-MCD; ADAC, Milpitas, CA). The spatial resolution of 5 mm of this scanner is comparable with a dedicated PET scanner. Acquisition involved a rotation of each detector 180° with 32 stops at 45 sec per stop. PET images were generated using

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