Pitfalls and uncommon problems in thyroid cancer management

Thyroid cancers are fairly common, but medical oncology departments will generally come across only the small minority of patients with advanced or recurrent disease that responds poorly to standard treatments. These patients require comprehensive oncological management, including radiotherapy and medical oncology as well as supportive care.

Thyroid cancers are quite common cancers and they can generally be cured. They are managed primarily by endocrinologists, surgeons specialised in endocrine surgery and specialists in nuclear medicine. A small proportion of patients, no more than 1 in 20, experience a poor outcome. Drawing on our experience of managing more than 250 cases of this kind at the Centre Léon-Bérard at Lyon, this e-grandround explores the different types of thyroid cancer and their diagnosis, behaviour and management, as well as key challenges such as loss of radio iodine uptake and the management of bulky metastases and metastases that have mutated from the primary cancer. It also looks at the potential of new drugs developed in this setting, several of which are also being studied in more common cancers.

Differentiated thyroid cancer

There are two histological subtypes of differentiated thyroid cancer: papillary thyroid carcinoma (PTC) and PTC

European School of Oncology
e-grandround

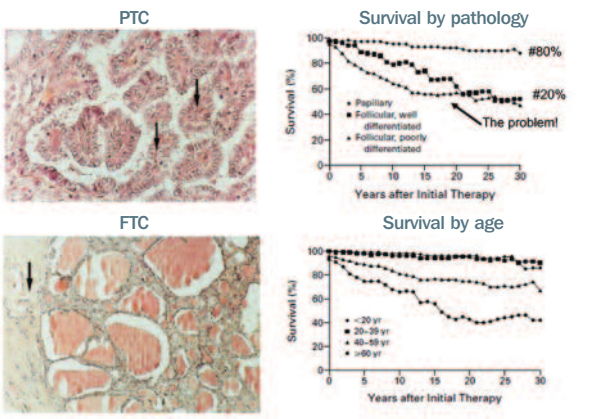
The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*.

In this issue, Jean-Pierre Droz, Professor Emeritus of Medical Oncology at the Centre Léon-Bérard, Lyon, France, reviews the medical treatment of advanced disease in patients with thyroid cancers that pose particular challenges, drawing on the centre's experience in the management of approximately 250 patients.

Christelle de la Fouchardière, also of the Centre Léon-Bérard, poses questions that explore the issue further. The presentation is summarised by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net/home.do

PAPILLARY AND FOLLICULAR THYROID CARCINOMA



Survival rates are poorer for follicular than papillary thyroid carcinoma, and they worsen with patient age

Source: © 1998 Massachusetts Medical Society. All rights reserved. MJ Schlumberger. Papillary and follicular thyroid carcinoma. *NEJM* 1998; 338:297–306

with follicular differentiation (FTC). A good review by Martin Jean Schlumberger published ten years ago in the *New England Journal of Medicine* (*NEJM* 1998, 338:297–306) showed that patients with PTC had a better prognosis than those with FTC, particularly those with poorly differentiated FTC. Age is also an adverse prognostic factor (see figure above).

In general, the guidelines for the treatment of differentiated thyroid cancer recommend initial management with a total thyroidectomy and radioactive iodine (I^{131}) therapy. Patients then have a good inhibition of thyroid stimulating hormone (TSH) production and their thyroglobulin is followed. In cases of recurrence, the standard treatment is radioactive iodine therapy (*Eur J Endocrinol* 2006, 154:787–803)

The first challenging issue in differentiated thyroid cancer is that there are patients with metastatic disease with radio iodine uptake who can lose their uptake. For example, the CT scans for a patient with differentiated thyroid cancer lung metastases, shown in the figure below, show an initially strong uptake of radio iodine. However, five years later, after four applications of radio iodine, there was no more uptake of radio iodine in the lungs.

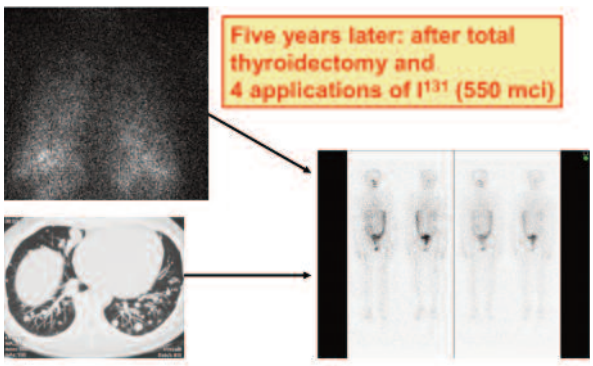
There are two explanations for this observation. The first is that the disease is still differentiated – papillary or follicular thyroid carcinoma – but it becomes functionally different with the loss of radio iodine uptake. The other possibility is that the disease becomes poorly differentiated. This is the problem of pathological switch. Poorly differentiated carcinoma is often called 'insular carcinoma'.

A case study that illustrates this was that of a 40-year-old woman who had initially multiple bulky bone metastases without lung metastases. In 1999, she had a thyroidectomy for papillary + follicular thyroid carcinoma without any undifferentiated components within the thyroid. She received several radio iodine applications and then had surgery to treat spinal cord compression and hip fracture with hip replacement. In 2002, she had a bulky iliac metastasis, which grew. A biopsy showed poorly differentiated carcinoma.

One year later, this woman had multiple lung micronodules without I^{131} uptake. Histology showed both solid and insular patterns. Iodine scintigraphy showed absolutely no uptake of iodine. We can assume that in this patient the development of lung metastases may have been linked to the switch from differentiated carcinoma to poorly differentiated carcinoma.

Another possible scenario is the coexistence of both histological patterns. For example, a 48-year-old woman had a thyroidectomy in 2000 for the combination of papillary thyroid carcinoma and poorly differentiated thyroid cancer. At the same time, she had lung and right shoulder/arm bone metastases. She received several applications of radio iodine, but despite a good iodine uptake she had growing shoulder metastases with fracture. The decision was made to perform surgery, with the upper part of the humerus being replaced. The figure opposite shows the humeral metastasis, the presence of lung metastasis and very good iodine uptake on the scintigraphy both

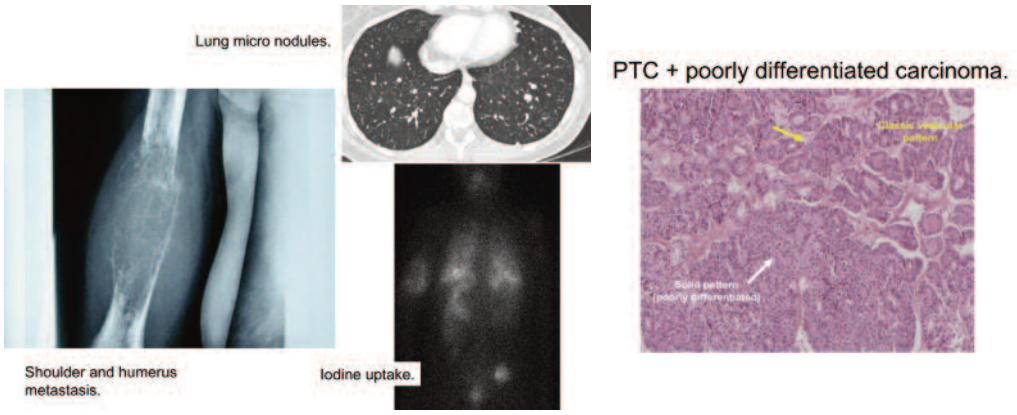
LOSS OF RADIO IODINE UPTAKE



Initially the radio iodine treatment was taken up in the lung metastases of this patient (top left). Five years later, however, there is no evidence of radio iodine uptake in the lungs (right-hand image) despite lung metastases being clearly revealed on CT scan (bottom left)

Source: Slides courtesy of Centre Léon-Bérard, Lyon

TWO HISTOLOGIES CAN COEXIST



At initial diagnosis, this patient had a papillary thyroid carcinoma with undifferentiated areas and multiple bulky bone metastases. The slide of a humeral metastasis, taken three years later, shows the cancer has areas of poor differentiation, which was associated with the development of lung metastases a year later

Source: Slides courtesy of Centre Léon-Bérard, Lyon

in the lung and in the arm. Histology showed a classic vesicular pattern and a solid pattern of poorly differentiated carcinoma.

There is growing interest in functional imaging with PET scans in patients with differentiated thyroid cancer. A case study illustrating its value is that of a 41-year-old woman who underwent a thyroidectomy for papillary thyroid carcinoma in 1995. Her thyroglobulin increased despite several administrations of radio iodine. She had absolutely no uptake. Eleven years later, a PET scan showed the presence of bone metastases in the pelvis (see top figure overleaf). This patient was managed with a RANK-ligand inhibitor.

A scan several months later showed extension of bone metastases. The thyroglobulin level increased despite the presence of good inhibition of thyroid-stimulating factor. There was no more iodine uptake, and the FDG radiotracer uptake showed metastases in the adrenal gland and extended metastases within the bone. As at the start, the use of functional imaging was interesting, but the metastases could also be seen on anatomical imaging in a CT scan.

The problem of bulky metastases

Bulky metastases pose a very difficult problem and there is no consensus on management. The challenge is illustrated by the case of a 50-year-old man with no known history of thyroid problems. In 2005, he felt pain in his spine, and was found to have a large-volume iliac metastasis and thyroid cancer. A biopsy of the metastasis showed the presence of follicular thyroid carcinoma. Shortly after, he had a thyroidectomy for a combination of papillary thyroid carcinoma and poorly differentiated thyroid cancer. He had major iodine uptake of I^{131}, and a decision was made to proceed with debulking surgery of the unique iliac bone metastasis.

The huge uptake of I^{131} on the right part of the pelvis can be seen in the bottom figure overleaf. There is residual uptake after thyroidectomy, although this is common. The original CT scan shows a huge metastasis within the bone, and also within the muscle. It is very unlikely that this patient could be managed only with I^{131}, because the activity would be small in this large tumour.

After debulking surgery, the PET scan shows there is still uptake of the FDG radiotracer, and this area is clearly tumoural, so there is a need to perform additional treatment with radio iodine.

Medullary carcinoma

Medullary carcinoma is not really cancer of the thyroid because it is derived from normal C cells.

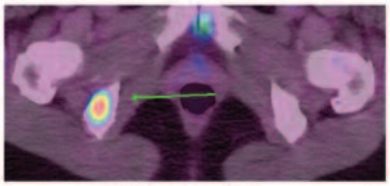
There are three main points in the recommendations for management:

- It is important to determine information on the genetics of the disease, and particularly the possibility of a hereditary medullary cancer or even a mutation in the RET gene.
- It is important to look for adrenal gland abnormality, and particularly a phaeochromocytoma, as well as hyperparathyroidy.
- Surgery is clearly the standard treatment. Patients must have thyroidectomy plus level VI compartmental lymph node resection. This is the only curative treatment.

A patient's calcitonin level, as well as carcinoembryonic antigen (CEA), must be followed carefully. If calcitonin is raised, imaging should be used for further investigation. A solitary metastasis should be managed with surgery, while a patient found to have extensive

THE VALUE OF PET SCANS

- Woman, 41 years; thyroid familial antecedents: goitre in father, mother, brother.
- 1995 thyroidectomy for goitre. PTC stage pT3b.
- Thyroglobulin increases despite 400 mci I^{131}. NO UPTAKE.
- 2006: FDG-PET scan=



- Inclusion in a RANK-L inhibitor protocol.

This PET scan picked up very clearly a bone metastasis in the pelvis of a woman who had undergone a thyroidectomy for papillary thyroid carcinoma 11 years earlier

PTC – papillary thyroid carcinoma, FDG – fluorodeoxyglucose radiotracer
Source: Slide courtesy of Centre Léon-Bérard, Lyon

metastases should be considered for a clinical trial.

Differential diagnosis of medullary carcinoma can be challenging. We have observed two patients where this has been a problem. The first was a 55-year-old man, who had backbone metastases with muscle invasion. He underwent a thyroidectomy and the initial diagnosis was differentiated carcinoma (papillary thyroid carcinoma). There was absolutely no radio iodine uptake and his thyroglobulin levels were low (0.3 ng/ml) without antibodies. Scintigraphy showed no radio iodine uptake on the bone metastases and MRI showed cervical and lumbar metastases, muscle invasion and spinal cord compression (see lower figure, p19).

What were the hypotheses? The first was dedifferentiation, with the possibility that it was a papillary thyroid carcinoma that may have switched to an insular or poorly differentiated carcinoma. An alternative possibility was metastatic disease of other origin. The most likely possibility, however, was medullary carcinoma. The serum tumour marker profile was strongly in favour of this diagnosis, with a slight elevation of carcinoembryonic antigen (20 ug/L), elevation of the NSE (neuro-specific enolase) biomarker (68 ng/ml) and elevation of calcitonin (800 ng/ml), which was very significant. Review of the pathology slides showed an immunohistochemistry profile that strongly supported a diagnosis of medullary carcinoma, with no uptake of thyroglobulin, staining with calcitonin and carcinoembryonic antigen.

IMAGING MEDULLARY THYROID CANCER

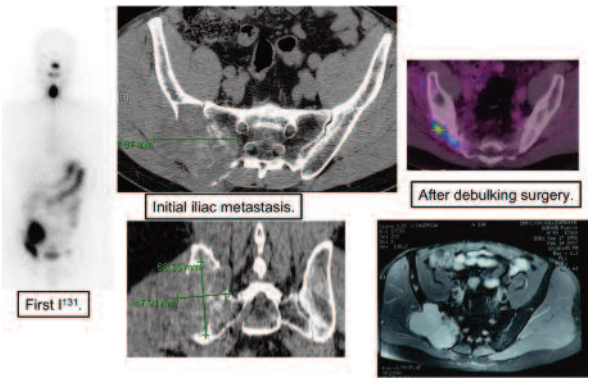
When a patient undergoes surgery and has increased serum calcitonin levels, a range of different imaging techniques are indicated. These included ultrasound to explore the neck, CT scan for the liver (but this can be difficult to interpret, MRI is also useful for the liver imaging), functional imaging with FDG-PET scan, octreoscan, MIBG-I^{131} scanning, an Indium scan and laparoscopy.

What about liver metastases? In medullary thyroid carcinoma, liver metastases are sometimes difficult to see; for example, some metastases are more visible on the portal phase of a CT scan than on the arterial phase. In these cases MRI may be more accurate, particularly with the use of gadolinium enhancement. Injection of gadolinium is the best method to visualise liver metastases in such a patient.

THE POTENTIAL OF TARGETED DRUGS

There are several different targets in thyroid cancers. These include the angiogenesis receptors, such as VEGF-R; PDGF-R, C-KIT and, more importantly RET, particularly in medullary carcinoma, and fusion genes RET/PTC in PTC, and BRAF in papillary thyroid carcinoma. A study with sorafenib suggested there is a relationship between the drug's activity and particular mutations of BRAF (MS Brose et al., abstract A6002, ASCO 2009). Other receptors are EGF-R and c-MET. RET is a transmembrane receptor, which is a tyrosine kinase. It needs dimerisation for activity.

BULKY METASTASES



There is no consensus on managing bulky metastases. This very large pelvic metastasis was debulked and the residual tumour – visualised on a PET scan – was then treated with radio iodine

Source: Slides courtesy of Centre Léon-Bérard, Lyon

Trials in differentiated thyroid cancer

Published phase II trials

There are three important trials in differentiated thyroid cancer. The first is a trial with motesanib, with the targets of VEGF-R, PDGF-R and C-KIT. The trial included 93 patients and showed a partial response rate of 14%, with 33% of patients having stable disease at more than six months (*NEJM* 359:31–42). More than 50% of patients had clinical benefit – a combination of partial response plus stable disease for more than six months.

The second trial is with sorafenib. Clinical benefit in a fairly large series was found to be around 70%.

The third trial is with axitinib, which acts on VEGF-R. This resulted in a 30% partial response rate and a 70% clinical benefit in total.

Published abstracts of phase II trials

Abstracts of early trials in differentiated thyroid cancer treated with sunitinib published in 2008 showed clinical benefit of around 80%. There is now an ongoing phase II randomised trial of vandetanib versus placebo.

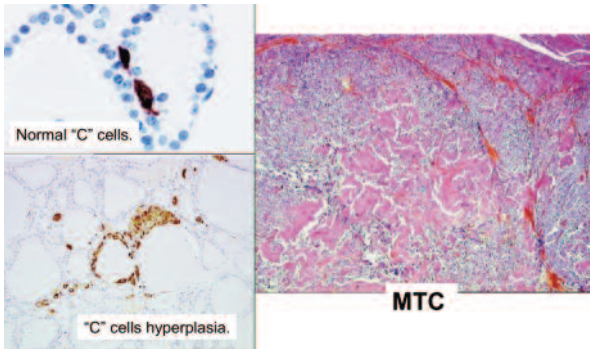
The results from trials with sorafenib in differentiated thyroid cancer show a good proportion of patients achieving partial response and stable disease, but anaplastic or poorly differentiated carcinoma does not respond.

However, there are adverse events with sorafenib, such as hand foot syndrome, which affects 90% of patients, as well as diarrhoea and hypertension. Dose reduction is required in 50% of patients treated with the drug, and 20% of patients came off the drug due to its toxicity.

Future trials

A randomised trial is planned of sorafenib versus placebo with crossover in patients with differentiated thyroid cancer. A phase II trial is also planned of the new drug E7080, which acts on PDGF-R, VEGF-R and EGF-R, in 104 patients with differentiated thyroid cancer who are refractory to I^{131}, either upfront or further down the line.

MEDULLARY CARCINOMA



Medullary cancer is derived from normal C cells

Source: Slides courtesy of Centre Léon-Bérard, Lyon

Trials in medullary carcinoma

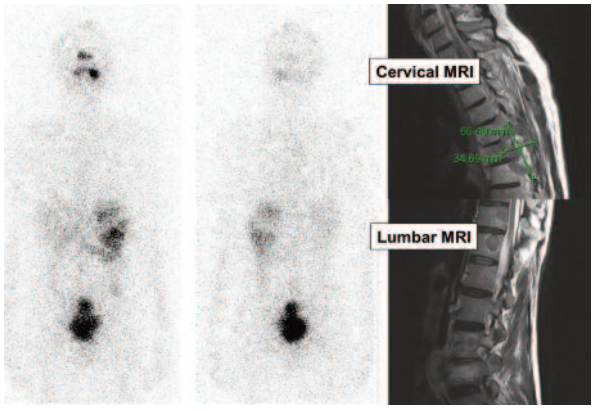
Published phase II trials

There is a very good study with motesanib where the rate of clinical benefit – mainly stable disease at more than six months – is around 80% (*JCO* 27:3794–3801).

Vandetanib, which acts on RET, EGF-R and VEGF-R, has been studied specifically in hereditary medullary carcinoma, showing a partial response rate of 20% and an overall clinical benefit of 70% (*JCO* 28:767–772).

Very small trials have also been conducted with gefitinib and axitinib.

PROBLEMS OF DIAGNOSIS



The two MRI images on the right show cervical and lumbar vertebral metastases and epidural involvement with medullar compression, yet scintigraphy shows no iodine uptake on the bone metastases

Source: Slides courtesy of Centre Léon-Bérard, Lyon

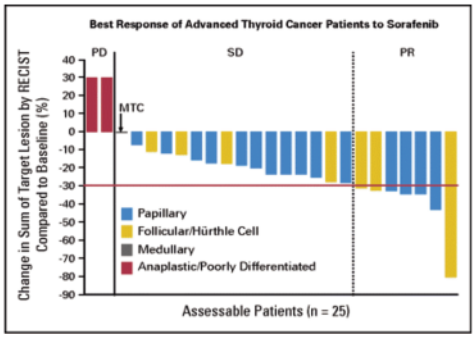
Published abstracts of phase II trials

There is a very interesting study of XL184, which acts on VEGF-R2 and RET and c-MET, with a response rate of 40% and clinical benefit of 80% (Kurzrock 2008, Proc 20th EORTC–NCI symposium on Molecular Targets and Cancer Therapeutics, abstract 379).

Future trials

The most important trial planned for medullary carcinoma is a study randomising to XL-184 versus placebo without crossover. There is also a phase II trial of E7080 planned in patients with progressive medullary carcinoma.

THE POTENTIAL OF TKIs



The tyrosine kinase inhibitor sorafenib induced disease stabilisation and partial response in a good proportion of thyroid cancer patients, but was ineffective in anaplastic or poorly differentiated thyroid cancers. Motesanib, axitinib and sunitinib have also shown some promise, and more TKIs, such as E7080 are in the pipeline for use in this setting

Source: Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved. V Gupta-Abramson et al. Phase II trial of sorafenib in advanced thyroid cancer. *JCO* 2008; 26:4714–4719

Drugs available in clinical practice

At the moment, no drug has been registered for the treatment of differentiated thyroid carcinoma or medullary carcinoma. In differentiated thyroid cancer, we consider that sorafenib is likely to be used in the future. There is interest in sunitinib, although efficacy has yet to be demonstrated. There is clearly uncertainty around the development of motesanib, and it is too early for vandetanib. In medullary carcinoma, the early results of new drugs are promising but it is too early to draw any conclusions for vandetanib and XL-184.

Metastatic sites

There are some surprising observations regarding the sites where metastasis occurs. The most common metastatic site is the cervical lymph nodes, followed by the mediastinal lymph nodes and lungs.

Bone metastases are also observed commonly. The main problem for bone metastasis is fracture, but spinal cord compression can also occur.

Uncommon metastatic sites

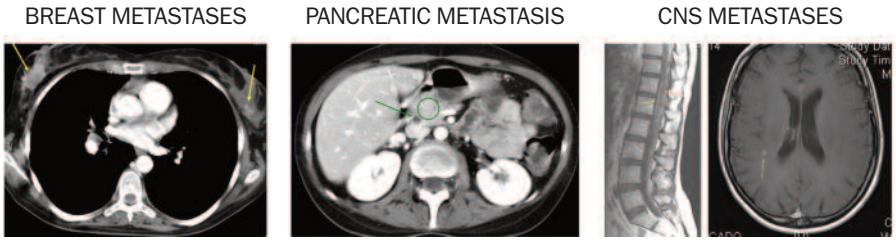
Metastases sometimes occur at very uncommon sites, which can complicate differential diagnoses. This is illustrated by the case history of a 35-year-old woman with no familial history who underwent a thyroidectomy for her thyroid tumour. The tumour was a locally involved, poorly differentiated medullary carcinoma, which was absolutely typical. She had elevated calcitonin after surgery, but no metastases at that time. Five months later, her calcitonin had increased, but, more importantly, CT scans showed uncommon metastatic disease. She had two metastases in the breast, which were confirmed by microbiopsy, and a pancreatic metastasis with dilatation of the biliary tract. The patient was treated with etoposide and cisplatin, but this failed. She then developed epidural and CNS involvement (see figure below).

Another patient had involvement of the bronchus, which could be differentiated from a primary lung cancer. This proved to be a thyroid tumour. A further patient had a kidney metastasis, with a solid tumour on the left kidney. It is important to remember that there are patients with kidney metastases whose primary tumour is thyroid, underlining the need to perform a biopsy to be certain of the diagnosis. We have also seen metastasis in the adrenal gland in a patient with differentiated thyroid cancer. In the case of medullary carcinoma, the problem is a differential diagnosis with phaeochromocytoma.

Another case showed a leukaemic reaction – a frail woman, aged 83 years, who had a huge thyroid cancer, which on biopsy proved to be an anaplastic thyroid carcinoma. She had hyperleukocytosis with leukaemoid reaction in both the blood and marrow smear. The possible mechanism for this may be hypersecretion of G-CSF and GM-CSF.

Another uncommon presentation

UNUSUAL METASTATIC SITES



It is unusual for thyroid carcinomas to metastasise to the breast, pancreas or central nervous system. These ones developed in a woman who had been diagnosed with a seemingly typical poorly differentiated medullary thyroid carcinoma

Source: Slides courtesy of Centre Léon-Bérard, Lyon

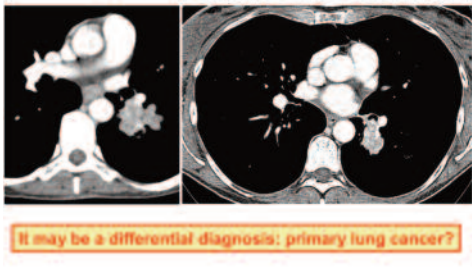
we have observed is paraneoplastic syndrome. This was found in a 40-year-old man who in 2000 had a thyroidectomy for locally advanced disease, which was found to be medullary carcinoma. His calcitonin level was greatly increased, but he had no metastases on CT scan at that time. One year later, he developed a neuropathy, and five years later he developed metastatic disease in the mediastinal lymph node and in the liver.

Paraneoplastic neuropathy developed as increasing sensitive neuropathy in the foot, leg, thigh and elbows, with pain and no paresthesia. There was slight hypoesthesia, but no other clinical abnormality. The diagnosis was neuronal sensitive neuropathy on EMG. We found no antineuronal antibodies. We know that subacute sensitive neuropathy is paraneoplastic in half (47%) of patients, and the majority have antibodies, although this was not the case in this patient.

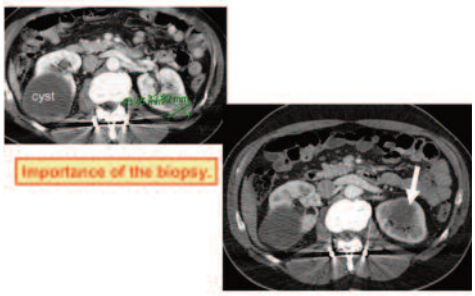
Question: *In the results from clinical trials, the majority of differentiated thyroid cancer patients show a very slow progression and maintain a good quality of life for months or years, even without any specific treatment. Is six months follow-up really appropriate to evaluate the response in new drug trials? And is a stable disease response really due to therapy, or the natural history of the disease?*

Answer: *I am also involved in renal cancer, which is treated with the same drugs, and there we have the same problem. In medullary cancer, the randomised trial that is comparing XL-184 against placebo without any crossover should be able to answer the question of whether there is an impact on survival. In trials, six months is generally considered to be a good surrogate for activity.*

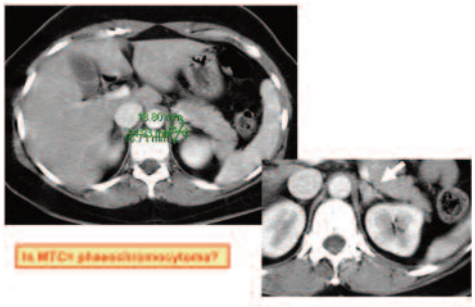
DIAGNOSTIC PITFALLS



(b) Kidney metastases



(c) Adrenal gland metastases



These lesions are all metastases from thyroid cancers, but without a careful differential diagnosis, they could mistakenly be identified as (a) originating from a lung cancer, (b) a primary kidney cancer, and (c) a phaeochromocytoma

Source: Slides courtesy of Centre Léon-Bérard, Lyon

I should mention that some trials have required evidence that a patient had progressive disease during the six months before starting the treatment as a condition for them joining the trial. This could be a good way to approach this problem.

To conclude, the question is well put, but I think the effect of these treatments is completely different from what we saw in the past with chemotherapy. It may be the beginning of a great story of the use of these treatments in patients who are not likely to receive standard treatment – surgery, radio iodine and even radiotherapy.

Uncommon pathologies

There are several variants or uncommon pathologies, including: poorly differentiated carcinoma (insular), Hürthle cell carcinoma, tall-cell carcinoma and diffuse sclerosing papillary thyroid carcinoma. In general, they have a worse prognosis than standard papillary, or even follicular, thyroid carcinoma.

Anaplastic thyroid carcinoma

Anaplastic thyroid carcinoma (ATC) is a rare tumour, accounting for less than 2% of thyroid cancers. It occurs in patients aged over 65 years. The origin is differentiated thyroid cancer or goitre. There are specific mutations, including RAS, BRAF and p53, and the diagnosis is generally made under a huge cervical mass (see figure overleaf). Approximately 40% of patients have metastases at diagnosis.

The pathology shows aspects of both papillary and anaplastic thyroid carcinoma. On immunochemistry, anaplastic thyroid carcinoma shows no staining for TTF-1 (thyroid transcription factor-1) or for thyroglobulin, as is shown with papillary thyroid carcinoma.

An example of anaplastic thyroid cancer is shown in the case of a 50-year-old woman, who presented with a huge ATC. In 1996, she had total thyroidectomy plus cutaneous cervical reconstruction. She received chemotherapy with doxorubicin 50 mg/m² + cisplatin 50 mg/m², with supportive care

(G-CSF + erythropoietin + nutritional supplementation) and radiotherapy (total dose around 60 Gy). The treatment schedule was two cycles of chemotherapy and then radiotherapy, followed by four cycles of chemotherapy. She completed the therapy and recovered very well and was followed by CT scan until 2006.

The patient's post-radiotherapy fibrosis was very limited, but there were several, very limited lung metastases. We administered radio iodine, and there was absolutely no uptake, but then this patient had a positive PET scan. We decided to perform a surgical excision of all metastases and we observed that the recurrence was due to a papillary differentiated tumour. She was treated four years ago and is currently in complete remission and very well.

Question: *Why did you decide to administer radio iodine in the patient who had an anaplastic thyroid carcinoma?*
Answer: *The initial diagnosis was anaplastic thyroid carcinoma plus a small proportion of papillary thyroid carcinoma. We took the chance. Ten years later, she had lung metastases we wanted to know whether radio iodine could be active. There was no uptake, so we then decided to operate. Fortunately, it was papillary thyroid carcinoma.*

TAKE HOME MESSAGES

- Careful pathological diagnosis is the cornerstone of decision making in thyroid cancer management.
- Total thyroidectomy remains the only curative treatment for thyroid cancer in general. It is added to radio iodine in differentiated cancer, but is the only curative treatment in medullary carcinoma.
- The majority of patients are cured by surgery and radio iodine.
- In progressive disease, it is important to control serum tumour markers, and to combine morphological and functional imaging.
- Targeted drugs become important in the clinical management of these rare cases, at least in the setting of clinical trials.

Question: *We have a 38-year-old man with papillary and follicular thyroid carcinoma, maybe in a mixed pattern, who has lung metastases but who is asymptomatic. He has received seven doses of radio iodine and has shown no radiological response but remains asymptomatic. How long should you continue with radio iodine treatment?*
Answer: *What is important is the patient's benefit. This patient is not curable, but while he is asymptomatic you can wait, you can observe and make decisions depending on progression. Sometimes, you can observe progression with imaging, such as a CT scan. It is important also to check for uptake. At some time, you must decide to include the patient in a trial, when he requests to do so or when there is progression or a symptom. It is a palliative treatment, and what you have to do is achieve the best quality of life for the patient. These new treatments are very interesting, but they are toxic.*

Question: *Are there any validated immunochemistry markers for premalignant thyroid lesions?*
Answer: *This is not my field of expertise. What I would say is that there is an evolution from an atypical adenoma, but there is no immunochemistry staining that is useful here. There are, however, interesting studies that look at the differences in gene expression between true differentiated carcinoma and suspected adenoma.*

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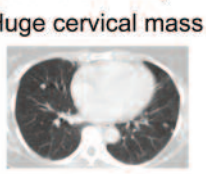
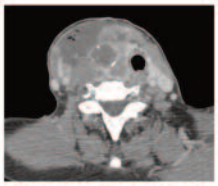
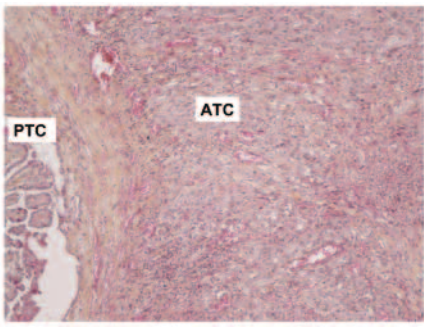
ANAPLASTIC THYROID CARCINOMA

- Incidence: 1.6% of TC, M/F 1:1 age > 65y
- Origin in DTC and goitre
- Mutations: RAS, BRAF, p53+++
- Huge cervical mass





- Metastases: 40% at diagnosis (lung, liver, CNS)



These cancers are very rare and only occur in older age groups

TC – thyroid cancer, DTC – differentiated thyroid cancer, CNS – central nervous system, PTC – papillary thyroid cancer, ATC – anaplastic thyroid cancer
Source: Slides courtesy of Centre Léon-Bérard, Lyon