



Respective Roles of Thyroglobulin, Radioiodine Imaging, and Positron Emission Tomography in the Assessment of Thyroid Cancer

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Depending on the iodine supply of an area, the incidence of thyroid cancer ranges between 4 and 12/100,000 per year. To detect thyroid cancer in an early stage, the assessment of thyroid nodules includes ultrasonography, ultrasonography-guided fine-needle aspiration biopsy, and conventional scintigraphic methods using ^{99m}Tc -pertechnetate, ^{99m}Tc -sestamibi or -tetrofosmin, and ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) in selected cases. After treatment of thyroid cancer, a consequent follow-up is necessary over a period of several years. For following up low-risk patients, recombinant thyroid-stimulating hormone-stimulated thyroglobulin and ultrasonography is sufficient in most cases. After total thyroidectomy and radioiodine ablation therapy, thyroid-stimulating hormone-stimulated thyroglobulin should be below the detection limit (eg, <0.5 ng/mL, R: 70-130). An increase of thyroglobulin over time is suspicious for recurrent or metastatic disease. Especially in high-risk patients, aside from the use of ultrasonography for the detection of local recurrence and cervical lymph node metastases, nuclear medicine methods such as radioiodine imaging and FDG-PET are the methods of choice for localizing metastatic disease. Radioiodine imaging detects well-differentiated recurrences and metastases with a high specificity but only moderate sensitivity. The sensitivity of radioiodine imaging depends on the activity administered. Therefore a low activity diagnostic ^{131}I whole-body scan (74-185 MBq) has a lower detection rate than a high activity post-therapy scan (3700-7400 MBq). In patients with low or dedifferentiated thyroid cancer and after several courses of radioiodine therapy caused by metastatic disease, iodine negative metastases may develop. In these cases, despite clearly elevated levels of thyroglobulin, radioiodine imaging is negative or demonstrates only faint iodine uptake. The method of choice to image these iodine negative metastases is FDG-PET. In recent years the combination of PET and computed tomography has been introduced. The fusion of the metabolic and morphologic information was able to increase the diagnostic accuracy, reduces pitfalls and changes therapeutic strategies in a reasonable number of patients.

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Thyroid cancer (TC) is a rare disease. Incidence within a population increases with age and varies considerably in different countries, with the highest incidence rates being reported in areas with a normal or even an high iodine supply. Of interest, in former iodine-deficient countries that now have iodine-sufficient areas, mainly because of salt iodination, the incidence of TC has increased.¹ In countries with

sufficient iodine supply or only moderate iodine deficiency, papillary TC is the dominant histopathologic form and accounts for more than 70%. In general, the prognosis of TC is very good. However, it depends on histopathology and tumor stage at first diagnosis. Therefore, it is important to diagnose TC at a very early stage. Clinical symptoms are rare, especially in areas with sufficient iodine supply. In most cases, TC is detected by chance via small ultrasonographically hypoechogenic thyroid nodules. For an early diagnosis of TC, ultrasonography-guided fine-needle aspiration biopsy (US-FNAB) of these small nodules is most important. Of course, scintigraphy using ^{99m}Tc -pertechnetate or nonspecific tumor-searching tracers such as ^{99m}Tc -sestamibi or ^{99m}Tc -tetrofosmin may be helpful in selected cases. The value

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of ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) currently is under consideration in the assessment of thyroid nodules.

After total thyroidectomy and radioiodine remnant ablation, the follow-up of TC includes an armamentarium of various tests. Recombinant thyroid-stimulating hormone (rhTSH)-stimulated thyroglobulin (Tg) is the basis of following up TC. Several imaging methods are available today for the localization of recurrences and metastases, eg, ultrasonography for the detection of local recurrences and cervical lymph node metastases, ^{131}I whole-body scintigraphy (^{131}I WBS) for iodine-positive metastases, and FDG-PET or PET/computed tomography (CT) for iodine-negative metastases. In this article, after a short overview about the preoperative assessment of thyroid nodules, the roles of Tg, radioiodine imaging, and FDG-PET in the follow up of TC will be described.

Preoperative Assessment of Thyroid Nodules

TC is mostly diagnosed by chance. The most appropriate method to differentiate between benign and malignant changes of small thyroid nodules is US and US-FNAB, particularly for the diagnosis of papillary TC.²⁻⁶ In contrast, preoperative diagnosis of follicular TC remains difficult. In case of unclear cytology or the cytological diagnosis of “follicular proliferation,” multitracer imaging may play a role.⁷ Because of the low diagnostic specificity of functional imaging for TC, such as $^{99\text{m}}\text{Tc}$ -pertechnetate or ^{123}I scintigraphy, other radio-nuclides and radiotracers with affinity to malignant lesions such as ^{201}Tl chloride, $^{99\text{m}}\text{Tc}$ -sestamibi, or $^{99\text{m}}\text{Tc}$ -tetrofosmin have been used to assess the probability of malignancy of thyroid nodules.⁸⁻¹² Neither ^{201}Tl nor cationic complexes such as $^{99\text{m}}\text{Tc}$ -sestamibi or $^{99\text{m}}\text{Tc}$ -tetrofosmin are able to clearly differentiate between benign and malignant sonographically hypoechoic, scintigraphically hypofunctioning thyroid nodules. Nevertheless, the results of such studies can be important for therapy planning, especially in case of nondiagnostic US-FNAB or multinodular goiter.

Recently, the value of FDG-PET was investigated not only for the follow up of TC but also for the preoperative assessment of hypoechoic and/or hypofunctioning thyroid nodules.¹³⁻¹⁷ Joensuu and coworkers found clearly increased FDG-PET uptake only in one patient with anaplastic thyroid cancer and one with oxyphilic thyroid carcinoma of 5 patients investigated.¹³ Three patients with papillary TC demonstrated only moderate FDG uptake. In contrast to this study, Uematsu and coworkers¹⁵ demonstrated in 11 patients that all malignant nodules could be separated from benign ones using a standardized uptake value (SUV) cutoff of 5 and time-activity curves.¹⁵ Mitchell and coworkers¹⁶ used FNAB and FDG-PET/CT before surgery in 31 patients with 48 lesions. Fifteen of 48 lesions were malignant, and 33 were benign. Nine of 15 malignant lesions demonstrated FDG uptake (sensitivity, 60%). Thirty of 33 benign lesions were FDG negative (specificity, 91%). The authors conclude that FDG-



Figure 1 FDG-PET/CT for preoperative assessment of a thyroid nodule with undetermined cytology. The hypofunctioning nodule demonstrated clear FDG uptake. Histology after thyroidectomy revealed follicular TC.

PET/CT with a high negative predictive value (NPV) of 83% for malignancy may be a useful tool in the evaluation of thyroid nodules with indeterminate FNAB.¹⁶ Our own experience in 43 patients with hypoechoic and/or hypofunctioning thyroid nodules (11 papillary TC, 3 follicular TC, 2 anaplastic carcinomas, 11 microfollicular adenomas, 10 oxyphilic adenomas and 2 macrofollicular adenomas, 4 regressive goiters) demonstrated that all patients with TC and oxyphilic adenomas had increased FDG uptake (Fig. 1).¹⁸ Using an SUV threshold of 2 for differentiating benign from malignant nodules, sensitivity, specificity, and NPVs were 100%, 63%, and 100% respectively. In a subgroup of 24 patients with cytological diagnosis “follicular proliferation,” FDG-PET was able to differentiate between follicular adenoma and carcinoma. From these studies it may be concluded, that tumor-seeking agents, including FDG-PET, are not able to 100% differentiate benign from malignant thyroid nodules. However, in case of nondiagnostic cytology or a cytological diagnosis “follicular proliferation,” FDG-PET seems the method of choice to decide whether surgery or a wait and watch strategy should be recommended.

Follow-Up of TC After Treatment

With the exception of papillary microcarcinoma (pT1a according to TNM 2003 supplement) total thyroidectomy, followed by radioiodine therapy and TSH suppressive thyroid hormone therapy, is the standard treatment of differentiated TC, at least in Europe. Radioiodine therapy is not only indicated to destroy any microscopic cells remaining after surgery, but also to increase the specificity of the tumor marker Tg. TSH-stimulated Tg should be negative (<0.5 ng/mL) after surgery and radioiodine therapy. In these cases each, the increase of Tg over time means recurrent or metastatic disease. To localize recurrence and metastases us of the neck, radioiodine imaging and FDG-PET (or better, PET/CT) as whole-body modalities for distant metastases are the methods of choice.

Tg as Tumor Marker for TC

Today, serum Tg as tumor marker for TC, measured by sensitive immunoradiometric assays, is found to be extremely valuable during follow-up of TC.¹⁹⁻²² After total thyroidectomy and radioiodine remnant ablation, Tg should be undetectable in case of complete remission. However, it has to be mentioned that the value of Tg is only reliable if Tg antibodies are undetectable and recovery of Tg is within the normal range, ie, between 70% and 130%. In the presence of Tg antibodies,²³ serum Tg can be falsely lowered if determined by an immunoradiometric assay. It has also to be mentioned that if Tg antibodies are measurable more than 1 year after surgery and radioiodine therapy, persistent thyroid tissue or recurrence has to be suspected. In case of increasing Tg, recurrence, lymph node metastases or distant metastases are likely. The serum Tg level under TSH elevation (after withdrawal of thyroid hormone over the course of 4-6 weeks or after recombinant intramuscular injection of TSH) is thought to be the most reliable indicator for persistent or recurrent disease.²⁴ However, there are some case reports with proven recurrent or metastatic disease but negative Tg.²⁵ Sometimes, it may be the result of oxyphilic subtype of DTC, in which ¹³¹I WBS also is negative and metastatic disease can only be detected by nonspecific tracers.²⁶ With the exception of these rare cases, Tg is an excellent tumor marker for following up TC. The sensitivity of Tg, however, depends on the TSH serum level and is much greater under TSH elevation >30 mU/L (98%) than under TSH-suppressive thyroid hormone therapy (80%). A negative TSH-stimulated Tg level is highly predictive for absence of disease. In 2 retrospective studies it could be demonstrated that, in case of negative TSH-stimulated Tg, routine diagnostic ¹³¹I WBS does not add any further information.^{27,28} For the most sensitive (TSH stimulated) measurement of Tg, withdrawal of thyroid hormone over a period of 4 to 6 weeks and hypothyroidism is now substituted by intramuscular injection of recombinant TSH: 2 times 0.9 mg rhTSH intramuscularly on 2 subsequent days.²⁹ With the introduction of rhTSH, it has been shown that the sensitivity of rhTSH-stimulated Tg is as high as after withdrawal of thyroid hormone after several weeks, although the values are somewhat lower.³⁰ Against this background, the question arises whether rhTSH-stimulated Tg alone is sufficient for the follow up of patients with TC. In 2 studies, it was concluded that, in general, TSH-stimulated Tg alone is not sufficient by itself to screen unselected patients.³¹⁻³³ However, a recently published consensus paper that differentiates between high- and low-risk patients concludes that, for low-risk patients in whom initial work up after treatment has demonstrated complete remission (negative radioiodine scanning, negative ultrasonography and TSH-stimulated Tg), ultrasonography of the neck and rhTSH-stimulated Tg is sufficient for further follow-up.³⁴ Ultrasensitive Tg assays measuring Tg levels as low as 0.07 ng/mL are now available. Whether these “supersensitive assays” add clinical information in the follow-up of TC or even substitute TSH stimulation of Tg is not clear up to now but unlikely.



Figure 2 Sonographically detected lymph node metastases after surgery and radioiodine remnant ablation of papillary thyroid cancer pT3N1Mx.

Ultrasonography

Because US is not the main topic of this article, only an overview is given. Like Tg and bTSH, US should be performed at any visit in the follow up of TC. It is the most sensitive method to detect local recurrence and lymph node metastases at an early stage, although it is not specific (Fig. 2).³⁵ In case of pathologic US findings in neck, US-FNAB should be performed. For low-risk patients, a combination of rhTSH-stimulated Tg and US may be sufficient in most cases, as described previously.³⁴ For high-risk patients or in case of increasing TSH-stimulated Tg, the whole armamentarium of nuclear medicine has to be used to detect metastases as early as possible, including especially radioiodine scanning and FDG-PET (or better, PET/CT).

Radioiodine Scanning in the Follow-up of DTC

Up to now, in most thyroid cancer centers an ¹³¹I or ¹²³I WBS was performed periodically over several years for following up of TC, either under thyroid hormone withdrawal or under rhTSH. However, it could be demonstrated that 2 negative ¹³¹I WBS within 1 year in combination with negative TSH-stimulated Tg have a very good predictive value for the absence of recurrent or metastatic disease.³⁶⁻³⁹ However, in a study by Robbins and coworkers,³¹ 13% of patients with negative TSH-stimulated Tg (<2 ng/mL) had evidence of disease. In this light, the question of a correct value for negative Tg arises. In our center after surgery and radioiodine therapy, a TSH-stimulated Tg less than 0.5 ng/mL is mandatory to consider a patient free of disease.⁴⁰ In a consensus paper by Schlumberger and coworkers³⁴ for low-risk patients, rhTSH-stimulated Tg and ultrasonography were described to be sufficient for following up TC. This is not true for high-risk patients, and many centers still perform radioiodine scanning in connection with TSH-stimulated serum Tg. Radioiodine (¹³¹I/¹²³I) is the most specific radionuclide to

image recurrences or distant metastases of TC. However, sensitivity is rather low and depends on the activity administered.⁴¹

There are several preconditions that have to be fulfilled before WBS using radioiodine can be performed.⁴² To image patients with radioiodine in the follow-up of TC, TSH-suppressive L-thyroxine therapy has to be withdrawn for several weeks to achieve a TSH of at least 30 mU/L, and a low iodine diet is recommended. Several authors claim that a TSH greater than 50 mU/L is required before radioiodine should be administered.^{43,44} This level, however leads to transient hypothyroidism, which causes several complaints and may stimulate the growth of tumor cells. Because of this fact, today, many thyroid centers use rhTSH (0.9 mg twice intramuscularly) instead of withdrawing L-thyroxine to achieve elevated TSH. During this procedure, the patient remains in euthyroidism, without symptoms of hypothyroidism. Before the administration of radioiodine, contamination caused by contrast media or iodine containing drugs has to be excluded. In this context, the determination of urinary iodine excretion is recommended. If these preconditions are fulfilled, ¹³¹I (mostly given orally) or ¹²³I (injected intravenously) is administered. The advantage of ¹²³I includes a favorable γ -energy of 159 keV with good-quality gamma camera imaging and the lack of β -energy and, therefore, the lack of thyroid stunning.³⁹ However, ¹²³I is expensive and not available for everyday use. The short half life of 13 hours also may be a disadvantage in imaging recurrent and metastatic disease. Furthermore, the ¹²³I activity administered and the time of acquisition are still a matter of debate. Concerning the diagnostic accuracy, ¹²³I is not superior to ¹³¹I scanning, and post-therapy ¹³¹I WBS sometimes demonstrates more lesions when compared with a diagnostic ¹²³I WBS. Therefore, most thyroid centers continue to use ¹³¹I for diagnostic WBS.

After surgery and radioiodine remnant ablation therapy, the first ¹³¹I WBS is performed as post-therapy ¹³¹I WBS 5 to 7 days after radioiodine therapy. In the majority of patients, this post-therapy ¹³¹I WBS demonstrates some activity in the remnants, depending on the completeness of surgery and nonspecific uptake in the salivary glands, the stomach, intestine, and urinary bladder (Fig. 3). Sometimes in this post-therapeutic administration of ¹³¹I WBS, additional metastases are found that were not known before (Fig. 4). Four to six months after radioiodine remnant ablation, the first diagnostic ¹³¹I WBS is performed to evaluate the success of treatment. At this time M-staging of the disease is possible. Under endogenous (4- to 6-week withdrawal of thyroid hormones) or exogenous TSH elevation (0.9 mg rhTSH administered intramuscularly on 2 subsequent days), ¹³¹I is administered orally and WBS is performed 48 to 72 hours later. In most studies 185 MBq ¹³¹I are recommended. Because of the possibility of thyroid stunning, in case of elevated Tg and planned radioiodine treatment, the administered activity for the diagnostic scan should not exceed 74 MBq. The specificity of ¹³¹I WBS ranges between 96% and 100%.⁴⁵⁻⁴⁷ Beside physiological uptake, some pitfalls of false-positive ¹³¹I WBS results have to be considered.⁴⁸ The sensitivity of ¹³¹I WBS is low and depends on the administered activity, and the type of histology. Ac-

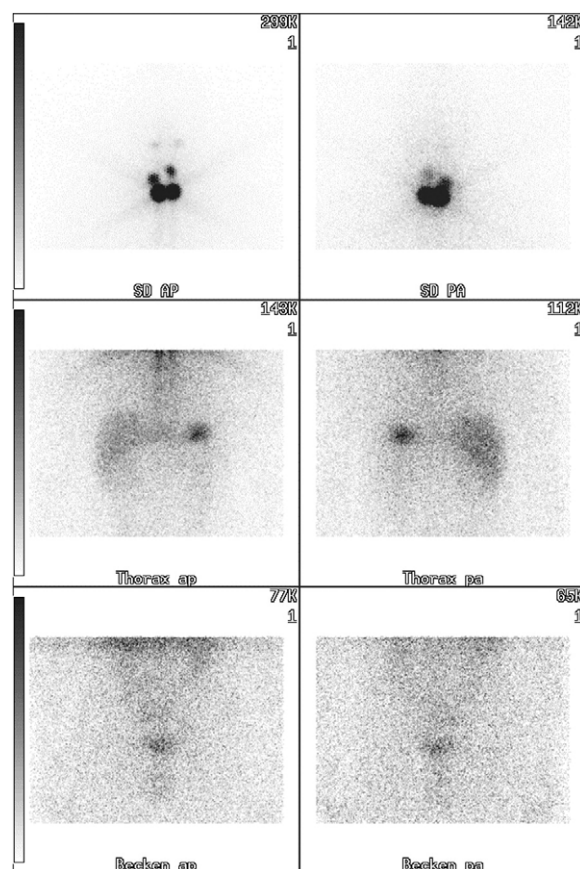


Figure 3 pt-¹³¹I WBS with remnant and lymph node metastases after incomplete surgery; nonspecific ¹³¹I uptake in the salivary glands (top), liver/stomach/gut (middle), and urinary bladder (bottom).

ording to the literature, the sensitivity of a diagnostic ¹³¹I WBS ranges between 45% and 75% and is somewhat lower for papillary compared with follicular TC.^{44-46,49,50}

Because of the low impact of diagnostic ¹³¹I WBS in low-risk patients with negative TSH-stimulated Tg and the low sensitivity of a low-dose diagnostic ¹³¹I WBS, with the possibility of stunning, in case of elevated Tg, some doubts regarding the value of this procedure have surfaced in recent years.^{51,52} For the future, it may be recommended that, in low-risk patients, rhTSH-stimulated Tg is sufficient and in patients with elevated Tg with evidence of disease high-dose radioiodine therapy and a post-therapy scan should be performed.^{53,54} The place for a low-dose diagnostic ¹³¹I WBS may remain in the follow-up of high-risk patients. However, the role of a low-dose radioiodine scan in this patients group also is increasingly a matter of discussion. There are several studies demonstrating that radioiodine therapy as the result of increasing Tg has a therapeutic effect and that post-therapy ¹³¹I WBS has a higher sensitivity compared with a low-activity diagnostic scan.^{47,55} Therefore, some centers prefer, in case of elevated or increasing Tg, radioiodine therapy and post-therapy ¹³¹I WBS only without a diagnostic scan (Fig. 5). An additional problem arises if TSH-stimulated Tg is elevated or increases over time (eg, >3 ng/mL) and the diagnostic ¹³¹I is negative. The reason for this false-negative ¹³¹I WBS may be

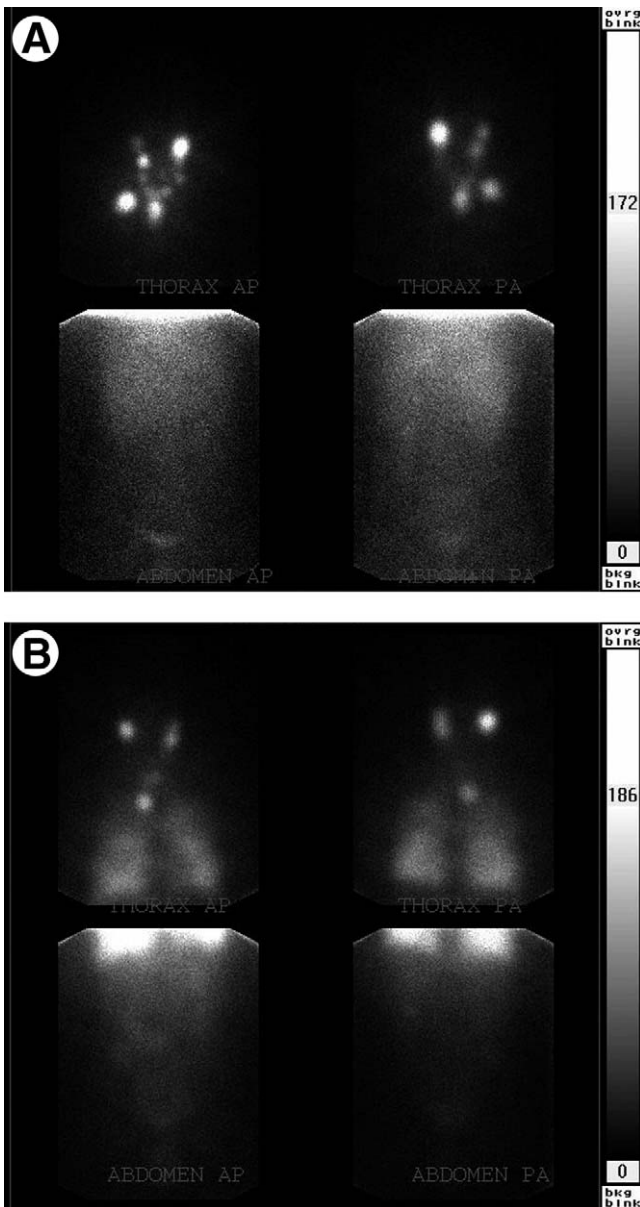


Figure 4 pt-¹³¹I WBS with remnant and lymph node metastases after incomplete surgery (A) After additional surgery, a second pt-¹³¹I WBS demonstrated iodine positive lung metastases not seen in the first pt-¹³¹I WBS (B).

an insufficient TSH stimulation, iodine contamination, small tumor volume, or iodine negative metastases.^{39,56} If the first and second reason is excluded, the patient should be scheduled for FDG-PET (PET/CT without contrast media) and should be treated with radioiodine followed by a post-therapy ¹³¹I WBS.

FDG-PET in the Follow-Up of TC

FDG-PET is well established in diagnosis, follow-up, and treatment monitoring of several malignancies. In less or dedifferentiated thyroid cancer, recurrences or metastases may lose the ability to concentrate iodine. ¹³¹I WBS may therefore be negative or is not able to demonstrate the complete extent

of the disease. In previous years, ²⁰¹Tl, ^{99m}Tc-tetrofosmin, and ^{99m}Tc-sestamibi were introduced to image iodine-negative metastases from TC. Because of the limited spatial resolution of single-photon emitters, as many as 25% of recurrences and metastases were missed by these methods. To overcome this problem, FDG-PET was introduced in the follow-up of patients with TC.⁵⁷ A comparative study in patients with dedifferentiated TC between post-therapy ¹³¹I WBS, ^{99m}Tc-tetrofosmin WBS, and FDG-PET demonstrated the superiority of PET for detecting iodine-negative metastases.⁵⁸ Whereas the role of FDG-PET in the preoperative assessment of thyroid nodules is not yet fully evaluated, the use in the follow-up of TC belongs to the 1a indications for ¹⁸F-FDG-PET in oncology.⁵⁹ In most centers, FDG-PET is performed after the patient has fasted overnight and presents with a blood glucose less than 140 mg/dL. Sixty to ninety minutes after the intravenous injection of 200 to 500 MBq, FDG (depending on the PET system, 2D, 3D acquisition) emission scanning is started. Transmission scanning is performed either before FDG injection (cold transmission) or after FDG injection (hot transmission).

Recently, CT transmission is available in combined PET/CT machines, where morphology and metabolism are

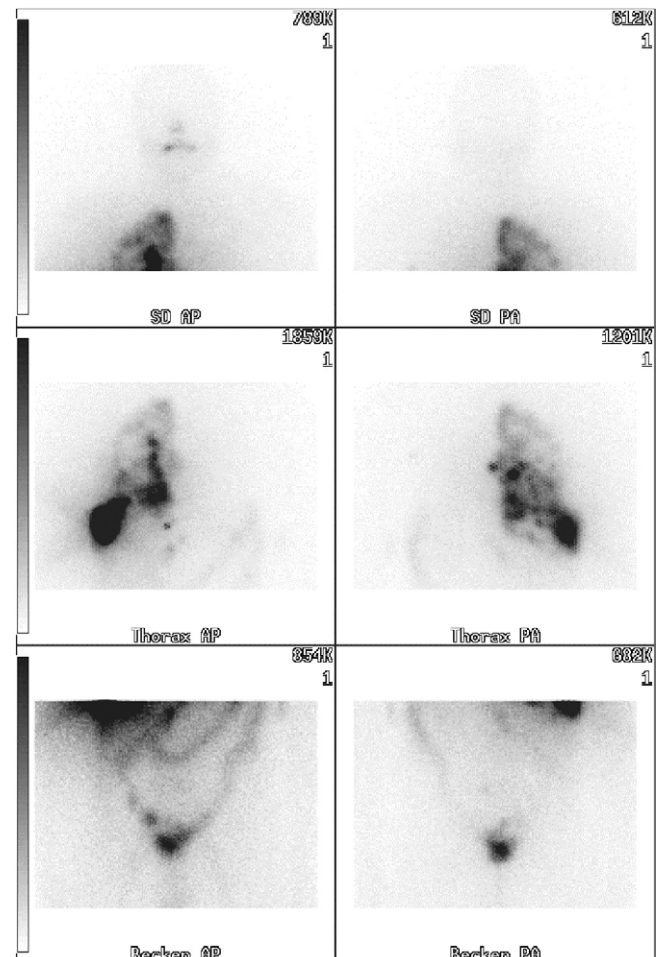


Figure 5 Multiple ¹³¹I-positive lesion in the post-therapy WBS performed because of increasing serum Tg. Head/neck/thorax (top); lung/abdomen (middle); abdomen/pelvis (bottom).

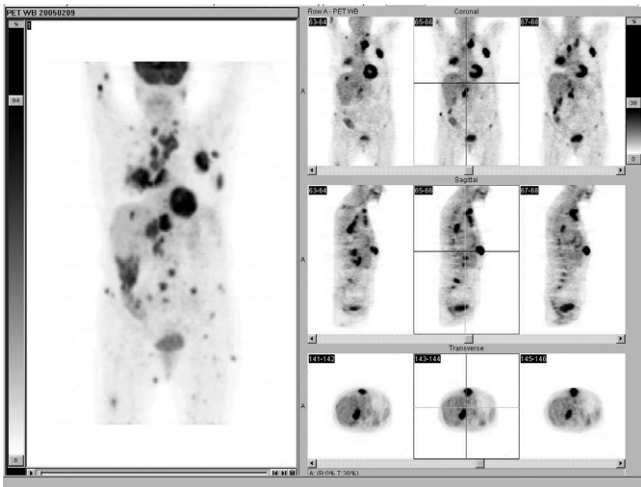


Figure 6 FDG-PET in a patient with strongly elevated Tg but negative post-therapy ^{131}I WBS. Multiple FDG-PET-positive metastases are shown, without the possibility of an exact localization.

imaged during one investigation. Already, the first investigations using FDG-PET in the follow-up of patients with TC demonstrated that FDG uptake represents less-differentiated thyroid cancer cells or dedifferentiation of cells. Feine and coworkers⁶⁰ investigated 41 patients, comparing FDG-PET and ^{131}I WBS in the follow-up of differentiated TC. Combined imaging resulted in a sensitivity of approximately 95% in detecting recurrences and metastases. Alternating uptake (^{131}I -negative but FDG-positive or ^{131}I -positive and FDG-

negative) was found in 90% of patients. The authors concluded that, beside an increase of sensitivity using ^{131}I WBS and FDG-PET, that the uptake of FDG seemed to be an indicator for poor differentiation.

In a multicenter trial, Grunwald and coworkers⁶¹ compared the sensitivity and specificity of FDG-PET, ^{131}I WBS, and $^{99\text{m}}\text{Tc}$ -sestamibi/ ^{201}Tl WBS. The sensitivity of FDG-PET, ^{131}I WBS, and $^{99\text{m}}\text{Tc}$ -sestamibi/ ^{201}Tl was 75%, 50%, and 53% and specificity 90%, 99%, and 92%, respectively. The sensitivity of FDG-PET increased to 85% in a subgroup of patients with ^{131}I -negative WBS. Similar results were obtained by our group comparing FDG-PET, $^{99\text{m}}\text{Tc}$ -tetrofosmin WBS, and post-therapy ^{131}I WBS in the follow-up of TC in 35 patients.^{58,62} In a retrospective study by Conti and coworkers,⁶³ 30 patients with TC, 24 with rising or increased levels of Tg, and 6 with elevated calcitonin underwent FDG-PET. In all 24 patients with papillary/follicular TC and in all 6 patients with medullary cancer, the authors were able to detect recurrent or metastatic diseases using FDG-PET, which was confirmed directly by surgery or indirectly by changes or persistence of laboratory findings in 17 of 24 patients with papillary/follicular and 4 of 6 patients with medullary TC.

From a group of 32 TC patients with elevated thyroglobulin but negative ^{131}I WBS, Altenvoerde and coworkers⁶⁴ performed FDG-PET in 12 patients. In 6 of 12 patients, FDG-PET was positive. The Tg level was much higher in FDG-PET-positive patients (23-277 ng/mL) compared with FDG-PET-negative patients (1.5-17 ng/mL). According to the German consensus conference in 2000, the sensitivity and

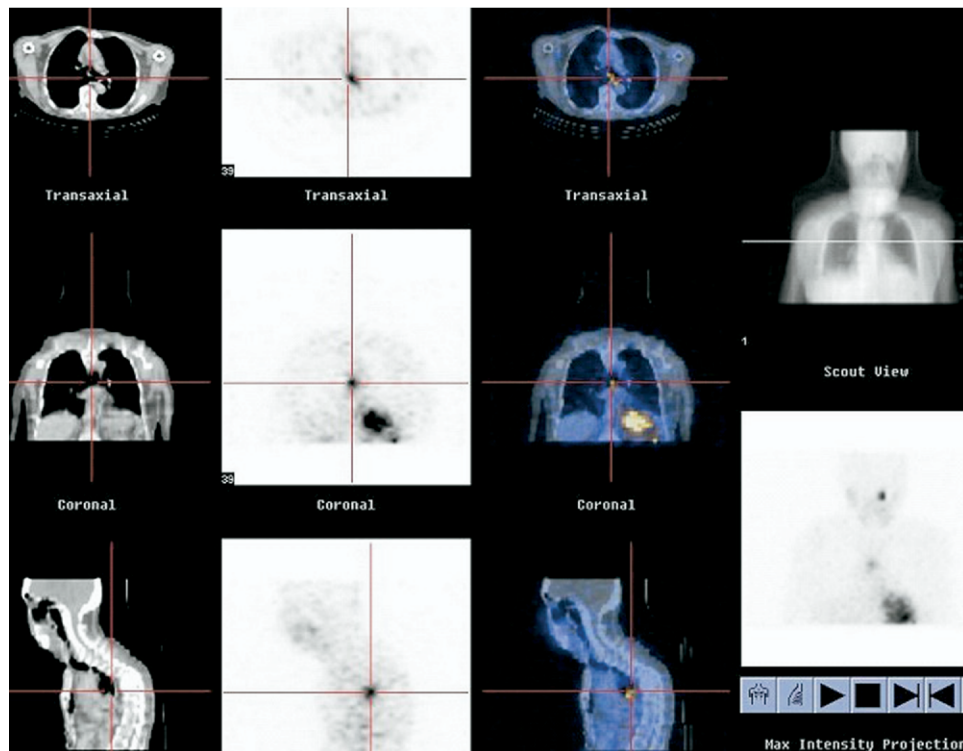


Figure 7 The use of SPECT/CT improves the localization of a thoracic iodine-positive lesion. From the ^{131}I WBS, it was not clear whether the lesion was located in the spine or in the posterior mediastinum. SPECT/CT clearly demonstrated a mediastinal soft-tissue metastasis. (Courtesy of Prof. Dr. A. Kurtaran, AKH Vienna.)

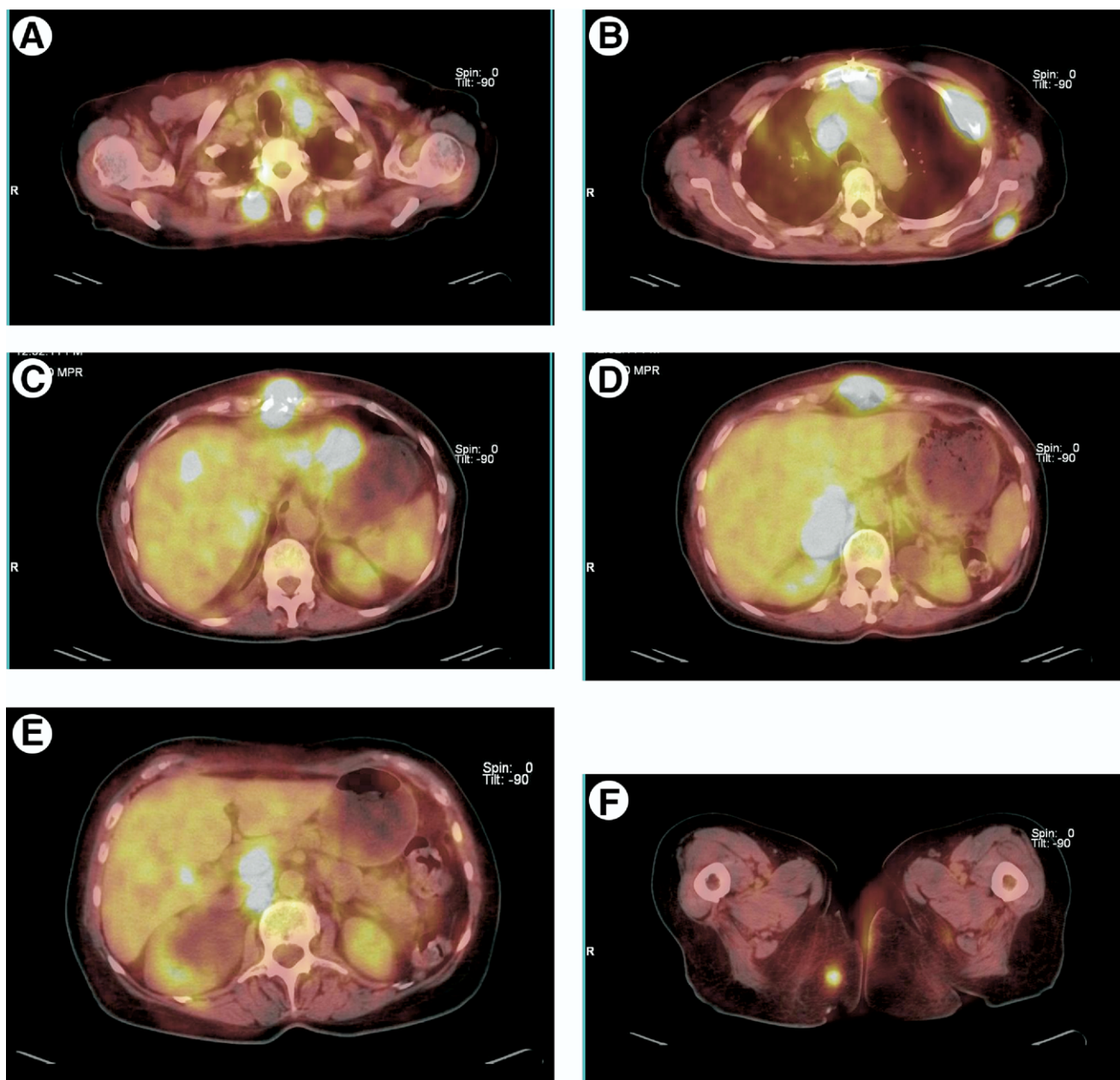


Figure 8 (A-F) Transaxial slices. PET/CT of the patient in Figure 5. Exact localization of the lesions as lymph node, lung, bone, liver adrenal gland, and soft-tissue metastases as the result of image fusion.

specificity of FDG-PET in detecting ^{131}I -negative metastases in case of elevated thyroglobulin was 85% to 94% and 90% to 95%, respectively.⁵⁹ In a study by Schluter and coworkers,⁶⁵ a total of 118 FDG-PET studies in 64 patients with increased levels of TG but negative ^{131}I WBS with respect to change of therapy due to outcome of FDG-PET was performed. Forty-four patients had a positive FDG-PET (34 true positive, 7 false positive, 2 with secondary malignancy, 1 nonevaluable), and 20 patients had negative PET scans (5 true negative, 15 false negative). According to these results, the positive predictive value was 83%, the NPV only 25%. Treatment strategy was changed in 19 of 34 patients with true-positive PET scans. It has to be mentioned that the sensitivity of FDG-PET is greater under endogenous or exogenous TSH stimula-

tion.^{66,67} Moog and coworkers⁶⁶ investigated 10 TC patients under TSH suppressive L-thyroxine therapy and after withdrawal of L-thyroxine (TSH > 22 mU/L). They could demonstrate that the tumor-to-background ratio increased after TSH stimulation from 3.85 to 5.84 ($P < 0.001$). Similar preliminary results with an increase of the standardized uptake value from 1.3 to 4.4 are reported by Petrich et al⁶⁷ using recombinant TSH before FDG-PET.

In our own series, we performed 221 FDG-PET studies in 161 patients with TC. From the 122 follow-up patients, 96 had differentiated (33 papillary and 63 follicular), 15 medullary, and 11 anaplastic histology of thyroid cancer.⁶² Within the 96 patients with differentiated histology, in Tg was elevated in 81 patients and, in a group of 15 patients,

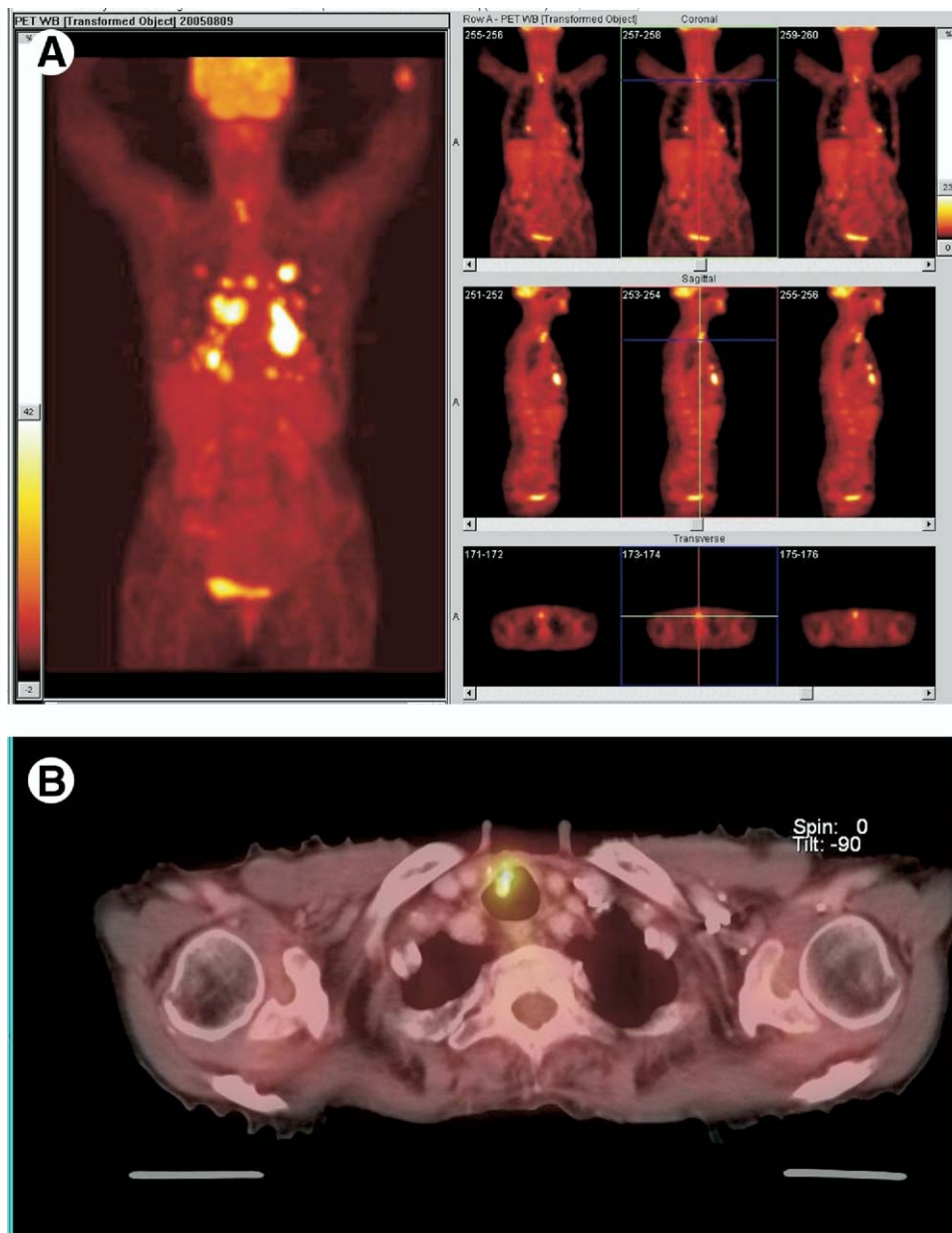


Figure 9 FDG-PET (MIP and slices) demonstrates multiple lung and bone metastases and an additional activity in the right cervical region (A). PET/CT demonstrated intraluminal tracheal metastases which was responsible for the clinical symptom of hemoptysis. Palliative treatment: laser resection of the intraluminal tumor (B).

FDG-PET was performed because of positive Tg-polymerase chain reaction but normal serum Tg. The sensitivity of FDG-PET for the detection of metastases in case of elevated Tg for all patients was 77%, in case of elevated Tg but negative ^{131}I WBS it increased to 88%. FDG-PET is a valuable tool to detect recurrences and metastases of TC, especially in case of elevated Tg and negative ^{131}I WBS (Fig. 6).

Recent Developments

For imaging purposes, the future is directed toward better anatomical localization of metabolic active tumor lesions using different radionuclides and tracers such as $^{131}\text{I}/^{123}\text{I}/^{124}\text{I}$, FDG, or somatostatin receptor analogs.

^{131}I SPECT/CT

Post-therapy ^{131}I WBS combined with SPECT/CT will be the imaging modality of choice after radioiodine therapy (Fig. 7). In a study by Ruf and coworkers,⁶⁸ 25 patients with inconclusive findings in planar scanning after ablative radioiodine therapy underwent SPECT/CT of the questionable region. Forty-one lesions were observed in the 25 patients. In 17 of 41 lesions, uptake was caused by remnant tissue, 13 of 41 lesions were caused by metastases, and 11 of 41 lesions were not malignant. In 44% of lesions, improved anatomical assignment was observed by using SPECT/CT. In patients with strongly elevated Tg but only faint uptake in the ^{131}I WBS, a combination with FDG-PET/CT is able to demonstrate the complete extent of the disease with exact anatomical local-

ization of iodine positive and iodine negative lesions.⁶⁹ This is not only important for exact staging and restaging of metastasizing TC but also for an individual based multimodality treatment of these patients, including radioiodine treatment, surgery, external radiotherapy, retinoic acid, and somatostatin receptor therapy (Fig. 8).

FDG-PET/CT

Although the introduction of PET has improved the follow-up of TC, the localization of FDG-positive lesions is sometimes difficult using PET alone. This difficulty is also true for other malignancies, especially for head and neck cancer. As early as 1998, Beyer et al⁷⁰ developed a combination of a (partial ring) PET and CT machine and published their first 100 clinical cases in the year 2000. This prototype of PET/CT was followed by the development of second- and third-generation machines, which ended up with a combination of high-end PET (LSO/GSO crystals) and high-end CT (64 slices) scanners. PET/CT is available from all major companies of PET imaging equipment. All these systems have in common that a commercial CT scanner is in conjunction with a commercial PET scanner. This construction creates the possibility of gathering data from CT and PET and fusing them without having manually to register the images. A standard acquisition protocol was created for daily routine in clinical environment. First, a topogram is taken by CT. After defining the region of interest to scan, a diagnostic or low-dose CT is recorded. Finally, data from the PET are collected. The whole procedure takes from 15 to 45 minutes depending on the scanner, the activity injected, and the crystal. The CT and PET images can be merged automatically. Because of the time difference between CT and PET, movement artifacts can occur and must be taken into consideration. The construction of the PET/CT device implies also the possibility of reconstruction errors caused by the low physical integration.

Nevertheless, the number of PET/CT devices ordered worldwide is increasing compared with the number of stand-alone PET. With the introduction of this new modality of imaging in oncology, the question arises whether PET/CT is superior to PET and CT alone and, if so, can PET/CT affect patients management better than both modalities alone. PET can assess, for example, metabolism, protein synthesis, gene expression, and tissue hypoxia depending on the tracer used; whereas CT mainly reflects anatomy and, to some degree, perfusion.⁷¹ In the combined modality, CT data are used for calculation of attenuation correction as well as for anatomic information. The question of whether CT should be performed as contrast-enhanced diagnostic CT or only as “low-dose CT” for anatomic correlation is not yet answered. There is also some debate on the use of oral contrast media for PET/CT imaging.⁷² First clinical results of PET/CT in oncology reveal that in general there is much better reliability of the results and higher diagnostic confidence using PET/CT compared with each modality alone.^{71,73,74} Because of the fusion of anatomy and metabolism, the exact localization of hypermetabolic spots (eg, osseous versus soft-tissue lesions) on the

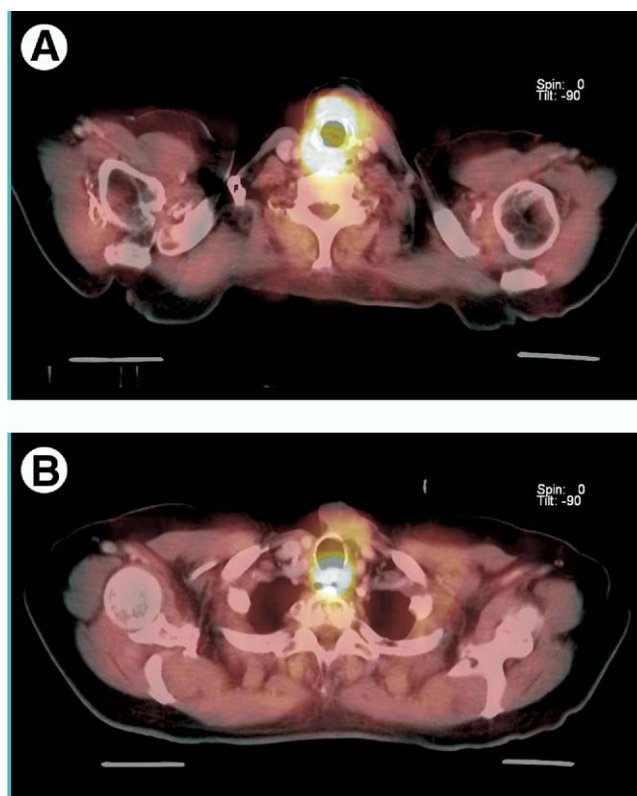


Figure 10 After surgery and three administrations of high-dose radioiodine therapy, ¹³¹I-negative/FDG-PET-positive metastases are present, caused by papillary thyroid cancer pT4N1M1 (the last pt-¹³¹I WBS was completely negative despite elevated Tg). Local recurrence before and retrotracheal (A) and local recurrence infiltrating the esophagus (B).

one hand and metabolic evaluation of anatomic lesions on the other hand can be achieved.

The combination of PET and CT is most helpful in the cervical and abdominal region. Our own experience in the first 2000 patients using PET/CT for staging and restaging of various tumors confirms that there is additional information in about 45% of patients and change of management in 15% of patients. In addition it could be demonstrated that pitfalls of PET (eg, normal structures in the head and neck region that are positive on FDG-PET, bowel activity, muscle activity, excretion via the kidneys and subsequent sometimes-circumscribed ureter activity, brown fat tissue etc.) can be reduced using PET/CT. An overview about the hardware, software, and current clinical role of PET/CT was published from a symposium “PET/CT: the holy grail of multi-modality imaging?”⁷⁵⁻⁷⁷ Only few data are available about PET/CT in patients with TC. In a study by Ong and coworkers,⁷⁸ 17 patients with elevated Tg but negative ¹³¹I WBS underwent FDG-PET/CT. Fifteen of 17 PET/CT scans revealed lesions consistent with metastases, giving a sensitivity of 88.2%. Unfortunately, this paper work little information on the additional value of PET/CT compared with PET alone. Nahas and coworkers⁷⁹ investigated the impact of PET/CT on the management of 33 patients with recurrent papillary thyroid cancer. In 67% of patients PET/CT supplied additional informa-

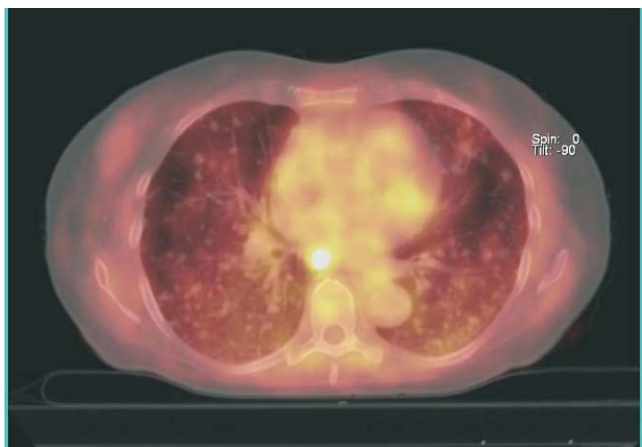


Figure 11 After surgery and eight administrations of high-dose radioiodine therapy, ^{131}I -negative/FDG-PET-positive metastases are present, caused by follicular thyroid cancer pT4NxM1 (the last pt- ^{131}I WBS was completely negative despite elevated Tg). CT demonstrates multiple lung metastases. Only the larger ones show a distinct FDG uptake.

tion that altered or confirmed the management plan. Twenty of the 33 patients underwent surgery, with an accuracy for PET/CT of 70% in comparing the results with histopathology. The sensitivity of PET/CT in identifying recurrent diseases was found to be 66% with a specificity of 100% and a positive predictive value of 100%. When PET/CT is positive, it is a powerful tool for predicting exact location of recurrent papillary TC. The authors conclude that PET/CT is most useful in the detection and management of recurrent papillary TC in patients with average Tg levels greater than 10 ng/mL.

In our own first series, 33 FDG-PET/CT investigations in 27 patients with TC were performed (follicular TC: 14; papillary TC: 10; medullary TC: 2, anaplastic TC: 1). In 6 of the 27 patients, a second investigation was performed after treatment (eg, surgery, external radiotherapy). Most of them had shown iodine-negative metastases or increased Tg levels but negative post-therapy ^{131}I WBS. In 67% of patients, PET/CT was more accurate than PET or CT alone, and in 17% PET/CT results led to change of treatment (eg, change of radiation field, radiation instead of surgery, surgery because of exact localization of recurrence, heparin treatment in stead of surgery because of tumor thrombosis) (Figs. 9-12).⁶⁹ First results of PET/CT in patients with TC provide increased diagnostic confidence, reduction of equivocal results in PET and CT alone, additional information in approximately 45%, and a change of therapeutic management in approximately 10% to 15% of patients.

Dosimetry Using ^{124}I PET or PET/CT

Because dosimetry is very cumbersome for radioiodine therapy, especially in metastatic disease, new ways to adapt the administered activity to the individual patients need are desirable. One possibility is the use of ^{124}I PET in combination with a 3-dimensional-internal dosimetry software. Sgouros and coworkers⁸⁰ performed 3 to 4 ^{124}I PET imaging studies

over a period of 7 days to calculate the individual dose for patients with metastatic thyroid cancer. Mean absorbed dose values and absorbed dose for individual tumors ranged from 1.2 to 540 Gy and 0.3 to 4000 Gy, respectively. In a report by Freudenberg and coworkers⁸¹ about the value of ^{124}I PET/CT in staging patients with TC, the authors concluded that ^{124}I PET/CT imaging is a promising technique to improve treatment planning in thyroid cancer. In the future, ^{124}I PET/CT may play an important role for individual dosimetry in patients with metastatic thyroid cancer.

In conclusion, rhTSH-stimulated Tg and US are the basis for following up patients with TC and are probably sufficient for use in low-risk patients. For all other patients, additional

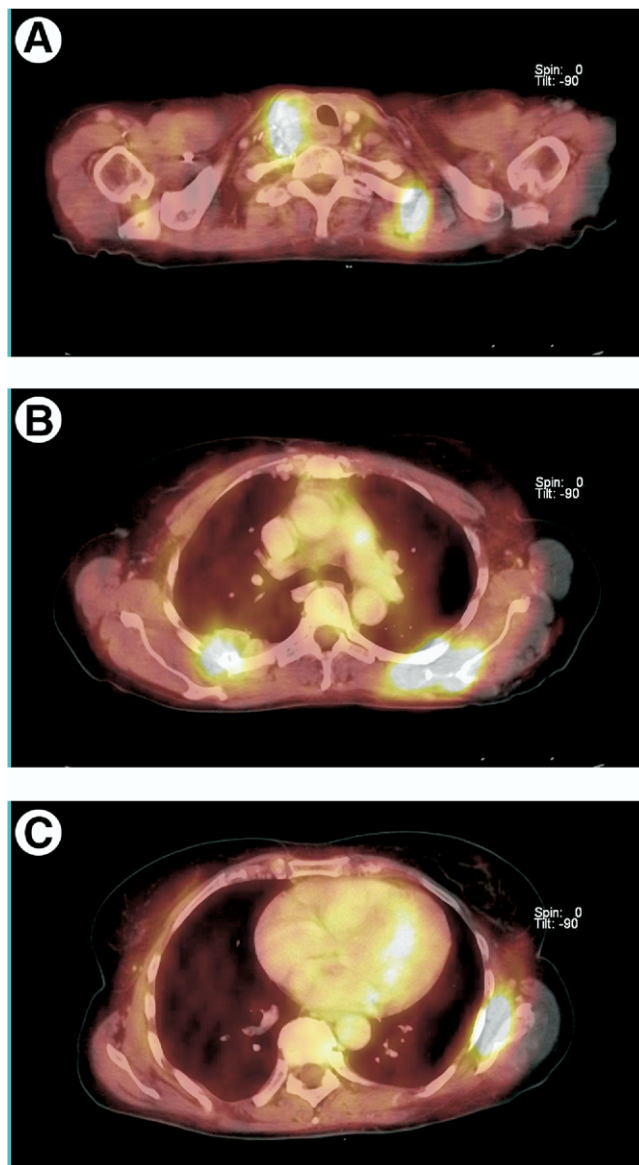


Figure 12 After surgery and seven administrations of high-dose radioiodine therapy, PET/CT shows ^{131}I -negative/FDG-PET-positive metastases caused by follicular thyroid cancer insular variant pT2NxMx (the last pt- ^{131}I WBS was completely negative despite elevated Tg). Local recurrence and multiple bone and soft tissue metastases are shown in images A-C.

^{131}I WBS (SPECT/CT), mostly in the form of post-therapy scan, and FDG-PET/CT are necessary to demonstrate the real extent of the disease. ^{124}I PET/CT may play a major role in the future for treatment planning with radioiodine. This whole armamentarium of modern nuclear medicine investigations may be necessary for individual treatment planning of high-risk patients with elevated serum Tg.⁸²

References

- Lind P, Kumnig G, Heinisch M, et al: Iodine supplementation in Austria: methods and results. *Thyroid* 12:903-907, 2002
- Rojewski MT, Gharib H: Nodular thyroid disease. Evaluation and management. *N Engl J Med* 313:428-436, 1985
- Watters DAK, Ahuya AT, Evans RM, et al: Role of ultrasound in the management of thyroid nodules. *Am J Surg* 164:654-657, 1992
- Gharib H, Goellner JR, Johnson DA: Fine needle aspiration cytology of the thyroid: a 12 year experience with 11,000 biopsies. *Clin Lab Med* 13:699-709, 1993
- Carmeci C, Jeffrey RB, McDougall IR, et al: Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. *Thyroid* 8:283-289, 1998
- Mikosch P, Gallowitsch HJ, Kresnik E, et al: Value of ultrasound-guided fine needle aspiration biopsy of thyroid nodules in an endemic goitre area. *Eur J Nucl Med* 27:62-69, 2002
- Lind P: Multi-tracer imaging of thyroid nodules: is there a role in the preoperative assessment of nodular goiter? *Eur J Nucl Med* 26:795-797, 1999(editorial)
- El-Desouki M: Tl 201 thyroid imaging in differentiating benign from malignant thyroid nodules. *Clin Nucl Med* 16:225-230, 1991
- Sundran FX, Mack P: Evaluation of thyroid nodules for malignancy using T-99m-sestamibi. *Nucl Med Commun* 16:687-693, 1995
- Mezosi E, Bajnok I, Gyory F, et al: The role of Tc-99m methoxyisobutyl-isonitrile (MIBI) scintigraphy in the differential diagnosis of cold thyroid nodules. *Eur J Nucl Med* 26:798-803, 1999
- Kresnik E, Gallowitsch HJ, Mikosch P, et al: Tc-99m MIBI scintigraphy of thyroid nodules in an endemic goiter area. *J Nucl Med* 38:62-65, 1997
- Kresnik E, Gallowitsch HJ, Mikosch P, et al: Evaluation of thyroid nodules with Tc-99m tetrofosmin dual phase scintigraphy. *Eur J Nucl Med* 24:716-721, 1997
- Joensuu H, Ahonen A, Klemi PJ: 18F-fluorodeoxyglucose imaging in the preoperative diagnosis of thyroid malignancy. *Eur J Nucl Med* 13:502-506, 1988
- Bloom AD, Adler LP, Shuck JM: Determination of malignancy of thyroid nodules with positron emission tomography. *Surgery* 114:728-734, 1993
- Uematsu H, Sadato N, Ohtsubo T, et al: Fluorine-18-fluorodeoxyglucose PET versus thallium-201 scintigraphy evaluation of thyroid tumors. *J Nucl Med* 39:453-459, 1998
- Mitchell JC, Grant F, Evenson AR, et al: Preoperative evaluation of thyroid nodules with (18)FDG-PET/CT. *Surgery* 138:1166-1175, 2005
- Sasaki M, Ichiya Y, Kuwabara Y, et al: An evaluation of FDG PET in the detection and differentiation of thyroid tumors. *Nucl Med Commun* 18:957-963, 1997
- Kresnik E, Gallowitsch HJ, Mikosch P, et al: Fluorine-18-fluorodeoxyglucose positron emission tomography in the preoperative assessment of thyroid nodules in an endemic goiter area. *Surgery* 133:294-299, 2003
- Van Herle AJ, Uller RP: Elevated thyroglobulin: a marker of metastases in differentiated thyroid carcinoma. *J Clin Invest* 56:272-276, 1975
- Pacini F, Lari R, Mazzeo S, et al: Diagnostic value of single serum thyroglobulin determination on and off thyroid suppressive therapy in the follow-up of patients with differentiated thyroid cancer. *Clin Endocrinol (Oxf)* 23:405-408, 1985
- Ronga G, Fiorentino A, Paserio E, et al: Can iodine-131 whole body scan be replaced by thyroglobulin measurement in the postsurgical follow up of differentiated thyroid carcinoma? *J Nucl Med* 31:1766-1771, 1990
- Ozata M, Suzuki S, Miyamoto T, et al: Serum thyroglobulin in the follow-up of patients with treated differentiated thyroid cancer. *J Clin Endocrinol Metab* 79:98-105, 1994
- Spencer CA, Takeuchi M, Kazarosyan M, et al: Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 83:1121-1127, 1998
- Pacini F: Follow up of differentiated thyroid cancer. *Eur J Nucl Med* :S492-S496, 2002 (suppl 2)
- Westbury C, Vini L, Fisher C, et al: Recurrent differentiated thyroid cancer without elevation of thyroglobulin. *Thyroid* 10:171-176, 2000
- Harder W, Lind P, Molnar M, et al: Thallium-201 uptake with negative I-131 scintigraphy and serum thyroglobulin in metastatic oxyphilic papillary thyroid carcinoma. *J Nucl Med* 39:236-238, 1997
- Cailaux AF, Baudin E, Travagli JP, et al: Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? *J Clin Endocrinol Metab* 85:175-178, 2000
- Pacini F, Cappezone M, Elisei R, et al: Diagnostic 131-iodine whole body scan may be avoided in thyroid cancer patients who have undetectable stimulated thyroglobulin levels after initial treatment. *J Clin Endocrinol Metab* 87:1492-1495, 2002
- Kohlfuerst S, Igerc I, Lind P: Recombinant thyrotropin is helpful in the follow up and I-131 therapy of patients with thyroid cancer: a report of the results and benefits using recombinant human thyrotropin in clinical routine. *Thyroid* 15:371-376, 2005
- Pacini F, Lippi F: Clinical experience with recombinant human thyroid-stimulating hormone (rhTSH): serum thyroglobulin measurement. *J Endocrinol Invest* 22:25-29, 1999 (suppl)
- Robbins RJ, Chon JT, Fleisher M, et al: Is the serum thyroglobulin response to recombinant human thyrotropin sufficient, by itself, to monitor for residual thyroid carcinoma. *J Clin Endocrinol Metab* 87:3242-3247, 2002
- Wartofsky L: Management of low-risk well differentiated thyroid cancer based only on thyroglobulin measurement after recombinant human thyrotropin. *Thyroid* 12:583-590, 2002
- Menzel C, Zaplatnikov K, Diel M, et al: The influence of functional imaging in differentiated thyroid cancer. *Nucl Med Commun* 25:239-243, 2004
- Schlumberger M, Berg G, Cohen O, et al: Follow-up of low risk patients with differentiated thyroid carcinoma: a European perspective. *Eur J Endocrinol* 150:105-112, 2004
- Haber RS: Role of ultrasonography in the diagnosis and management of thyroid cancer. *Endocr Pract* 6:396-400, 2000
- Mazzaferri E, Robbins RJ, Spencer CA, et al: A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *J Clin Endocrinol Metab* 88:1433-1441, 2003
- Fatourech V, Hay ID: Treating the patient with differentiated thyroid cancer with thyroglobulin-positive, iodine-131 diagnostic scan negative metastases: including comments on the role of serum thyroglobulin monitoring in tumor surveillance. *Semin Nucl Med* 30:107, 2000
- Mazzaferri E, Kloos RT: Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? *J Clin Endocrinol Metab* 87:1490-1498, 2002
- Intenzo CM, Jabbour S, Dam HQ, et al: Changing concepts in the management of differentiated thyroid cancer. *Semin Nucl Med* 35:257-265, 2005
- Lind P, Igerc I, Kohlfuerst S: Diagnosis, treatment and follow-up in case of differentiated thyroid cancer. *Wien Med Wschr* 19/20:429-435, 2005
- Waxman A, Ramanna L, Chapman N et al: The significance of I-131 scan dose in patients with thyroid cancer: determination of ablation. Concise communication. *J Nucl Med* 22:861-865, 1981
- Lind P: I-131 whole body scintigraphy in thyroid cancer patients. *Q J Nucl Med* 43:188-194, 1999
- Dadparvar S, Krishna L, Slizofski WJ, et al: The role of Iodine-131 and

- Thallium-201 imaging and serum thyroglobulin in the management of differentiated thyroid carcinoma. *Cancer* 11:3767-3773, 1993
44. Franceschi M, Kusic Z, Franceschi D, et al: Thyroglobulin determination, neck ultrasonography and iodine-131 whole-body scintigraphy in differentiated thyroid carcinoma. *J Nucl Med* 37:446-451, 1996
 45. Van-Sorge-Van Boxtel RAV, Van Eck-Smit BLF, Goslings BM: Comparison of serum thyroglobulin, I-131 and Tl-201 scintigraphy in the postoperative follow up differentiated thyroid cancer. *Nuc Med Commun* 14:365-372, 1992
 46. Filesi M, Signore A, Ventroni G, et al: Role of initial iodine-131 whole-body scan and serum thyroglobulin in differentiated thyroid carcinoma metastases. *J Nucl Med* 39:1542-1546, 1998
 47. Spies WG, Wojtowicz CH, Spies SM, et al: Value of post-therapy whole-body 131-I imaging in the evaluation of patients with thyroid carcinoma having undergone high-dose 131-I therapy. *Clin Nucl Med* 14:793-800, 1989
 48. Sutter CW, Masilungan BG, Stadalnic RC: False positive results of 131-I whole-body scan in patients with thyroid cancer. *Semin Nucl Med* 25:279-282, 1995
 49. Lubin E, Mechlis-Frish S, Zatz S, et al: Serum thyroglobulin and iodine-131 whole-body scan in the diagnosis and assessment of treatment for metastatic differentiated thyroid carcinoma. *J Nucl Med* 35:257-262, 1994
 50. Simpson WJ, Panzarella T, Curruthers JS, et al: Papillary and follicular thyroid cancer; impact of treatment in 1578 patients. *Int J Rad Oncol Biol Phys* 14:1063-1075, 1988
 51. Leger FA, Izembart M, Dagoussset F, et al: Decreased uptake of therapeutic doses of iodine-131 after 185 MBq iodine-131 diagnostic imaging for thyroid remnants in differentiated thyroid carcinoma. *Eur J Nucl Med* 25:242-246, 1998
 52. Coakly AJ. Thyroid stunning. *Eur J Nucl Med* 25:203-204, 1998
 53. Pineda JD, Lee T, Ain K, et al: I-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. *J Clin Endocrinol Metab* 80:1488-1492, 1995
 54. Lind P: Should high hTg levels in the absence of iodine uptake be treated. *Eur J Nucl Med* 30:157-160, 2003
 55. Pace L, Klain M, Albanese C, et al: Short-term outcome of differentiated thyroid cancer patients receiving a second iodine-131 therapy on the basis of a detectable serum thyroglobulin level after initial treatment. *Eur J Nucl Med Mol Imaging* 33:179-183, 2006
 56. Ma C, Kuang A, Xie J, et al: Possible explanations for patients with discordant findings of serum thyroglobulin and 131I whole-body scanning. *J Nucl Med* 46:1473-1480, 2005
 57. Joensuu H, Ahonen A: Imaging of metastases of thyroid carcinoma with fluorine-18-fluorodeoxyglucose. *J Nucl Med* 28:910-914, 1987
 58. Lind P, Gallowitsch HJ, Mikosch P, et al: Comparison of different tracers in the follow up of differentiated thyroid carcinoma. *Acta Med Austriaca* 26:115-118, 1999
 59. Reske SN, Kotzerke J: FDG PET for clinical use. Results of the 3rd German Interdisciplinary Consensus Conference, "Onko PET III", 21. July and 19. September 2000. *Eur J Nucl Med* 28:1707-1723, 2001
 60. Feine U, Lizenmayer R, Hanke JP, et al: Fluorine-18 FDG and iodine-131 uptake in thyroid cancer. *J Nucl Med* 37:1468-1472, 1996
 61. Grünwald F, Menzel C, Bender H, et al: Comparison of 18FDG-PET with 131-iodine and 99m Tc-sestamibi scintigraphy in differentiated thyroid cancer. *Thyroid* 7:327-335, 1997
 62. Lind P, Kresnik E, Kumnig G, et al: F-18-FDG PET in following up thyroid cancer. *Acta Med Austriaca* 30:17-21, 2003
 63. Conti PS, Durski JM, Bacqai F, et al: Imaging of locally recurrent and metastatic thyroid cancer with positron emission tomography. *Thyroid* 9:797-804, 1999
 64. Altenvoerde G, Lerch H, Kuwert T, et al: Positron emission tomography with F-18-deoxyglucose in patients with differentiated thyroid carcinoma, elevated thyroglobulin levels and negative iodine scans. *Langebecks Arch Surg* 383:160-163, 1998
 65. Schluetter B, Bohuslavizki KH, Beyer W, et al: Impact of FDG PET on patients with well differentiated thyroid cancer who present with elevated thyroglobulin and negative I-131 scan. *J Nucl Med* 42:71-76, 2001
 66. Moog F, Linke R, Manthey N, et al: Influence of thyroid-stimulating hormone levels on uptake of FDG in recurrent and metastatic differentiated thyroid carcinoma. *J Nucl Med* 41:1989-1995, 2000
 67. Petrich T, Börner AR, Weckesser E: Follow up of thyroid cancer patients using rhTSH-preliminary results. *Nucl Med* 40:7-14, 2001.
 68. Ruf J, Lehmkuhl L, Bertram H, et al: Impact of SPECT and integrated low-dose CT after radioiodine therapy on the management of patients with thyroid carcinoma. *Nucl Med Commun* 25:1177-1182, 2004
 69. Lind P, Igerc I: PET and PET/CT in the following up of thyroid cancer patients, in Langsteiger W, Sungler P, Lind P, et al (eds): *Thyroid cancer four 2004*. KOOP, Vienna, 2004 (CD ROM)
 70. Beyer T, Townsend DW, Brun T, et al: A combination of PET/CT scanner for clinical oncology. *J Nucl Med* 41:1369-1379, 2000
 71. Schöder H, Erdi YE, Larson SM, et al: PET/CT: a new imaging technology in nuclear medicine. *Eur J Nucl Med Mol Imaging* 30:1419-1437, 2003
 72. Hausegger K, Reinprecht P, Kau T, et al: Clinical experience with a commercially available negative oral contrast medium in PET/CT. *Fortschr Roentgenstr* 177:796-799, 2005
 73. Lardinois D, Weder W, Hany TF, et al: Staging of non-small-cell lung-cancer with integrated positron emission tomography and computed tomography. *N Engl J Med* 348:2500-2507, 2003
 74. Burger I, Görres G, von Shulthess G et al: PET/CT: diagnostic improvement in recurrent colorectal carcinoma compared to PET alone. *Radiology* 225:424, 2002
 75. Beyer T: Towards truly integrated hardware fusion with PET/CT. *Nucl Med* 44:S5-S12, 2005 (suppl 1)
 76. Pietrzyk U: Does PET/CT render software registration obsolete? *Nucl Med* 44:S13-S17, 2005 (suppl 1)
 77. Czernin J, Auerbach MA: Clinical PET/CT imaging. *Nucl Med* 44:S18-S23, 2005(suppl 1)
 78. Ong SC, Ng DC, Sundram FX: Initial experience in use of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography in thyroid carcinoma patients with elevated thyroglobulin but negative iodine-131 whole body scans. *Singapore Med* 46:297-301, 2005
 79. Nahas Z, Goldenberg D, Fakhry C, et al: The role of positron emission tomography/computed tomography in the management of recurrent papillary thyroid carcinoma. *Laryngoscope* 115:237-243, 2005
 80. Sgouros G, Kolbert KS, Sheik A, et al: Patient-specific dosimetry for I-131 thyroid cancer therapy using I-124 PET and 3-dimensional-internal dosimetry (3D-ID) software. *J Nucl Med* 48:1366-1372, 2004
 81. Freudenberg LS, Antoch G, Jentzen G, et al: Value of 124-I-PET/CT in staging of patients with differentiated thyroid cancer. *Eur Radiol* 14:2092-2098, 2004
 82. Lind P: Differentiated thyroid cancer, in Ell PJ, Gambhir SS (eds): *Nuclear Medicine in Clinical Diagnosis and Treatment*. Edinburgh, Churchill Livingstone, 2004, 145-164