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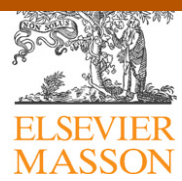

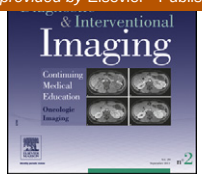

CONTINUING EDUCATION PROGRAM: FOCUS. . .

The role of imaging in staging and monitoring testicular cancer

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Abstract The prognosis for testicular cancer is excellent, with a 5-year survival rate greater than 95%. Patients affected can therefore expect to be cured after treatment. Successful treatment requires assessment of the condition at the various stages of its management. Imaging plays a major role in initial analysis of the lymphatic extension and in looking for metastases. It is essential for evaluating the response to treatment and during follow-up after treatment. CT is the most commonly used imaging method in this context, but the role of PET is currently developing. The purpose of this paper is to review the role of the imaging methods commonly used in the management of testicular cancer.

Testicular cancer accounts for 1% of malignant tumours in men. It is the commonest cancer in men between 20 and 40 years of age. It is rare before the age of 15 and after 50 years old. Its incidence has doubled in the last 40 years to reach the figure of four to six/100,000 inhabitants in developed countries [1].

95% of testicular cancers are seminomatous or non-seminomatous germ cell tumours: seminomatous tumours occur above all in men between the ages of 35 and 45 years (median = 38 years), while non-seminomatous tumours occur mainly in men between 15 and 35 years old (median = 28 years).

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Despite its increasing incidence, testicular cancer has become a model of curable cancer over the last 20 years, due to the different therapeutic protocols based on surgery (inguinal orchiectomy), radiotherapy, and chemotherapy including platinum salts. The cure rate for early stages is 99%, and for advanced stages with a good prognosis, intermediate prognosis and poor prognosis, 90%, 75 to 80% and 50% respectively [2]. The prognosis depends on early diagnosis and the histopathological type of the tumour.

Imaging using ultrasound examination of the scrotum plays a major role in initial diagnosis of the tumour. It also has a prominent position in staging, looking for lymph node or visceral metastasis, in evaluating the response to treatment after radiotherapy or chemotherapy, and in monitoring treated patients for possible recurrence.

The aim of this paper is to clarify and justify the imaging examinations to be carried out in the initial staging of testicular cancer and in assessment of the tumour during treatment and post-therapeutic follow-up.

Imaging examinations to be performed in staging testicular cancer

Several classifications are used in the literature for the initial assessment of a germ cell tumour of the testis. In imaging, it is recommended to apply the TNM international classification criteria, which differentiate between the local tumour and lymph or haematogenous extensions [3—6] (Boxed text 1). With these TNM classification criteria, it is possible to include patients in one of the four stages of the AJCC classification [7] (Table 1), which is often used to determine the prognosis and patient survival, the latter also being provided by the International Germ Cell Cancer Collaborative Group (IGCCCG) classification [2] (Table 2).

Boxed text 1 TNM classification 2002 [6].

T. Only pathological classification is used after orchiectomy.

pTx: Tumour cannot be assessed (no castration).

pT0: No tumour (e.g. fibrous scar).

pTis: Carcinoma in situ (or intratubular neoplasia: ITP).

pT1: Tumour limited to the testis and/or the epididymis without vascular or lymphatic invasion. The lesion may infiltrate the tunica albuginea but not the tunica vaginalis.

pT2: Tumour limited to the testis and/or the epididymis with vascular or lymphatic invasion, or lesion crossing the tunica albuginea and invading the tunica vaginalis.

pT3: Tumour infiltrating the spermatic cord.

pT4: Tumour infiltrating the wall of the scrotum.

N: Only concerns the regional lymph nodes (interaortocaval, paraaortic, paracaval, preaortic, precaval, retroaortic, retrocaval). Other lymph node areas are considered metastatic zones (N = pN).

Nx: Lymph nodes cannot be assessed.

N0: No lymph node metastasis.

N1: 1 or more lymph nodes of less than 2 cm.

N2: 1 or more lymph nodes between 2 and 5 cm.

N3: Lymph nodes of more than 5 cm.

M: Distant metastases.

Mx: Metastases cannot be assessed.

M0: No metastasis.

M1: Distant metastases.

M1a: Non-regional nodal or pulmonary metastases.

M1b: Other metastatic sites.

The T stage

In determining the T stage, there is currently little or no contribution from imaging. Ultrasound examination of the scrotum does indeed confirm the diagnosis of a solid intratesticular tumour [8,9] (Fig. 1a), but it does not provide sufficiently reliable information to analyse the key points of the T stage: whether the tunica albuginea, tunica vaginalis, epididymis or spermatic cord are involved and looking for vascular or lymphatic emboli [3—5]. MRI of the testes seems to be more efficient than ultrasound for detecting involvement of the tunica albuginea, the epididymis and the spermatic cord [10], but only the histological analysis of the specimen after inguinal orchiectomy is today taken into account in determining the T stage of testicular cancer, which is thus always a postoperative pT stage [3—5].

Table 1 AJCC classification [7].

Stage I	Tumour limited to the testis (normal CT and markers)
Stage I serological	Tumour limited to the testis with persistence of elevated markers
Stage II	Subdiaphragmatic lymph node involvement
II a	<2 cm
II b	2 to 5 cm
II c	>5 cm
Stage III	Supradiaphragmatic lymph node or pulmonary or other visceral involvement

This classification applies only to testicular germ cell tumours.

The N stage

To determine the N stage, it must be remembered that the lymphatic drainage of the testis occurs preferentially along the spermatic vessels and that the first lymph nodes involved (the regional nodes") in neoplastic extension are in the retroperitoneum at the confluence of the spermatic veins and the inferior vena cava. In exploration of a left testicular cancer, these nodes should be sought under the left renal vein near the junction of the left spermatic vein (Fig. 1b). For a right testis, these nodes should be sought in the right paracaval, precaval or interaortocaval regions level with vertebra L2 (Fig. 2). These retroperitoneal lymph node sites, satellites of the spermatic veins, need to be analysed as a priority to determine the N stage. Beyond these

Table 2 International Germ Cell Cancer Collaborative Group (IGCCCG) classification [2].

	Non-seminomatous tumours	Seminomas
Good prognosis	Primitive testicular or retroperitoneal No extrapulmonary visceral metastasis alphaFP < 1000 ng/mL and HCG < 5000 IU/L and LDH < 1.5 × N	All initial sites and no non-pulmonary visceral metastases and normal alphaFP[a]
Intermediate prognosis	Primitive testicular or retroperitoneal No extrapulmonary visceral metastasis — Markers (one only): alphaFP > or equal to 1000 and < 10,000 ng/mL HCG > or equal to 5000 and < 50,000 IU/mL LDH > or equal to 1.5 × N and < 10 × N	All initial sites and presence of non-pulmonary visceral metastases and normal alphaFP[a]
Poor prognosis	Primitive mediastinal or extrapulmonary visceral metastasis/metastases or alphaFP > 10,000 ng/mL or HCG > 50,000 IU/mL or LDH > 10 × N	

[a] Possibly elevation of total HCG.

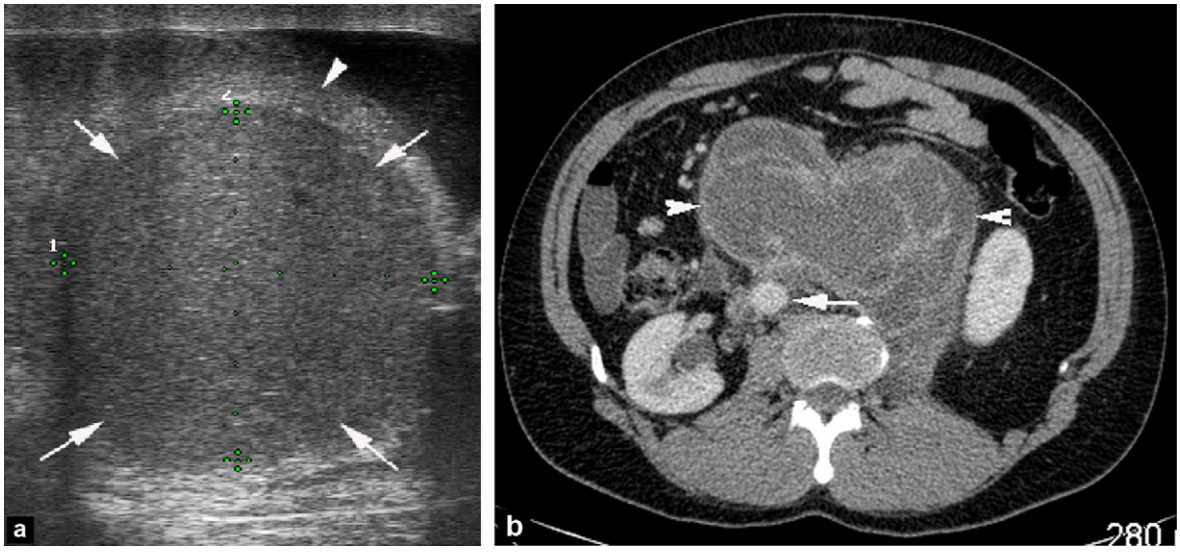

Figure 1. Regional adenomegaly of a left testicular seminoma: a: initial assessment — ultrasound of the left part of the scrotum: well-delimited hypoechoic left testicular mass (arrows). Normal testicular tissue (arrowhead); b: initial assessment — chest/abdomen/pelvis CT scan with injection of contrast agent; abdominal slice passing through the renal pedicles: left latero-aortic retroperitoneal lymph node satellite mass of the left renal vein (arrowheads), displacing the aorta and inferior vena cava to the right (arrow).

regional sites, any lymph node involvement is considered as metastatic and should be included in the M stage.

Unlike the T stage, current recommendations clearly call for imaging examinations to determine the N stage [3—5], and more specifically, for systematically undertaking a chest/abdomen/pelvis CT scan immediately before or after orchiectomy. The value of a CT scan in this context was reported in the 1990s [11], but no recent papers have been published on the possible contribution of multislice" technology in this indication, one of the conclusions of a meta-analysis published in 2009 [12].

Neoplastic lymph node diffusion (stage greater than N0) is confirmed in the scan if a hypertrophied lymph node (adenomegaly) is found in the retroperitoneum. The short diameter of the lymph nodes should be the measurement considered. Taking 1 cm as the limit, CT scan specificity is excellent (100%). Its sensitivity, however, is poor (37%), as micrometastases do not cause lymph node hypertrophy and are therefore systematically missed (the method's false negatives) [11].

Differentiation between stages N1, N2 and N3 is however easy with a CT scan once adenomegalies have been isolated in the retroperitoneum. If the adenomegalies are less than 2 cm in diameter, the stage is N1; between 2 and 5 cm, it is N2 and more than 5 cm corresponds to stage N3 [6].

If we limit ourselves to simply analysing lymph node measurements and looking for adenomegaly, MRI performs similarly to CT for detecting retroperitoneal lymph node metastases. Indeed, the percentage of micrometastases not causing lymph node hypertrophy is similar in MRI and CT scans [13]. A few recent publications have reported the advantage of combining conventional MRI sequences

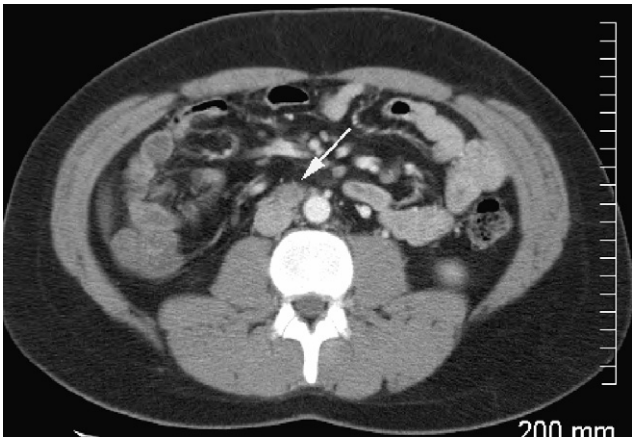

Figure 2. Regional adenomegaly of a right testicular seminoma. Initial assessment — chest/abdomen/pelvis CT scan with injection of contrast agent: abdominal slice passing through the renal pedicles: interaortocaval retroperitoneal adenomegaly (arrow), corresponding to a regional lymph node extension of the right testicular seminoma.

with injection of a contrast medium targeting lymph nodes (USPIO), so as to be able to analyse the lymph node content and thus pick out micrometastases [14,15]. This technique, employed above all for prostate cancer, is still currently very little used, because it is restricting for both the patient and the radiology team. MRI is therefore only proposed in this indication as a replacement for a CT scan, and only in patients in whom injection of an iodinated contrast agent is contraindicated [3,4]. Lymph node analysis is limited to looking for adenomegalies.

A recent study by the National Cancer Research Institute Testis Cancer Clinical Studies group [16] evaluated the performance of 18FDG PET in nodal staging of testicular cancers with a good prognosis, chemotherapy being offered to PET positive patients and monitoring to PET negative patients. Given a rate of recurrence in patients with negative PET scans which was too high (33 patients out of 87), this study was interrupted. The sensitivity of 18FDG PET does not at present seem to be sufficient to detect lymph node micrometastases and single out patients with a low risk of recurrence. Its use is not recommended in the initial staging of testicular cancer.

The M stage

The M1 stage consists of visceral metastatic and non-regional lymph node involvement (e.g. subdiaphragmatic lymph node involvement). Visceral metastases, principally pulmonary and to a lesser extent, liver, brain or bone, are caused by the extension of testicular cancer via a haematogenous route. A CT scan is currently the most precise and most rapid imaging method for exploring the entire trunk, looking for metastases in the lungs and other target organs [3—5]. The superiority of a CT scan of the thorax over a chest X-ray has been demonstrated in this context [17]. However, for seminomatous tumours with a good prognosis, a CT scan of the thorax can be replaced by an ordinary chest X-ray [3,4], irradiation from an ordinary chest X-ray being about 40 times less than from a CT scan of the chest (0.1 mSv as against 4 mSv).

Cerebral MRI may be proposed in addition to the chest/abdomen/pelvis CT scan when a secondary brain localisation is suspected from clinical data, and systematically for testicular tumours with a poor prognosis [3,4]. Its performance in detecting brain metastases is superior to that of a CT scan. A spinal MRI may also be proposed when vertebral metastasis has been shown on the CT scan.

Bone scintigraphy using technetium-99m labelled phosphate derivatives is recommended in patients when bone metastasis is suspected from clinical or laboratory tests [3,4]. However, 18FDG PET is not indicated in initial staging of testicular cancer.

Imaging examinations to be performed for evaluation of metastatic testicular cancer during treatment

This section deals exclusively with metastatic testicular cancer requiring treatment in addition to inguinal orchiectomy. This chemotherapeutic treatment, including platinum salts (the BEP protocol: bleomycin, etoposide, cisplatin) is highly effective on nodal masses and visceral metastases. The purpose of imaging is to monitor the evolution of the metastatic targets under treatment by measuring their diameter over several consecutive examinations, taking the initial staging as the reference. According to the RECIST 1.1 criteria [18], monitoring lymph node targets uses measurement of the shortest diameter of an adenomegaly and monitoring visceral targets measures the longest diameter of the lesion. At the most, two lymph node targets and two targets per organ need to be included in this monitoring (and up to 5 targets in total). Changes in the sum of the diameters determine the response to treatment. A reduction of at least 30% indicates a partial or total response and an increase of at least 20% shows progression. In addition, the appearance of a new lesion is a major factor indicating progression.

With its high spatial resolution and its anatomical precision, the chest/abdomen/pelvis CT scan is the standard examination for analysing the response of metastases of testicular cancer to treatment [3,4,19,20]. Monitoring is focused in the majority of cases on retroperitoneal lymph node masses (Figs. 3—5) and/or on secondary lung nodules. If injection of an iodinated contrast agent is contraindicated, an abdominopelvic MRI with a gadolinium injection can be proposed to monitor abdominal targets, and a chest CT scan without an injection of contrast agent to monitor pulmonary targets. Current recommendations of the French Association of Urology (AFU) advocate a chest/abdomen/pelvis CT scan 4 weeks after the end of chemotherapy. In major chemotherapy (three to four BEP courses), a CT scan after two courses is optional [21].

After chemotherapy, a residual nodal mass may remain (Figs. 4 and 5). This should be measured on the CT scan to decide whether to pursue additional treatment (salvage chemotherapy or surgery) or provide monitoring. The decision to surgically remove a residual mass depends on the seminomatous or non-seminomatous nature of the original tumour and the size of the residual mass (long axis). The rule

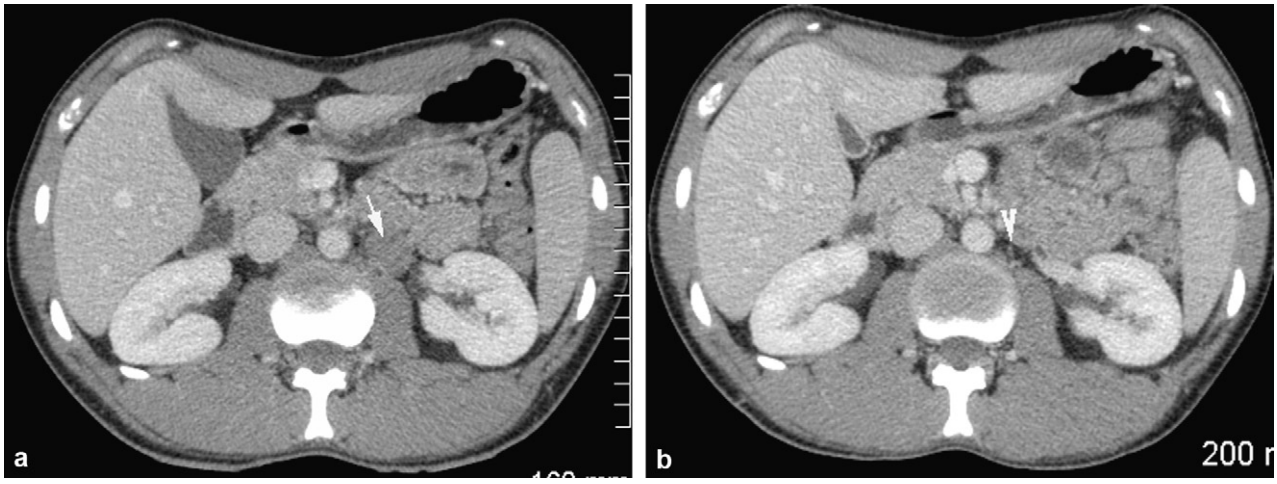

Figure 3. Complete response of an adenomegaly of the left spermatic cord in a left testicular non-seminomatous tumour treated by BEP chemotherapy: a: initial assessmentBEPchest/abdomen/pelvis CT scan with injection of contrast agent: abdominal slice passing through the renal pedicles: satellite adenomegaly of the left renal vein (arrow); b: re-evaluation after three courses of BEPBEPchest/abdomen/pelvis CT scan with injection of contrast agent: abdominal slice passing through the renal pedicles: complete disappearance of the adenomegaly (arrow).

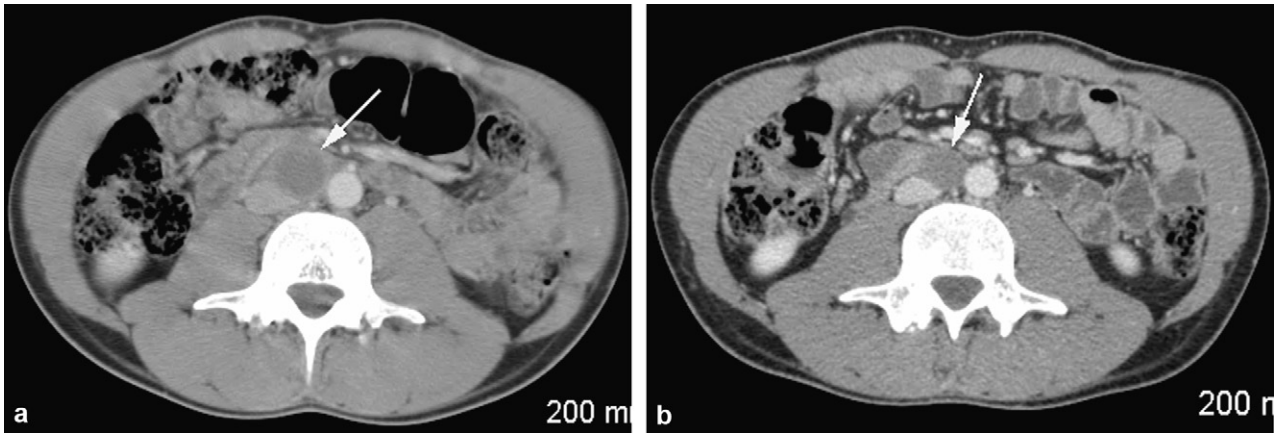

Figure 4. Residual mass of less than 3 cm of a right non-seminomatous tumour after BEP chemotherapy: a: initial assessment — chest/abdomen/pelvis CT scan with injection of contrast agent: abdominal slice passing through the renal pedicles: interaortocaval adenomegaly of 3 cm (arrow) corresponding to a regional lymph node extension; b: re-evaluation after three courses of BEP — chest/abdomen/pelvis CT scan with injection of contrast agent: persistence of a retroperitoneal adenomegaly measuring less than 3 cm located in the interaortocaval region (arrow).

is to propose systematic surgical resection of residual masses with a long axis of at least 3 cm [22]. Since morbidity from such a procedure is not negligible, the fundamental question concerns the vitality and severity of these residual masses, and since the end of treatment CT scan cannot answer this question, several studies have evaluated 18FDG PET in this indication [23—28]. Some have concluded that the absence of fixation of a mass of long axis greater than or equal to 3 cm seems to indicate the absence of persistent tumour tissue within this mass, PET reliability not apparently being so good for masses of less than 3 cm. Other authors consider that there are false-positive fixations of residual masses corresponding not to tumour tissue but to inflammation, necrosis or fibrosis. Regarding the risk of progression to a mature teratoma (especially for non-seminomatous tumours), some authors have concluded that PET could not differentiate a mature teratoma from healing fibrosis, or necrosis. PET thus has no clear indication in monitoring the residual masses of testicular cancer. Interpretation seems to be problematic even, in non-seminomatous tumours. The current findings of the AFU, however, insist on the fact that 18FDG PET is useful for reassessing metastatic seminomatous tumours with residual masses 4 to 6 weeks after chemotherapy, in order to choose between simply monitoring or treating them [21]. Two different situations must be defined depending on the size of the residual masses (±3 cm). In the case of a mass less than 3 cm, careful monitoring is recommended. PET is optional because it is non-specific. If the mass is greater than 3 cm, a PET scan is recommended to assess the presence of metabolic activity providing evidence of active tumour tissue. Retroperitoneal lymph node dissection (unilateral) is recommended especially if the mass is fixed in the PET scan.

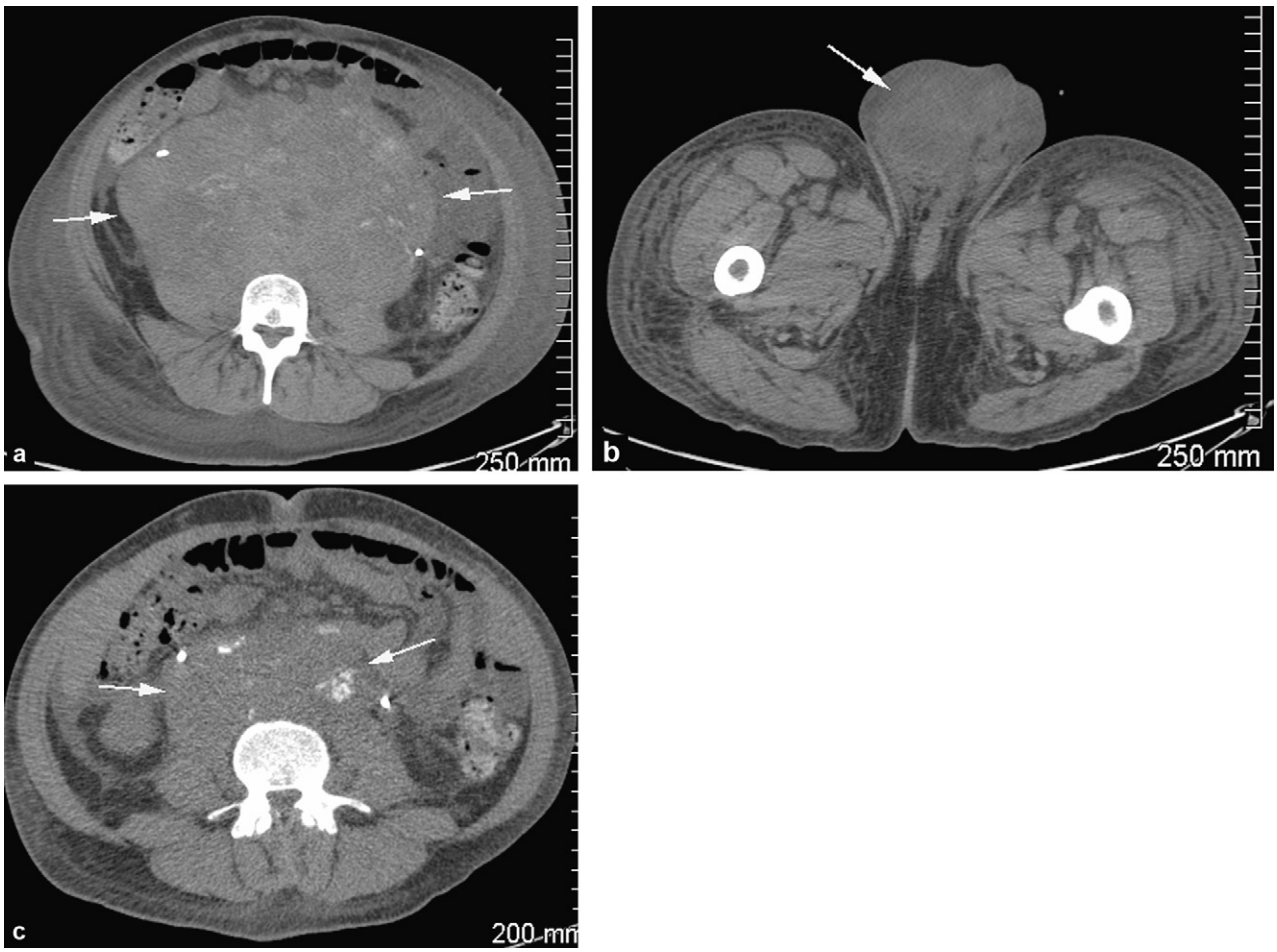

Figure 5. Residual mass of more than 3 cm of a right non-seminomatous tumour after BEP chemotherapy: a: initial assessment — chest/abdomen/pelvis CT scan with injection of contrast agent: abdominal slice passing through the renal pedicles: very large retroperitoneal nodal mass (arrows); b: initial assessment — chest/abdomen/pelvis CT scan with injection of contrast agent: abdominal slice through the perineum: right testicular mass (arrow); c: re-evaluation after four courses of BEP — chest/abdomen/pelvis CT scan with injection of contrast agent: persistence of a retroperitoneal mass with a long axis greater than 3 cm (arrows).

Imaging examinations to be performed in post-treatment monitoring of testicular cancer

As with any type of cancer, the monitoring strategy after treatment is fundamental for early detection of recurrence. In the case of the testis, recurrence mainly occurs in the retroperitoneal lymph nodes and the common iliac chains (60 to 97% of cases) [19,29] and occurs in 80% of cases within 1 year following orchiectomy and in 90%, within 2 years [30]. Late recurrence may also occur after 10 years or more [29]. The two important factors for recurrence seem to be the tumour being initially greater than or equal to 4 cm in size and invasion of the rete testis [29,31].

A special feature of testicular cancer is the ability to treat early recurrence with a very high survival rate after treatment (98%). This makes monitoring a real therapeutic option for cancers with a good prognosis and can, in certain circumstances, avoid excessive initial treatment. This monitoring is however demanding and should be reserved for compliant, lucid patients [3,4].

Optimal monitoring uses CT scans covering the thorax, abdomen and pelvis [3—5]. The frequency of these scans is very variable, depending on whether the tumour is seminomatous or non-seminomatous, on staging and the initial treatment. It can be very demanding. For example, in a patient with a non-seminomatous tumour with a good prognosis (pT1 N0 M0), a CT scan is currently recommended every 3 months during the first year and then every 4 months in the second year and every 6 months for the three following years [3—5]. This large number of scans poses the problem of the cumulative X-ray dose for the often very young patients. In an attempt to reduce this dose, a study reported the possibility, when monitoring tumours with a good prognosis, of performing just a chest X-ray with an abdominopelvic scan [17,32]. Another study prospectively followed two groups of patients with non-seminomatous tumours with a good prognosis: one group had five chest/abdomen/pelvis monitoring scans at 3, 6, 9, 12 and 24 months after orchiectomy and the other had two CT scans at 3 and 12 months. This article found that there was no greater benefit in the group of patients who had five CT scans over the group who had only two [33].

An abdominopelvic MRI is only indicated in patients with a contraindication for the injection of an iodinated contrast agent and in association with a CT scan of the chest without injection. The frequency of these two examinations is the same as for the chest/abdomen/pelvis scans [3—5].

Systematically performing a PET scan for monitoring testicular carcinoma is not recommended at present. One paper has however stressed its usefulness in patients with elevated serum markers unexplained by the chest/abdomen/pelvis scan [26].

It is recommended that the remaining testicle should be monitored, with regular self-examination and an annual ultrasound examination [3—5].

Conclusion

For diagnosing a testicular mass, echography is the prime first-line examination to undertake in addition to the clinical examination. The diagnosis of cancer and the degree of local involvement is provided by surgical removal of the testis (inguinal orchiectomy). Lymph node and visceral staging is achieved by a chest/abdomen/pelvis CT scan.

Monitoring during treatment and post-treatment follow-up rely heavily on CT scans, leaving only very few indications for MRI and PET scans. This poses the problem of the dose of X-rays delivered to often young patients whose prognosis is frequently good. Randomised studies must be performed in the future to optimise the radiation dose delivered to patients and to determine the most effective monitoring possible.

TAKE-HOME MESSAGES

- The initial staging of testicular cancer should use the TNM classification. The T stage is determined by histopathological analysis of the orchiectomy tissue, and the N and M stages by performing a chest/abdomen/pelvis CT scan. Indications for MRI are limited and are not systematic. 18FDG PET currently has no place in this context.
- The efficacy of treatment of metastases of testicular cancer is evaluated by performing a chest/abdomen/pelvis CT scan at the end of chemotherapy. 18FDG PET may be indicated for analysing the viability of residual nodal masses in seminomatous tumours.
- Post-treatment monitoring of testicular cancer should be by regular chest/abdomen/pelvis scans during the first 5 years. The frequency of examinations depends on the type of tumour, the initial staging and the treatment given. This monitoring should not ignore the remaining testis which should be checked by the patient himself and annually by ultrasound.

Clinical case

History of the disease

This 44-year-old man, with three children, consulted on 23rd March 2009 for the development, over several months, of a painless enlargement of the left side of the scrotum. On clinical examination, there was a left intrascrotal mass which was hard on palpation. Ultrasound confirmed the testicular origin and the nature of the tissue of the lesion, which measured approximately 6 cm in length. Markers taken on the same day (beta HCG, alpha foeto-protein) were normal.

Inguinal orchiectomy was performed on 25th March 2009. Analysis of the resected tissue provided a diagnosis of simple pT2 stage seminoma.

A chest/abdomen/pelvis (CAP) CT scan was performed on 27th March 2009. This showed a sub-renal retroperitoneal nodal mass encompassing the aorta and inferior vena cava measuring 8 cm in diameter (Fig. 6a). There was also left supraclavicular adenomegaly.

At the multidisciplinary meeting on 6th April 2009, it was decided to give four courses of BEP (bleomycin, etoposide, cisplatin) adjuvant chemotherapy.

The situation was monitored on 9th July 2009 by a CAP scan after the four courses of chemotherapy. This produced the conclusion that there was a therapeutic response greater than 50% and that there was a lymph node mass of 4 cm persisting in the retroperitoneum (Fig. 6b).

An 18FDG PET scan was performed on 17th July 2009; no fixation of this mass was found (Fig. 6c).

Lymph node dissection was performed on 14th August 2009. Examination of the tissue from surgery revealed exclusively the presence of necrotic tissue.

Questions

A. After the initial CAP scan, what were the TNM classification N and M stages in this patient?
B. Why was a PET scan performed in this context?

Answers

A. The retroperitoneal adenomegalies were “satellites” of the spermatic vessels. They were regional adenomegalies the large diameter of which was assessed to be 8 cm (i.e. greater than 5 cm). The N stage was therefore N3. The left supraclavicular adenomegaly could not be considered as “regional” and should not therefore be included in the N stage, but in an M stage. The M stage was therefore “M1”. The TNM classification in this patient was therefore pT2 N3 M1;
B. The PET scan was used to search for factors indicating active tumour tissue in the residual mass. If there had been fixation of this mass, the high probability of persistent tumour activity would have led to VIP salvage chemotherapy (ifosfamide, etoposide, cisplatin). The lack of fixation was a determining factor for deferring this salvage chemotherapy. Nevertheless, lymph node dissection was performed, because the large axis of the mass was greater than 3 cm.

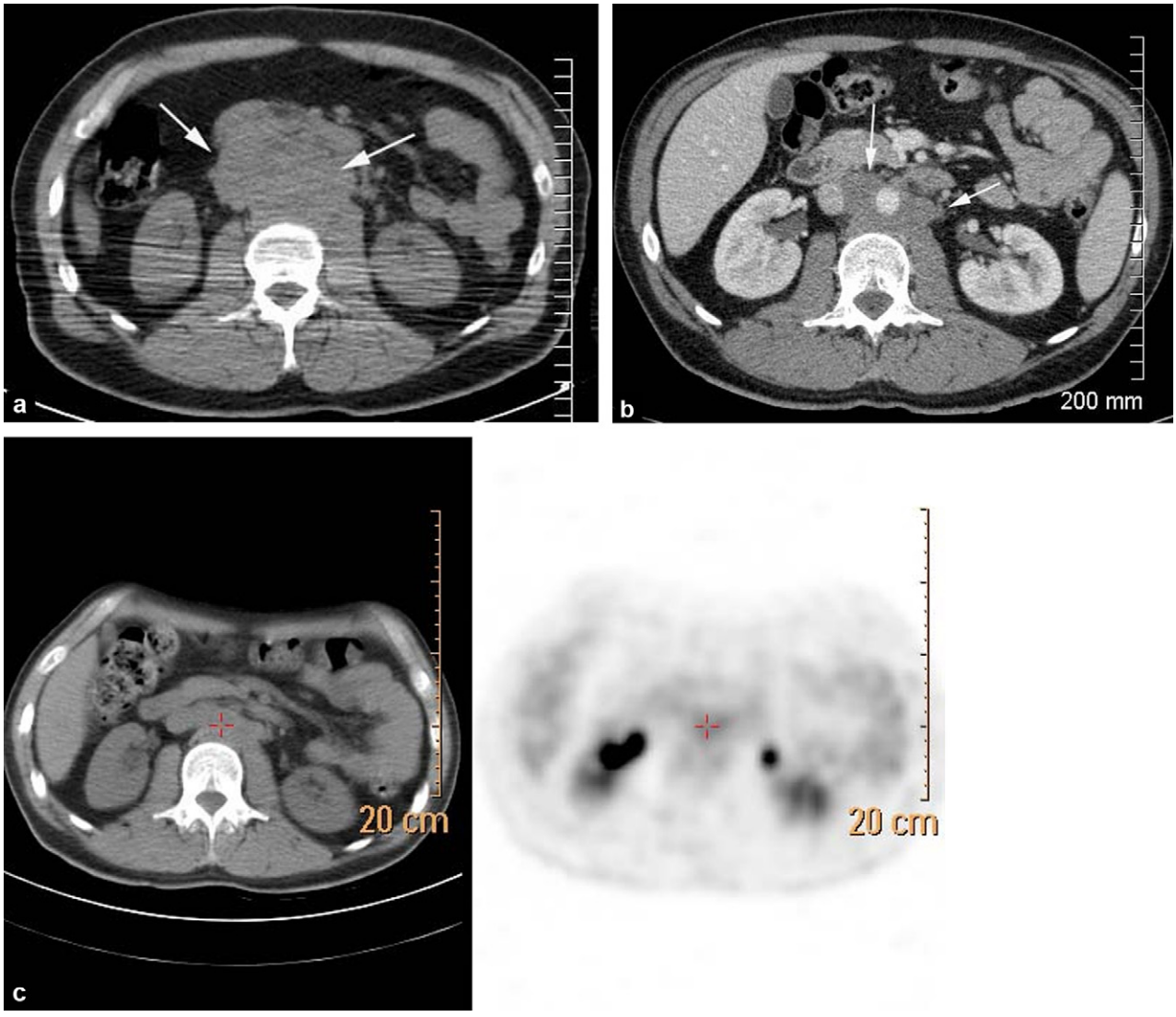

Figure 6. a: initial assessment-chest/abdomen/pelvis CT: scan without injection of contrast agent; abdominal slice passing through the renal pedicles: very large retroperitoneal mass of 8 cm corresponding to a regional lymph node extension (arrows); b: re-evaluation after 4 courses of BEP; chest/abdomen/pelvis CT scan with injection of contrast agent; abdominal slice passing through the renal pedicles: partial response (50%) demonstrated by a retroperitoneal residual mass measuring more than 3 cm (arrows); c: 18FDG PET: absence of fixation of the residual retroperitoneal mass (cross).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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