Diagnostic strategy in thyroid cancer is conditioned by epidemiological, pathophysiological, cost-effective issues changing with age and countries. Nuclear medicine has a role mainly in differentiated carcinomas, i.e. in the large majority of thyroid cancers. In diagnosis of thyroid nodule $^{99m}$Tc-perthecnetate is indicated in patients with low TSH levels, multinodular goiter, solid nodules at US negative at FNA. Radiolabeled somatostatin analogs or Metaiodobenzylguanidine (MIBG) can be used in suspicion of medullary carcinoma. There is no role in staging. WBS with $^{131}$I has a role after surgical resection of the thyroid gland and it is no more suggested before ablative therapy, because of the possible stunning effect. In the follow-up thyroglobulin (Tg) test is mandatory both after therapy withdrawal or after rhTSH administration. Some authors already suggest to use this test alone, as 1st step, in patients with differentiated carcinoma at low risk of recurrence, but this approach is not yet generally accepted and it has not yet been validated in tumors at intermediate/high risk. WBS with $^{131}$I is ever indicated when autoantibodies can affect reliability of Tg values and in presence of high Tg levels to better define a radio metabolic therapy. In case of negative WBS, PET-FDG can be proposed. In WBS, $^{123}$I can be an alternative to $^{131}$I, but it is not yet generally accepted mainly because of its higher costs. The clinical use of rhTSH to increase accuracy both of Tg and WBS can be already accepted in patients at high risk following hypothyroidism, with a worst prognosis or a low pituitary response.

KEY WORDS: Thyroidal neoplasms, radionuclide imaging - Radiopharmaceuticals - Iodine, radioisotopes - Technetium TC. $^{99m}$Sestamibi - Tomography, emission computed, single photon - PET-FDG, tumor seaking.
can be obtained both in familial screening of patients with MEN-II and to exclude familial disease in patients at first diagnosis of medullary carcinoma. Genetic analysis can also permit a prognostic evaluation, mainly in papillary tumours, giving information on the possible evolution to anaplastic cancer.

Table I shows the current European figures on the incidence of primary thyroid tumors (Source Cancer Mondial - http://www-dep.iarc.fr/).

<table>
<thead>
<tr>
<th>Population</th>
<th>Cases</th>
<th>Crude</th>
<th>ASR (E)</th>
<th>ASR (W)</th>
<th>Deaths</th>
<th>Crude</th>
<th>ASR (E)</th>
<th>ASR (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5,185</td>
<td>1.75</td>
<td>1.66</td>
<td>1.31</td>
<td>1,057</td>
<td>0.58</td>
<td>0.53</td>
<td>0.35</td>
</tr>
<tr>
<td>Female</td>
<td>11,127</td>
<td>5.84</td>
<td>5.35</td>
<td>4.42</td>
<td>2,093</td>
<td>1.10</td>
<td>0.71</td>
<td>0.46</td>
</tr>
<tr>
<td>All</td>
<td>14,312</td>
<td>3.84</td>
<td>3.54</td>
<td>2.88</td>
<td>3,150</td>
<td>0.85</td>
<td>0.64</td>
<td>0.42</td>
</tr>
</tbody>
</table>

ASR: age-standardized rate, *i.e.* a summary measure of a rate that a population would have if it had a standard age structure. ASR (E): ASR Europe; ASR (W): ASR World.

Table II.—Histological classification of thyroid tumors (WHO).

<table>
<thead>
<tr>
<th>Epithelial tumors</th>
<th>Benign tumors</th>
<th>Malignant tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular adenoma</td>
<td>Others: adenolipoma, hyalin trabecular adenoma</td>
<td>Follicular carcinoma: minimally invasive; extensively invasive: oxyphilic, clear cell, insular variant</td>
</tr>
<tr>
<td>Papillary carcinoma: microcarcinoma, encapsulated variant, follicular variant, oxyphilic variant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medullary Ca</td>
<td>Undifferentiated anaplastic Ca</td>
<td></td>
</tr>
<tr>
<td>Others: mucinous, mucoepidermoid, squamous cell carcinoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not epithelial tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenchymal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignant lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratoma, paragangioma, thymoma, spindle cell tumor with mucinous cysts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other malignant types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic tumors</td>
</tr>
</tbody>
</table>

Tumor aggressiveness is related both to the tumor type (undifferentiated carcinoma) as well as to the age and sex of the patient. Aggressive tumours are more frequent in patients over 40 years with a higher frequency in subjects older than 50 years. A peculiar behaviour is observed in pediatrics. Nevertheless thyroid cancer is frequently diagnosed in advanced stage, a favourable prognosis is present because of an excellent therapeutic response, but in children under 10 years affected by very aggressive forms. With respect to sex a worst prognosis is observed in males. Countries with a high iodine intake present a higher tumor incidence having at the same time a higher degree of differentiation (common: papillary carcinoma; less common: follicular and anaplastic). A higher mortality has been described in countries with iodine deficiency because of the relatively higher frequency of anaplastic and follicular types with respect to papillary ones.

Papillary carcinoma is characterized by lymphatic spread into local lymph nodes, while follicular carcinoma presents a hematological spread with metastases more frequently in lungs and bones.

The most used classification of thyroid tumors is shown in Table II. Other classifications, giving a more complete information, include IUAC/AJCC, AMES, Chicago University, AGES, MACIS.

Tumor spread is described using the TNM system. The therapeutic approach includes near total and total thyroidectomy followed by radioiodine treatment in well-differentiated carcinomas with intermediate/high risk of recurrence, *i.e.* in the large majority of cases. Ablative radiometabolic therapy can be avoided in cases of carcinoma at low risk of recurrence, defined on the basis of individual (age, sex) and neoplastic (stage, size, histotype) prognostic factors. This approach is not accepted by all authors both because of the not easy definition of rigorous risk categories and of the worst capability in utilizing neoplastic markers in follow-up, mainly due to the low reliabil-
ity of Tg determination and of $^{131}$I whole body scan (WBS), in presence of normal thyroid remnant. In few cases not responding to radiometabolic therapy or with critical locations (as first respiratory and digestive tract involvement) external radiation therapy might be required while chemotherapy is only rarely used, mainly in patients with undifferentiated carcinoma, without other therapeutic perspectives.17

Clinical evaluation and non nuclear medicine diagnostic procedures

Primary evidence of the disease can be either localized to the neck region, including cervical lymph nodes, or more rarely can be related to distant metastases. In this case, most frequent events are due to lesions in bones (follicular cancer) and in lungs, but a first diagnosis can exceptionally start from metastases in the liver or other organs.

Metastatic tumors to the thyroid include specially renal cancer and lymphomas. In lymphomas, thyroid can be also the first clinical evidence of the disease (thyroid lymphoma).

The investigation of a patient with suspected thyroid tumour has ever to begin with clinical history and objective examination. Patients can present recent goiter growth, hoarseness, cervical lymph nodes, fatigue, dyspnoea, dysphagia, weight loss, pain in goiter or in the retroauricular region, pain in bony structures, ischialgia, paresis.18

At clinical examination signs suggesting malignancy are a firm goiter with reduced mobility, fixation to cervical structures, regional lymph nodes, Horner’s syndrome on the affected side of the thyroid, tenderness in bony structures.19

In the clinical history, the presence of familial cases of medullary carcinoma, an external radiation exposure at young age or a possible connection with events as the Chernobyl accident, have to be investigated.20

In the large majority of cases, with a percentage strongly growing in last years, the first suspicion starts, also in absence of clinical symptoms, from the occasional evidence of a cervical tumefaction or of a solitary nodule detected clinically or at ultrasonography (US).21

Today, US represents in the large majority of cases the first instrumental approach in diagnosis of thyroid cancer, with a debated clinical role in differential analysis of cervical lymph nodes at first diagnosis.22

It is a reliable method to delineate anatomy and detect nodules with a differential evaluation based on their pattern and shape. A high predictive negative value for cancer can be calculated in presence of signs related to a pure liquid structure, benign calcifications, a regular rim or other data in agreement with a favourable prognosis.23

In these cases a wait and see strategy, also utilizing an hormonal therapy, can be suggested. At the opposite, nodules not presenting signs defined as benign at US, i.e. the large majority of solid and/or mixed nodules,24 have to be furtherly evaluated, because of the possible presence of cancer with a probability dependent on many parameters both ultrasonographic and clinical using most recent techniques and technological devices.26, 27

US is a sensitive albeit non specific diagnostic test that can identify up to 2 mm cystic nodules and 3 mm solid lesions. Has to be pointed out that because of the high prevalence, also due to a the very high sensitivity of diagnostic procedures, thyroid nodules acquire a clinical relevance only over 1 cm, but in presence of negative prognostic factors. The diagnostic accuracy can be partially improved using Doppler techniques in a minority of cases.26, 29

This approach permits a further differential analysis based on vascularity, that can be helpful mainly in multinodular goiters also to better guide FNA.

Because of the low number of tumors presenting typical malignant vascular patterns and of the possible presence of malignancy also in nodules without signs of vascularity at US26 the clinical improvement is not very high and it is mainly related to the possible increase of positive predictive value.31, 32

Interesting perspectives are connected with the use of contrast media, recently proposed, nevertheless are not yet present in the literature significant data supporting their incremental role.33

In order to improve clinical usefulness US can also be used as a guide to fine needle aspiration (FNA).34

Using this approach, a better accuracy for a cytological diagnosis can be achieved because of reduction of false negative results, mainly in cases of multinodular goiter with nodules presenting different and/or mixed structure. At the present it has been not defined a clinical relevance of US in lymph node staging with respect to the clinical evaluation. It has also to be pointed out that US is affected by some limitations that do not permit, as example, a mediastinal evaluation or a reliable differential diagnosis of recurrence.
Another general limit is due to the operator dependency and therefore to an accuracy strongly connected with experience and technical capability.

Fine needle aspiration of suspicious nodules defined as fine needle aspiration biopsy (FNAB) or cytology (FNAC) on the basis of the technical approach is mandatory before a surgical choice, representing a major procedure in defining diagnosis of cancer.

The positive predictive value is very high and strongly suggests a surgical approach. At the opposite, a negative result that, including inadequate sampling, is present in up to 20% and over of cases with cancer, has to be carefully evaluated, taking in account anamnesis and all clinical and diagnostic information, because of the large variability in the definition of negative predictive values.

It means that negative results at FNA, with main reference to those defined as non diagnostic, cannot exclude malignancy and have to be furtherly evaluated. Using a reliable technique and with an analysis performed by expert pathologists false negative results are mainly related to minimally invasive (or capsuled) follicular cancer. This tumor cannot be differentiated with respect to follicular adenoma without an accurate pathological analysis evaluating also capsule and vessels. In a limited number of cases a cytological or bioptical analysis of cervical lymph nodes, if suspicious, can be also requested. Major limitations for FNA are related both to the negative patient compliance, mainly in presence of a multinodular goiter, and with the strong dependence of accuracy by the experience of retriever and pathologist. In this sense, while FNA can be proposed also as first line procedure for a clinically palpable solitary nodule in absence of signs of hyperthyroidism in a reference center, it cannot be used alone in the large majority of cases and never in patients with multinodular goiter.

No significant clinical contribution in diagnosis is added by X-ray, computed tomography (CT) or magnetic resonance (MRI).

Waiting for a further improvement linked with a larger diffusion of new procedures, as multislice CT, and to the advent of more clinically effective contrast media, MRI and CT can find a role mainly in the analysis of mediastinal masses, also to better define a surgical strategy evaluating vessels and other structures.

With respect to hematochemical data, Tg does not have a role both in diagnosis and staging because of a very low accuracy in defining malignancy. It can be only proposed in presence of a bone metastasis without knowledge of the primary tumour. In this condition values over 4 000 ng/ml are in agreement with thyroid Ca and give a strong support to an accurate thyroid evaluation considering also not standard approaches.

High values of calcitonin are present in medullary cancer. Its dosage has been proposed as screening in patients with thyroid nodules undergoing surgery without a previous diagnosis of thyroid cancer, but this indication is debated on the basis of the low prevalence of the disease. Its clinical role can be found in subjects with suspicious familial medullary tumour, also in absence of a genetic diagnosis. A higher sensitivity, and therefore a better clinical accuracy, is achieved after pentagastrin administration.

Dosage of TSH has ever to be performed to define thyroid function both for a diagnostic purpose and before to start a hormone therapy. In particular, low values of TSH are in agreement with hyperthyroidism and therefore they can give a further support to a diagnosis of benign thyroid nodules. A lower clinical interest can be found in subjects with suspicious familial medullary tumour.

Chest X-ray, US, CT and, at lower extent, MRI can play a role in detecting distant metastases. For mediastinal evaluation CT and MRI can both demonstrate lymph node enlargement and define the presence of masses. No univocal and accurate results can be obtained in diagnosis of local recurrence.

A clinical relevance because of high accuracy is connected with US in follow-up of patients with papillary cancer to define cervical lymph node involvement.

Chest X-ray is still the first line procedure to detect lung metastases, but preliminary results obtained with spiral CT already support its indication, mainly in young patients, because of the higher accuracy also in lesions under 1 cm.

In follow-up Tg test is a major marker of recurrence and/or metastases of differentiated thyroid carcinoma, after total or near total thyroidectomy followed by radiometabolic therapy. Undetectable serum levels of Tg, during suppressive thyroxine therapy, are strongly related with the absence of persistent or recurrent carcinoma, but in presence of anti Tg antibodies (Ab) determining not reliable results.
A higher sensitivity and therefore a better accuracy can be achieved after hormone therapy withdrawal, determining elevated TSH values. A similar improvement, also if at lower extent, has been demonstrated by analyzing values obtained 72 h after administration of exogenous recombinant human TSH (rhTSH).54, 55

**Nuclear medicine diagnostic procedures**

*Imaging with iodomimetic tracers: thyroid scintigraphy and WBS*

Imaging of thyroid tumors is performed by nuclear medicine since 1942. One of the earliest reports documented the uptake of $^{131}$I in thyroid metastases.56 This was followed by a therapeutical application of $^{131}$I as reported by Becker, Seidlin et al.57

The underlying mechanism that permits imaging is the Na-iodine-symporter which is responsible for iodine uptake.58, 59 This function, saved also at level of metastases in differentiated carcinoma, can however be either absent at the initial diagnosis of the tumour (undifferentiated or anaplastic neoplasms) or it can also disappear during the course of the disease (loss of differentiation).60

Recent preliminary data, that have to be furtherly supported, suggest the capability of retinoic acid to determine redifferentiation, improving results both in whole body diagnosis and in radiometabolic therapy.61 Other factors influencing radioiodine concentration have been described. In particular, because radioiodine is in competition with stable iodine and it is affected from conditions decreasing its uptake, all causes of possible interference have to be known. As example, administration of thyroxin therapy and knowledge of previous iodine exposure (as CT with contrast media) have to be taken in account.

A more rigorous analysis as that needed before a therapeutic dose of $^{131}$I mainly to decrease radiation to critical organs is not necessary. In this sense, conditions as fasting and a frequent voiding can be suggested, but are not mandatory.

At diagnostic level, radioisotopes of iodine of possible clinical interest are $^{131}$I, $^{123}$I and $^{124}$I. $^{131}$I is a $\gamma$ and $\beta$ emitter radionuclide, used both in diagnosis and in radiometabolic therapy. At diagnostic level, whereas it is used for WBS in follow-up, it is discouraged in diagnosis of primary tumor, because of a too high radiation dose to the patient in presence of an unsatisfactory count rate. $^{123}$I is a pure $\gamma$ emitter with very favorable characteristics for imaging.62 Nevertheless, the significantly higher cost with respect to $^{99m}$Tc perthecnetate and a lower adaptability to a routine use have limited its diffusion.63 A relatively more favorable cost-effectiveness can support its use in younger patients, but clear advantages both with respect to $^{99m}$Tc scan and to $^{131}$I WBS have not yet been generally accepted.64-66 The emission of Auger electrons could be theoretically used for therapy, but not clinical studies have been performed to evaluate this possibility.

$^{124}$I is a positron emitter radionuclide with very interesting characteristics for a quantitative analysis of thyroid uptake.57 Nevertheless, because it can be produced only with high energy cyclotrons, it is available and used only for research purpose in few centres around the world. Has to be pointed out that $^{124}$I has a physical half life (4.2 days) that can permit an utilization also at long distance from the production site. A future larger diffusion can be supported because of the possible improvement both in diagnosis and for therapeutic strategies. With respect to diagnosis, $^{124}$I can permit an evaluation using PET-CT, allowing an integrated image with a reliable information both functional and morphostructural also in nodules under 1 cm. Using $^{124}$I better results could be also achieved in WBS, with main reference to a possible improvement in sensitivity giving a stronger support to a therapeutic radiometabolic strategy. The advantage in this field is furtherly increased by the possibility of an individual dosimetry as premise to a more correct therapeutic dosage of $^{131}$I.67

To diagnose thyroid diseases $^{99m}$Tc pertechnetate, a biological analogous of iodine utilizing the same uptake mechanism nevertheless it is not organified, can also be used. Because of better physical and practical characteristics with respects to radioisotopes of Iodine, $^{99m}$Tc-pertechnetate is the first choice iodomimetic tracer for thyroid scan. To justify its routine use it has to be pointed out that a substantial overlap with respect to radioiodine has been demonstrated in the large majority of nodules presenting 3 different uptake patterns: cold, with uptake lower with respect to the surrounding tissue; warm, character-
ized by overlapping concentrations; hot, presenting a higher uptake with respect to normal thyroid.

A discrepancy has been observed in few cases of differentiated thyroid carcinoma, warm at \( ^{99m}Tc \) and cold at radioiodine. This condition is depending on the earlier timing of evaluation of \( ^{99m}Tc \) scan with respect to radioiodine and to the lack of organization for perihcotic. For these reasons, mainly if \( ^{99m}Tc \) scan is performed only few minutes after radiotracer’s administration, a cancer with high blood flow and/or volume can very rarely appear warm at \( ^{99m}Tc \) and cold at radioiodine. Advantages for radioiodine, both \( 131I \) or \( 123I \), in comparison with \( ^{99m}Tc \) are present in case of extra-cervical locations, with main reference to the analysis of a mediastinal involvement.

In the definition of the clinical role of thyroid scintigraphy it has to be pointed out that cold nodules can harbor thyroid cancer, but they can be also determined by several other mechanisms leading to a decreased iodine uptake such as: regressive alterations, cystic degeneration, inflammatory destruction, benign not functioning adenomas. The incidence of malignancy in cold nodules increases with the degree of iodine intake, e.g. Austria 5.5%, Italy 8.2%, UK 11.4%, USA 20.5%. Positive predictive value of cold nodules for cancer remain very low in presence of signs strongly suggesting a benign lesion at US, 37–40.

On the other hand, warm nodules at \( ^{99m}Tc \) do not exclude the presence of thyroid carcinomas, nevertheless they are strongly connected with a very high negative predictive value. A further improvement in accuracy can be achieved using T3 suppression Werner’s test to unmask benign autonomous functioning adenomas.

Hot nodules express ever a benign diagnosis, being connected with hyperfunctioning autonomous adenomas. This is a major reason to support the use of TSH dosage and thyroid scan also before FNA. By the way, thyroid scan is ever suggested in patients with suppressed TSH, being a first line procedure. A clinical indication can also be found in multinodular goiter as integrative procedure with respect to US to better define nodules to aspirate. In the case of a diagnostic strategy based on the direct connection between US and FNA, thyroid scan can be suggested in presence of solid nodules at US, negative at FNA. This approach is strongly supported also to avoid the disclosure of an autonomous adenoma following an hormone suppressive therapy frequently started in a wait and see strategy.

While \( ^{99m}Tc \) perthecenate is the 1st choice radio-pharmaceutical for diagnosis of primary neoplasms, at the opposite, because of pathophysiological and technical reasons, it is not used in follow-up of patients with differentiated thyroid cancer. In these cases, uptake of radioiodine has been demonstrated, in absence of thyroid tissue, also in metastases giving support to the use of \( 131I \) both for a whole body diagnosis and for radiometabolic therapy.

In follow up \( 131I \) is still the most frequent 1st choice radiocompound. Its main advantages are the low cost, the large availability and the longer half-life, permitting a kinetic analysis up to 48 h and longer, better defining the clinical mean of dubious uptakes.

Moreover, the lower attenuation determined by higher energy radiations can permit in some cases better results in detecting lesions localized in bone or deeply. One of the main disadvantages is the so-called “stunning effect”, i.e. a possible reduction of the uptake of a therapeutic dose administered immediately after that a diagnostic information has been acquired. It means that therapeutic efficacy of a treatment with \( 131I \) can be reduced when WBS using this radionuclide immediately precede therapeutic administration.

For the diagnosis of thyroid cancer recurrences and metastases \( 123I \) can also be used. Its \( \gamma \) emission is optimally revealed by Anger camera while the shorter half-life with respect to \( 131I \) and the absence of corpuscolate emission allow the administration of higher activities with significant improvement in counting rate, in absence of a stunning effect. For these features some authors advocate its use as a substitute of \( 131I \) for WBS.

As previously said, disadvantages of \( 123I \) with respect to \( 131I \) are at first the higher cost, then the shorter half-life not permitting in some cases an analysis at the time of the best tumor/background ratio and the lower energy creating, also if very rarely, problems in detecting deep lesions. Significant advantages, strongly supporting its use, are the absence of a stunning effect and the capability to give a faster diagnosis in presence of a substantially overlapping accuracy.

Traditionally, both WBS and radiometabolic therapy are performed after thyroxin therapy withdrawal, to determine increasing values of TSH favoring radioiodine uptake. This approach is affected by biological and clinical disadvantages, due to hypothyroidism determined and to an increased risk of a prognostic worsening. More recently, the introduction of human
recombinant α-TSH\textsuperscript{75} provided an effective tool for both diagnostic WBS using 13\textsuperscript{1}I or 12\textsuperscript{3}I and, not yet completely validated, therapy with 13\textsuperscript{1}I. Its use is already aimed at patients who present clinical symptoms or high risks during T\textsubscript{4}-withdrawal (brain and vertebral metastases, neurological signs, heart disease), in those who cannot produce endogenous TSH, in presence of aggressive Ca with low iodine uptake.

Focal 13\textsuperscript{1}I uptake in WBS strongly suggest the presence of a recurrence or of differentiated metastases. Error sources due to conditions as inflammatory lung disease, lung cancer, thymoma, pericardial effusion, esophageal diverticulum, Meckel's diverticulum, hiatal hernia, esophagitis, sinusitis have to be remembered.

**Tumor seeking radiopharmaceuticals**

Both in diagnosis and in follow-up of thyroid carcinoma so-called tumor seeking indicators can be also proposed. The uptake of 18-F fluoro-deoxyglucose (FDG) has been demonstrated both in primary and metastatic tumors.\textsuperscript{76, 77}

Its concentration is related to unfavourable prognostic factors and can be present also in lesions not showing radioiodine uptake, both because of pathophysiological and technical reasons, the latter due to a better resolution.\textsuperscript{78}

Uptake is less dependent with respect to radioiodine on TSH levels, nevertheless some studies demonstrated an increased neoplastic concentration in presence of higher TSH values.\textsuperscript{79, 80}

Waiting for further information supporting these preliminary data, FDG scan is performed not withdrawing thyroxin administration. This choice is also supported by the clinical use of PET-FDG in patients with a bad prognosis at high probability of undifferentiated lesions not responding to pituitary stimulation and with a theoretical clinical risk of worsening following therapeutic withdrawal.\textsuperscript{81}

While no indication is present for diagnosis of primary cancer, a clinical role can be supported as additional imaging strategy for patients who do not show iodine uptake at WBS, mainly in case of concomitant pathological levels of thyroglobulin. The possible presence of false positive results due both to a 2\textsuperscript{nd} tumor or to active inflammatory disease have to be taken in account.\textsuperscript{82}

Clinical relevance of PET-FDG as premise to a radiometabolic therapy using 13\textsuperscript{1}I has to be furtherly evaluated,\textsuperscript{83} also waiting for a major improvement in strategies that can affect re-differentiation, determining restoration of radioiodine uptake in lesions previously negative at WBS with this radiocompound.\textsuperscript{84}

In fact, lesions seen by PET-FDG but not at 13\textsuperscript{1}I WBS are in agreement, in presence of detectable values of Tg, with at least partially differentiated neoplastic lesions, giving however support to a radiometabolic therapy.\textsuperscript{85, 86}

A possible alternative to FDG, mainly used in differential diagnosis of thyroid nodules more than in a whole body evaluation, is connected with the use of γ emitters,\textsuperscript{87} radiocompounds as 20\textsuperscript{3}Tl chloride,\textsuperscript{88} 99m\textsuperscript{Tc} sestamibi,\textsuperscript{89, 90} 99m\textsuperscript{Tc} Tetrofosmin,\textsuperscript{91, 92} 11\textsuperscript{1}In- or 99m\textsuperscript{Tc}-somatostatin analogs.\textsuperscript{93}

In diagnosis of nodules cold at thyroid scan, 20\textsuperscript{3}Tl provides a tool for the differentiation of benign and malignant tumors.\textsuperscript{94, 95} Benign lesions are characterized by low uptake or rapid washout. The opposite is found in nodules with malignant disease.\textsuperscript{97}

A similar capability in differentiating thyroid nodules has been also demonstrated using 99m\textsuperscript{Tc} sestamibi\textsuperscript{98} or 99m\textsuperscript{Tc} Tetrofosmin. In presence of a cold nodule at pertechnetate, while a low or absent Sestamibi uptake strongly support a benign diagnosis, at the opposite an intense sestamibi concentration, persistent in the late image at 2 h after injection, is suspicious for malignancy.\textsuperscript{99}

A possible error source can be determined in some cases of autoimmune disease or in oxyphillic adenomas, presenting the same pattern. A substantially overlapping behaviour is observed using 99m\textsuperscript{Tc} Tetrofosmin.\textsuperscript{100}

All these tracers, however, lack the ability to specifically differentiate thyroid malignancy and cannot be used alone for an accurate diagnosis of cancer. Disease confirmation might require additional diagnostic procedures such as biopsies.\textsuperscript{101}

For these reasons a clinical role can be suggested only in few cases to define the urgency of a surgical strategy, when other approaches do not reach a significant positive predictive value and a wait and see strategy has been proposed.\textsuperscript{102}

In particular, tumor seeking indicators could find a role in this diagnostic scenario because of an incremental diagnostic value, also if slight, with respect to ultrasounds mainly in directing FNA in multinodular goiter.\textsuperscript{103}

As regards with 11\textsuperscript{1}In- or 99m\textsuperscript{Tc}-somatostatin analogs the major clinical interest can be found in diagnosis, staging and follow-up of medullary cancer, because of
the increased number of somatostatin receptors in neuroectodermal tumors. For this indication also \(^{131}\text{I}\) or \(^{123}\text{I}\) metaiodobenzylguanidine (MIBG), tracing catecholamine metabolism, can also be proposed. Recently the sentinel node procedure, clinically relevant in breast cancer staging and already used in other tumors as melanoma, has been proposed also in thyroid carcinoma. However there are not sufficient data to support its use to define a therapeutic strategy or before a surgical choice. Interesting perspectives are also linked to preliminary data on other radioguided surgical procedures, but these studies have to be furtherly evaluated.

**Diagnosis of thyroid nodules**

The knowledge of personal and family history, the analysis of risks factors and the clinical examination are essential in the diagnostic approach of any thyroid mass. The prevalence of palpable nodules in adult population in Europe is approximately from 4% to 8%, but there is a larger number of patients undergoing the diagnostic tree both because of functional symptoms and of the occasional observation of non palpable nodules at US, also in absence of clinical signs of disease. Diagnostic strategy is conditioned by many epidemiological and pathophysiological issues, by cost-effective evaluations changing with age and countries, by socioeconomical features mainly based on the presence of professional and technical capabilities at local level.

The diagnosis of thyroid cancer currently starts from clinical examination and US, combined with determination of TSH to define function. The indices of inflammation and autoimmunity (autoimmune diseases can mimic cancer), FT3 and FT4 as further data for a functional analysis, should be also evaluated.

There is an open debate about the routine measurement of serum calcitonin, as basal levels of calcitonin are increased in patients with sporadic or familial medullary thyroid cancer (MTC). Large majority of centers use this approach only in those patients with the family history positive for MTC (or with cytologic diagnosis suspicious for MTC or MEN). Few centers apply this laboratory test as a routine work-up in patients undergoing surgery without a cytological diagnosis of carcinoma, nevertheless the low prevalence of the disease. Tg test dosage can only be requested at first diagnosis in case of bone metastasis without evidence of the primary tumor. At US the size to define a nodule clinically relevant to direct a diagnostic and therapeutic strategy has to be decided. The majority of centers consider 1 cm as the threshold, but in case of negative prognostic factors, an ultrasonographic pattern suspicious for cancer, clinical signs of hyperthyroidism. A further improvement in accuracy, helpful in multinodular goiter, can be added by color Doppler techniques slightly increasing positive predictive value, but without effect in a better definition of benignity. In presence of nodules solid or mixed at US, FNA is ever indicated, but in presence of ultrasonographic signs or low TSH levels defining a high negative predictive value for cancer.

Thyroid scan with iodomimetic radiotracers is able to define functional characteristics of a nodule finding indication at first in all patients with low levels of TSH, in agreement with a benign disease. Another clear indication is the multinodular goiter in order to evaluate the different functional status of the thyroid areas and to better guide FNA. In multinodular goiter, nodules suspicious for cancer are, in the majority of cases, solid at US and cold at scintigraphy. A high negative predictive value is connected with nodules liquid (or presenting other signs of benignity) at US and in those concentrating \(^{99m}\text{Tc}\) (warm or hot) at thyroid scan. In particular, a hot nodule at thyroid scan is certainly benign and does not require further diagnostic investigation. A certainty of benignity in warm nodules can be achieved using T3 suppression Werner’s test unmasking autonomous functioning adenomas.

There is no general consensus about the proposal of a thyroid scan also in presence of normal values of TSH in all patients with a solitary solid nodule at US. The rationale to support this approach is that nodules warm at thyroid scan increase negative predictive values giving a stronger reliability to a wait and see strategy. Furthermore, thyroid scan has to be done before to start a hormone therapy to avoid disclosure of a functional adenoma.

The radiopharmaceutical of choice for diagnostic imaging of thyroid diseases should be \(^{99m}\text{Tc}\) pertechnetate, for dosimetric and practical reasons. Iodine has to be considered only when a particular functional information is requested; in this case \(^{123}\text{I}\) is indicated. Some authors still accept to use \(^{131}\text{I}\) exclusively in adult patients, in case of retrosternal mediastinal struma. In all cases the standard examination is the planar study in the anterior projection. Further projections,
with main reference to the oblique ones, can be performed, if necessary. At present, there are no clear indications for SPET, that can occasionally add useful information at mediastinal level. The use of a pin-hole collimator can be preferred, but it is not mandatory.

The resolution power of $\gamma$ camera has to be considered. In fact the scintigraphic imaging has a clinical value only for nodules with a diameter greater than 1 cm (except for patients with hyperthyroidism). The diagnostic role of scintigraphy in non-hyperfunctioning nodules smaller than 1 cm in diameter is very poor and its use has to be always discouraged.

Radiopharmaceuticals different from iodine and $^{99m}$Tc have limited clinical value in the diagnosis of thyroid nodules. Oncotropic agents as $^{99m}$Tc Sestamibi/Tetrofosmin and $^{201}$Tl Chloride have been proposed to increase the predictive value in presence of cold nodules at thyroid scintigraphy or to orient the FNA in the multinodular goiters.\textsuperscript{110, 111}

These approaches did not find until now an application in the current routine and they can be proposed only in few cases to better define the urgency of a surgical choice with respect to a wait and see strategy. Similarly, PET-FDG has no role in the diagnostic evaluation of a patient with thyroid nodules.\textsuperscript{112}

Radiopharmaceuticals with uptake mechanisms connected with the presence of neuroendocrine tissue, such as $^{111}$In/$^{99m}$Tc somatostatin analogs, $^{123}$I/$^{131}$I MIBG are indicated in presence of a suspicion of medullary thyroid carcinoma. MTC has to be suspected in presence of any thyroid mass and elevated calcitonin and/or CEA levels or in presence of a familial history supporting this hypothesis.

## Pre-surgical staging

After diagnosis of thyroid cancer the nuclear medicine modalities have no role in staging, as the evaluation of the extent of disease is usually performed by means of conventional morphological diagnostic methods (US, chest X-ray, CT). A sentinel lymphnode approach, as used in breast cancer and in melanomas, has been proposed, but there are no clinical studies supporting this procedure. At the same way the clinical role for bone scintigraphy is limited, but in case of clinical symptoms suspicious for bone metastases. In patients with clinical signs of metastases and in presence of any thyroid or loco-regional mass the PET-FDG whole-body could be useful to better evaluate the thyroid cancer spread. Nevertheless this information could be helpful to better define a therapeutic strategy, there are no sufficient clinical data to routinely support this indication.

## Post-surgical studies and follow-up

Some authors suggest to avoid metabolic radiotherapy in differentiated tumours at low risk of recurrence. In these cases follow-up can be performed only with clinical controls, ultrasounds and Tg dosage presenting however a low reliability because of the presence of thyroid remnant. In the large majority of patients total or near total thyroidectomy is followed by radionuclide ablation with therapeutic doses of $^{131}$I. This approach is strongly supported also to have a better reference point for evaluating recurrent disease in follow-up in absence of normal thyroid tissue and starting from not measurable values of Tg.\textsuperscript{113}

In follow-up there are different diagnostic information that have to be acquired regarding evaluation of thyroid remnant, diagnosis of recurrence or persistent carcinoma, detection of distant metastases, definition of the presence of pathological radiiodine uptake as premise to a radiometabolic therapy.\textsuperscript{114}

After surgery and before radiometabolic therapy the patient can be imaged with $^{131}$I which is the tracer of choice, but this approach is actually discussed because of the possible stunning effect decreasing efficacy of the following therapeutic dose. Therefore a direct radionuclide ablation with therapeutic doses of $^{131}$I is preferred.\textsuperscript{115}

Anyhow $^{131}$I whole body after thyroid resection is able to demonstrate the thyroid remnant and to show distant metastases. The possible use of $^{123}$I, not determining the stunning phenomenon, is under evaluation, but its use did not reach yet sufficient effectiveness to be justified.\textsuperscript{116, 117}

In follow-up, head and neck US have to be performed both to evaluate thyroid bed and lymph node status. In particular, a good accuracy in lymph node analysis of patients with papillary cancer can be obtained.\textsuperscript{118}

Useful information can also be acquired with chest X-ray, CT and, at lower extent, MRI, evaluating both distant metastases and mediastinal involvement. An increasing interest because of high accuracy is connected, mainly in younger patients, with multislice
CT for detection of pulmonary metastases. This approach can be already supported if clinically requested.

Patients with differentiated thyroid cancer who underwent a total or near total thyroidectomy followed by a radioiodine treatment are treated with hormone replacement in the form of l-thyroxine, in order to depress TSH levels. Two major approaches can traditionally define the presence of recurrence or metastases: Tg level measurements, in absence of autoantibodies, and $^{131}$I WBS. Tg is, in general, undetectable in absence of cancer and of thyroid tissue. A low reliability is determined by the presence of antibodies, that have always to be evaluated. Tg dosage can be clinically relevant during suppressive hormonal therapy, but it presents a significant increase in sensitivity and therefore accuracy after its withdrawal. Effective results can be achieved also after exogenous rhTSH administration, nevertheless lower values of TSH are reached with respect to the standard procedure. $^{131}$I WBS presents a lower sensitivity with respect to Tg dosage, but its use is indicated to evaluate the efficacy of ablative therapy, to better define a dosimetry before a therapeutic administration of $^{131}$I, to study patients in presence of autoantibodies against Tg. Also for WBS, standard procedure is based on l-T4 withdrawal, but there is a growing interest on WBS after rhTSH administration, already demonstrated as accurate method, substantially comparable to the standard one, nevertheless a slight lower sensitivity in defining thyroid remnant. This approach is affected by the disadvantage of a high cost that is however counterbalanced by a better compliance and a lower number of lost working days due to hypothyroidism. Its use is already aimed at patients who present clinical symptoms or high risks during T4-withdrawal, in those who cannot produce endogenous TSH, in presence of aggressive carcinoma with low iodine uptake.

While there is a general consensus in the use of WBS in analysis of patients against Tg, there is at present debate on the role of WBS with $^{131}$I as general 1st line standard diagnostic procedure.\(^{119}\)

Moreover, is under discussion the use of rhTSH as alternative to therapy withdrawal in improving accuracy both of Tg dosage and of WBS. Finally, the choice of $^{131}$I instead of $^{123}$I is also debated.\(^{120}\)

The lack of a general consensus is mainly due to difficulties in calculating cost/effectiveness, also because of favourable prognosis of thyroid carcinoma, requiring many years and patients for a correct analysis. It has however to be pointed out that high costs of rhTSH and $^{123}$I discourage in many centres their routine clinical use. Waiting for further data strongly supporting their incremental value with respect to traditional approaches, a possible gain of rhTSH could be better calculated evaluating costs of working days lost for hypothyroidism after therapy withdrawal, while a clinical indication is already present in patients at high risk, with an unfavourable prognosis, with low pituitary response.

The traditional follow-up is done by measuring thyroglobulin levels and performing WBS with $^{131}$I together. $^{131}$I WBS and thyroglobulin measurements have to be performed during a l-thyroxine withdrawal for a sufficient time to permit an adequate rise of TSH (>50 U/ml). Tg values are not reliable in presence of antibodies that should be periodically tested.

In a radically operated patient any focal images in a non-physiological site due to the radioiodine uptake and/or an elevated or a rinsing of serum thyroglobulin (in the absence of anti-thyroglobulin antibodies) may be a useful indicator of residual or recurrent thyroid cancer. The serial Tg measurements can substitute $^{131}$I WBS; the adoption of the combined tests, the choice of the Tg test alone, their frequency during treatment. All these approaches should be furtherly studied and have a definitive clinical validation.\(^{122}\)

Recently the human recombinant TSH (rhTSH) has been proposed as a drug prior thyroglobulin measurements in order to avoid the l-thyroxine withdrawal.\(^{121}\) This approach has been approved by the authorities only for diagnostic use but the concept is valid also $^{131}$I therapy. All these approaches should be furtherly studied and have a definitive clinical validation.\(^{122}\)

An increased consensus is growing on a strategy using serial measurement of thyroglobulin after l-T4 withdrawal or rhTSH stimulation, as the unique test (without the $^{131}$I WBS) to check the thyroid cancer relapses. In particular, in a recent Consensus report\(^ {123}\) on the role of Tg in low risk patients with papillary thyroid carcinoma the incremental capability of rhTSH in better defining the presence of neoplastic disease both with respect to baseline values and to diagnostic WBS with $^{131}$I has been demonstrated. A TSH stimulated Tg test using a Tg cutoff of 2 µg/L (either after thyroid hormone withdrawal or 72 h after rhTSH) is sufficiently sensitive to be used as the principal information in the follow-up management of low risk
patients with differentiated thyroid carcinoma. According to these indications, the routine use of diagnostic WBS should be discouraged. In these patients WBS has to be performed only in cases with pathological levels of Tg, or in presence of Ab affecting the clinical relevance of Tg dosage. By the way antiTg Abs are present in up to 10% of the patients requiring follow-up after diagnosis and therapy of differentiated thyroid carcinoma. At the present Tg remains certainly the reference diagnostic test, while 131I WBS seems to lose its role as 1st choice mainly in patients with no thyroid remnants and no clinical or biochemical evidence of residual tumors, recurrence or metastases. A Tg cutoff of 2 µg/L has to be used either after thyroid hormone withdrawal or rhTSH. In presence of lower values no further studies but a neck US has to be performed. This strategy can be already accepted in patients with differentiated carcinoma at low-risk. If a value lower than 2 µg/L can exclude the presence of malignancy, in differentiated carcinoma and in the absence of Ab, on the contrary elevated serum Tg levels do not guarantee the iodine avidity of the tumour. The iodine avidity depends on several factors (histological type, tissue differentiation, treatments and interfering drugs, etc.) and can change during the time. There is an increasing consensus about the fact that patients with high levels of Tg and 131I negative WBS should be studied by means of alternative nuclear medicine modalities in order to visualize metastases.124

This should be done by 99mTc-Sestamibi/Tetrofosmin 125, 126 or better by PET-FDG.127, 128

Both 99mTc-Sestamibi and PET scans do not need any withdrawal from thyroid hormone medication.129 For this reason these procedures can be already indicated in those patients who do not tolerate the requested condition of hypothyroidism. Nevertheless the clinical evidence of the possible role of a positive PET-FDG scan and of high Tg values as indicators of an effective radiometabolic therapy with 131I has not yet been demonstrated, this approach can be suggested on the basis of some data.130

The first is the evidence of a higher sensitivity of WBS scan performed after therapeutic doses of 131I with respect to the diagnostic ones, suggesting technical reasons as partial explanation of the lower sensitivity of diagnostic WBS, with respect to Tg dosage. Moreover, a thyroid metastasis can be heterogeneous in functional capabilities with main reference to the iodine uptake. But it has been clearly demonstrated that also malignant cells not concentrating radioiodine, adjacent to cells presenting uptake, can be killed if at a distance lower with respect to the maximum range of β rays emitted by 131I (0.43 mm).

Conclusions

Nuclear medicine can find an important role in thyroid cancer. In diagnosis of primary tumor thyroid scan with 99mTc pertechnetate is indicated in patients with low TSH levels, in multinodular goiter, in presence of a solid nodule at US negative at FNA. No significant incremental information is added in diagnosis both from PET-FDG and other tumor seeking radiotracers, but radiolabeled somatostatin analogs or MIBG in suspicion of medullary carcinoma. While there is no role in pre-surgical staging, a discussion is open on the correct position of nuclear medicine procedures in follow-up. After surgery is growing up the choice to avoid WBS with 131I before ablative therapy, because of the possible stunning effect.

In follow-up, at present, a central point is related to Tg dosage both after therapy withdrawal and, more recently, after rhTSH administration. This measurement could be used alone, as 1st test, in patients with differentiated carcinoma at low risk of recurrence. WBS with 131I is indicated in presence of high Tg values or when antibodies can affect reliability of serum analysis. This approach is not yet generally accepted in tumors at intermediate/high risk. WBS has ever to be performed in presence of high Tg levels before a radiometabolic therapy. In case of negative WBS, PET-FDG can be suggested. In WBS the use of 123I has been proposed, but there are not yet data supporting its general use instead of 131I because of higher costs. With respect to the use of rhTSH to increase accuracy both of Tg and WBS, its clinical use can be already accepted in patients at high risk, with a worst prognosis, with a low pituitary response.

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