Interdisciplinary evidence-based recommendations for the follow-up of testicular cancer patients: a joint effort

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Interdisciplinary evidence-based recommendations for the follow-up of testicular cancer patients: a joint effort

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Summary

Detailed recommendations for the treatment of testicular cancer exist and due to the stringent application of the standard therapies, most patients can nowadays be cured. Moreover in the treatment of early stage disease, active surveillance is now a cornerstone of treatment. Hence there is a clear need for recommendations regarding the long-term follow-up of these young patients. These have to be safe, feasible and the intensity of procedures have to reflect the known risk of recurrence.

Different proposals have been published but they differ widely especially in terms of frequency and modality of imaging. In the last few years, new evidence has become available regarding the relapse pattern of different disease stages of testicular cancer, the use of imaging in follow-up and the risks of excessive radiation due to imaging, in particular with CT scans. In this article, an interdisciplinary, multinational working group has reviewed the evidence and based on this has formulated practical recommendations for the follow-up of patients with testicular cancer.

Key words: follow-up; malignant germ cell tumour; recommendations; testicular cancer

Introduction

Substantial progress has been made in the treatment of malignant germ cell tumours of the testis in the last three decades. Until the mid-seventies, radiotherapy was the only curative option for these patients. Since the introduction of cisplatin-based chemotherapy, the majority of patients with metastatic testicular cancer can now be cured. European recommendations for the diagnosis and treatment of germ cell tumours have been published and recently updated [1, 2]. Due to the stringent application of standard chemotherapy followed by resection of residual disease, relapse rates and mortality have been reduced even more within the last 15 years [3].

Moreover, the increased use of "active surveillance" programs for patients with stage I seminomatous and non-seminomatous germ cell tumours has changed the landscape. Active surveillance means that no adjuvant treatment is administered despite a known risk for recurrence. Instead, the patient is followed closely and treatment is started as soon as recurrence is detected. This has become an accepted approach because the survival rates between active surveillance and adjuvant therapies

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are comparable. Therefore "active surveillance" is more than just follow-up, but a strategy to avoid overtreatment and to use chemotherapy only for those patients who do really need it. Surveillance-based options particularly require clear recommendations for follow-up schedules. These have to be safe, feasible and the frequency of procedures have to reflect the known risk of recurrence.

There is no international consensus regarding the follow-up of patients with stage I malignant germ cell tumours or patients in complete remission after curative treatment. Oncological and urological organisations/societies in different countries have published their guidelines: European Association of Urology (EAU) [4], German Cancer Study Group [5], American NCCN guidelines [6] and European ESMO guidelines [7, 8]. These guidelines differ considerably especially in regard to the frequencies and types of imaging procedures.

A recent publication has shown that evidence-based follow-ups could be formulated based on the knowledge of different recurrence risks and recurrence patterns [9]. Patients should therefore be grouped into risk categories. An ideal follow-up schedule identifies a recurrence early without causing harm by using unnecessary radiation in these young long-term survivors.

The excessive risks of the radiation due to single or repeated computed tomography (CT) have been calculated [10, 11]. A single chest CT scan has about a 1000-times higher radiation dose than a single posterio-anterior chest X-ray [10]. The radiation exposure of each CT scan carries a small carcinogenic risk which is even more important in the young patient population. For example: a typical CT examination of the abdomen with an effective dose of 10 mSv increases the risk of fatal cancer induction by approximately 1:2000. Repeated examinations lead to a cumulative risk: if for example a patient has a yearly CT scan from the age of 20 until the age of 75, his risk of developing a malignancy due to these examinations may be as high as 4% [11]. While these calculations are discussed controversially, it is clear that every effort should be made to minimise the radiation burden.

All of these considerations have to be taken into account when devising follow-up schedules for young patients who have a relatively low risk of recurrence. Risk-adaptation of the guidelines is certainly of high importance.

Apart from tumour recurrence, follow-ups should include detection of long-term side effects of chemotherapy and radiotherapy. Hypogonadism, metabolic syndrome and cardiovascular disease as well as secondary malignancies are the most important long-term sequelae [12–16]. Patients who have undergone chemotherapy as well as radiotherapy have a particularly excessive risk for cardiovascular events or secondary tumours [14].

The following recommendations were initially developed by an interdisciplinary working group of Swiss medical oncologists, urologists and radiation oncologists in 2007 and 2008. They were presented and discussed by a multinational group with oncologists from both Germany and Austria in 2009. They represent the opinion of the involved authors according to the existing evidence and are based on broad personal experience. However, they do not represent certified guidelines.

The recommendations should help clinicians who are treating patients with testicular cancer. However, they can only cover the most frequent clinical situations and may have to be adapted to the specific features in an individual patient. It is important to recognise that a tertiary centre with special expertise in the follow-up and treatment of testicular cancer has to be contacted in selected cases.

The evidence and recommendations have been graded according to the guidelines defined by the American Society of Clinical Oncology. They are explained in Appendix A and are given in the text in square brackets.

Classification of follow-up groups

Testicular cancers are generally classified as seminomatous (seminoma) and non-seminomatous germ cell tumours (non-seminoma) of the testis. Mixed germ cell tumours belong to the group of non-seminomas.

The stage of disease and the choice of treatment (active surveillance vs chemotherapy vs radiotherapy) play a very important role for defining follow-up schedules. This is most obvious in the case of stage I disease where the risk of recurrence differs substantially between patients that have received adjuvant treatment or not. Whether chemotherapy or radiotherapy has been applied, influences the pattern of recurrence and long-term toxicity and therefore also has to be taken into account.

Metastatic testicular cancers are classified according to the International Germ Cell Cancer Collaborative Group (IGCCCG [17]) risk groups. Allocation according to good, intermediate or poor prognosis group is highly prognostic with 5-year survival differing from >90%, 75% and 50%, respectively.

In respect to follow-up schedules, we have devised nine groups:

Seminomatous germ cell tumours (Seminoma):

– Seminoma stage I

  - Adjuvant chemotherapy with carboplatin
  - Adjuvant radiotherapy
  - Active surveillance
- Seminoma stage IIA/B, treated with radiotherapy
- Seminoma stage IIB/C and III: good prognosis group with complete remission after chemotherapy [residual disease <3 cm or residual disease >3 cm with negative positron emission tomography-(PET-)CT two months after end of treatment].

For the rare case of seminoma patients with residual postchemotherapy disease >3 cm and a positive PET-CT (performed at an adequate chemotherapy-PET interval of at least two months) or patients with metastatic seminoma in the intermediate prognosis group, individual follow-up is recommended, preferably at centres with special expertise in the field.

Non-seminomatous germ cell tumours (Non-seminoma):

- Non-seminoma stage I
  - Active surveillance, low risk
  - Active surveillance, high risk
  - Adjuvant chemotherapy
- Non-seminoma stage II–III: good prognosis group with complete remission after chemotherapy (CR after chemotherapy alone or after resection of residual masses).

Patients with metastatic non-seminomatous germ cell tumours who have non-resectable residual disease as well as patients with metastatic non-seminomatous germ cell tumours in the intermediate/poor prognosis group are not included in the recommendations. These patients require follow-up on an individual basis by an experienced centre.

Modalities of follow-up

General recommendations

Follow-ups should be performed by a physician who has profound knowledge and experience in the treatment and follow-up of patients with germ cell tumours.

Thorough medical history and examination including palpation of axillary, supra- and infradiaphragmal regional lymphnodes and of the remaining testis are the cornerstone of each follow-up visit. Serum tumour markers, AFP (alpha-fetoprotein), HCG (human chorionic gonadotropin) and LDH (lactate dehydrogenase), must be checked at every visit. If possible, the tumour markers should always be checked in the same qualified laboratory. The role of LDH in the follow-up is debatable. It has limited sensitivity and specificity and a high rate of false-positive tests are found. However, as shown in a recent publication, it can contribute to identify recurrence in a significant number of cases [18]. Cautious interpretation of LDH is certainly necessary.

Evidence for the choice of imaging modality

Undoubtedly, CT scans of the thorax, abdomen and pelvis have to be performed for staging purposes at the time of diagnosis of a testicular cancer.

There are only few publications, however, that have focused on the modalities of imaging in the follow-up of testicular cancers. Two retrospective studies [19, 20] are noteworthy. White et al. showed that a CT of the pelvis is generally not necessary in this setting because recurrence outside the abdomen is very rare. There is a group of patients at increased risk of pelvic recurrence who must have pelvic CT included: bulky abdominal disease (>5 cm), previous history of maldescent testis or orchidopexy, history of previous scrotal surgery and invasion of the carcinoma into the tunica vaginalis of the testis [19] [Level III, B]. As a matter of fact, in most departments of radiology the pelvis is included in the CT of the abdomen due to the short examination times with new scanners. However, there is clearly more radiation exposure by adding the pelvis. It is therefore generally recommended only to scan the pelvis if the above mentioned risk factors are present or if the patient has received radiotherapy treatment for seminoma stage I (no "dogleg" radiotherapy).

Another publication [20] raises the question of whether a CT of the thorax is necessary or if standard chest X rays are sufficient for follow-up of patients with stage I non-seminoma. In this retrospective analysis, tumour recurrence was diagnosed in all cases by raised tumour markers, abdominal disease or visible metastases in conventional imaging, suggesting that an additional chest CT would have been of little additional value [20] [Level III, B]. Therefore we recommend chest X rays instead of chest CTs for routine follow-ups of most testicular cancer patients. In case of chest X rays, only posterio–anterior imaging is recommended.

Whether ultrasound could replace a CT scan of the abdomen for the evaluation of the retroperitoneum, is under debate. Certainly, abdominal ultrasound is highly dependent on the experience of the examiner and the anatomy and preparation of the patient. Ultrasound appears to have similar sensitivity and specificity for detection of retroperitoneal metastases in patients with testicular cancer as compared to a CT of the abdomen [21, 22] [Level III, B]. However, we recommend a CT scan in all cases where there is need to find a small retroperitoneal mass because ultrasound of the retroperitoneum has not been validated in pro-

spective trials and must be regarded as experimental for this purpose. Whenever the main aim is to exclude the presence of a larger retroperitoneal mass (e.g., growing teratoma), we recommend an ultrasound of the abdomen, mainly for the purpose of sparing additional radiation risk. If either the physician is not skilled enough or the patient is not suitable for ultrasound, a CT scan of the abdomen is the better choice.

The use of magnetic resonance imaging (MRI) of the retroperitoneum is a reasonable alternative imaging modality with no radiation exposure. However, there is no general access to MRI in all areas and experience with its interpretation is limited at the moment. Therefore MRI of the retroperitoneum is currently not generally recommended, but remains an option for specialised centres with MRI resources and experienced radiologists. Trials evaluating the use of MRI are running.

Contrary to its use for the evaluation of pure seminoma postchemotherapy residual lesions, PET or PET-CT have no role in the follow-up of malignant germ cell tumours of the testis [23] [Level III, B].

Ultrasound of the remaining testis

Patients after contralateral testis biopsy without evidence of testicular intraepithelial neoplasia (TIN, carcinoma in situ) do not need ultrasound of the testis at follow-up. The same holds true for patients whose remaining testis has been irradiated due to TIN. Patients <30 years with a low testis volume (<12 ml) are at a higher risk of developing a contralateral tumor [1]. Biopsy should be offered in these cases. Without a biopsy, we recommend that these patients have an annual ultrasound of the testis for 10 years. We further recommend manual clinical examination of the contralateral testis with every follow-up visit and a consecutive ultrasound in case of any suspicious findings.

It should be recommended to all patients that they do self-examination of the remaining testis.

Follow-up for long-term toxicity

Patients who have been cured with chemotherapy or radiotherapy may develop late toxicity [12–16]. This includes cardiovascular disease, metabolic syndrome (arterial hypertension, impaired glucose tolerance, hyperlipidemia, obesity) as well as hypogonadism and secondary malignancies. Regular check-ups of blood pressure, weight, Body Mass Index (BMI) as well as blood lipids are recommended at baseline and annually afterwards. Patients should be checked for hormonal imbalances (total testosterone, LH, FSH) one year after diagnosis and then on a yearly basis. In case of pathological findings or a suggestive history of hypogonadism (e.g., missing morning erection), the hormonal status should be determined repeatedly on an individual basis. In case of symptomatic testosterone deficiency, substitution has to be discussed.

It is very important that these patients are advised to adapt their lifestyle to control additional risk factors (e.g., no smoking, weight control, regular physical exercise).

The general recommendations for patients with testicular cancer are included in the respective follow-up schedules.

Recommendations for follow-up

Seminomatous germ cell tumours (Seminoma)

Stage I seminomas have a recurrence risk of 12–31% depending on tumour size and invasion of the rete testis. However, both risk factors have not been evaluated prospectively [24]. Active surveillance or adjuvant treatment with either radiotherapy or chemotherapy with carboplatin are equal treatment options according to published guidelines [1, 2]. For follow-up purposes it is important to distinguish the different risks of recurrence related to each modality. Patients after adjuvant treatment with radiotherapy or carboplatin are expected to have a recurrence risk of only about 5%. Therefore the follow-up schedule can be adapted accordingly. Martin et al. have calculated the annual risk of recurrence using more than 5000 stage I seminoma patients from different trials [25] [Level III, B]. They could show that, independent of the treatment modality, the risk of recurrence is highest in the first two years and decreases rapidly afterwards. The risk of recurrence 5 years after adjuvant treatment is <0.3% annually. In a recently published meta-analysis, Mead et al. demonstrated that recurrence in 2466 patients after adjuvant treatment for stage I seminoma very rarely occurred after more than 3 years (0.2% of all patients). Moreover, they found that 7 of 11 recurrences were found by scheduled abdominal CTs (at 12 and 24 months) after adjuvant carboplatin. However, CT scans of the chest and pelvis can safely be omitted in this patient group as they did not detect recurrences [26] [Level III, B] (table 1). In contrast, isolated pelvic and mediastinal recurrence can be found after adjuvant radiotherapy (paraaortic strip only) and therefore the follow-up tools and schedule have to be adapted accordingly (table 2).

There is controversy regarding the question of how many imaging investigations should be performed for active surveillance of stage I seminoma patients. A trial addressing this very question has just been initiated in the UK (TRISST; [27]). In this 4-arm trial, 3 vs 7 scans and CT vs MRI are evaluated. Until these results will be

Table 1

Seminoma stage I: after adjuvant carboplatin.

YEAR 1												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
CT abdomen												x
Ultrasound abdomen						x						
Ultrasound contralateral testis[1]												x

YEAR 2												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
CT abdomen												x
Ultrasound abdomen						x						
Ultrasound contralateral testis[1]												x

YEAR 3												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
Ultrasound abdomen						x						x
Ultrasound contralateral testis[1]												x

YEARS 4 and 5												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 6 - 10												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI												x
HCG, AFP, LDH												x
Creat, lipids, Testosterone, LH, FSH												x
Ultrasound contralateral testis[1]												x

Abbreviations: BP = blood pressure, BMI = Body Mass Index, Creat = serum creatinine
[1] ultrasound of contralateral testis in patients without biopsy of contralateral testis

available, we propose to perform four CT scans within the first two years. After that, CT may be replaced by ultrasound. This is a practical approach minimising the radiation exposure by maintaining the imaging frequency with an acceptable alternative imaging modality (table 3). Follow-up with imaging is discontinued after 5 years.

Regarding stage II seminoma patients, standard treatment is radiotherapy (stage IIA and B). Chemotherapy is a valuable alternative for all stages and is the standard for stage IIC. For stage II patients after radiotherapy, the follow-up schedule is the same as for stage I patients. In cases where no "dogleg" radiotherapy has been performed (standard treatment includes "dogleg" radiotherapy), a CT scan of the pelvis has to be included (table 4).

Patients after chemotherapy for metastatic disease in the good prognosis group who have achieved a complete remission are expected to have a low recurrence rate (10–18%). After two years, no more regular CT imaging is recommended (table 5).

In general, we recommend continuing clinical follow-ups (see general recommendations) for up to 10 years. In the case of treated patients, specific long-term toxicity (e.g., gastritis, cardiovascular disease, secondary malignancies) may occur and patients' symptoms and complaints should be taken seriously.

Table 2

Seminoma stage I: after adjuvant radiotherapy.

YEAR 1												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
CT abdomino-pelvic												x
Ultrasound abdomen						x						
Ultrasound contralateral testis[1]												x

YEAR 2												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
Ultrasound abdomen						x						x
Ultrasound contralateral testis[1]												x

YEAR 3												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 4 and 5												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound contralateral testis[1]												x

YEARS 6 - 10												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI												x
HCG, AFP, LDH												x
Creat, lipids, Testosterone, LH, FSH												x
Ultrasound contralateral testis[1]												x

Abbreviations: BP = blood pressure, BMI = Body Mass Index, Creat = serum creatinine

[1] ultrasound of contralateral testis in patients without biopsy of contralateral testis

Table 3

Seminoma stage I: active surveillance.

YEAR 1												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
CT abdomen						x						x
Ultrasound abdomen			x						x			
Ultrasound contralateral testis[1]												x

YEAR 2												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
CT abdomen						x						x
Ultrasound abdomen			x						x			
Ultrasound contralateral testis[1]												x

YEAR 3												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen						x						x
Ultrasound contralateral testis[1]												x

YEARS 4 and 5												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 6 - 10												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI												x
HCG, AFP, LDH												x
Creat, lipids, Testosterone, LH, FSH												x
Ultrasound contralateral testis[1]												x

Abbreviations: BP = blood pressure, BMI = Body Mass Index, Creat = serum creatinine
[1] ultrasound of contralateral testis in patients without biopsy of contralateral testis

Table 4

Seminoma stage IIA and IIB: after radiotherapy.

YEAR 1												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
CT abdomen												x
Ultrasound abdomen						x						
Ultrasound contralateral testis[1]												x

YEAR 2												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
Ultrasound abdomen						x						x
Ultrasound contralateral testis[1]												x

YEAR 3												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 4 and 5												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound contralateral testis[1]												x

YEARS 6 - 10												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI												x
HCG, AFP, LDH												x
Creat, lipids, Testosterone, LH, FSH												x
Ultrasound contralateral testis[1]												x

Abbreviations: BP = blood pressure, BMI = Body Mass Index, Creat = serum creatinine
[1] ultrasound of contralateral testis in patients without biopsy of contralateral testis

Table 5

Seminoma stage IIB/C–III: good prognosis group after chemotherapy (CR or residual disease <3 cm or residual disease >3 cm but PET negative).

YEAR 1												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						(x)						(x)
CT abdomen						x						x
CT chest						x[2]						x[2]
Ultrasound contralateral testis[1]												x

YEAR 2												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						(x)
CT abdomen												x
CT chest												x[2]
Ultrasound abdomen						x						
Ultrasound contralateral testis[1]												x

YEAR 3												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 4 and 5												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound contralateral testis[1]												x

YEARS 6 - 10												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI												x
HCG, AFP, LDH												x
Creat, lipids, Testosterone, LH, FSH												x
Ultrasound contralateral testis[1]												x

Abbreviations: BP = blood pressure, BMI = Body Mass Index, Creat = serum creatinine
[1] ultrasound of contralateral testis in patients without biopsy of contralateral testis
[2] only if presence of supradiaphragmal disease at presentation

Non-seminomatous germ cell tumours (Non-seminoma)

Stage I non-seminomatous germ cell tumours are divided into a low-risk group with a recurrence risk of approximately 15–20% and a high-risk group with a recurrence risk of 40–50%. The presence of vascular invasion in the primary testis tumour has become the most important and widely accepted risk factor for relapse [28, 29]. Following the risk-adapted treatment strategy, surveillance has been recommended for low-risk (no vascular invasion) stage I non-seminomas [1, 2], whereas high-risk (with vascular invasion) patients have been offered adjuvant chemotherapy with 2 cycles of BEP (bleomycin, etoposide, cisplatin), which reduces the risk of recurrence from 50% to approximately 2% [30]. The additional benefit of adjuvant chemotherapy is a reduced need for follow-up (table 8). Active surveillance is also an option for high-risk patients who are not willing to undergo adjuvant chemotherapy [1, 2]. Active surveillance can spare unnecessary chemotherapy for a significant proportion of patients but careful follow-ups are needed to ensure that recurrence is diagnosed while the patient is still in a good prognosis group situation, in order to maintain the excel-

Table 6

Non-seminoma stage I low risk: active surveillance.

YEAR 1												
Date												
Month	1	2	3	4	5	6	7	8	9	10	11	12
History, clinical exam, BP, BMI		x		x		x		x		x		x
HCG, AFP, LDH		x		x		x		x		x		x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray		x		x		x		x		x		x
CT abdomen				x								x
Ultrasound contralateral testis[1]												x

YEAR 2												
Date												
Month	1	2	3	4	5	6	7	8	9	10	11	12
History, clinical exam, BP, BMI		x		x		x		x		x		x
HCG, AFP, LDH		x		x		x		x		x		x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray		x		x		x		x		x		x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEAR 3												
Date												
Month	1	2	3	4	5	6	7	8	9	10	11	12
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 4 and 5												
Date												
Month	1	2	3	4	5	6	7	8	9	10	11	12
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 6 - 10												
Date												
Month	1	2	3	4	5	6	7	8	9	10	11	12
History, clinical exam, BP, BMI												x
HCG, AFP, LDH												x
Creat, lipids, Testosterone, LH, FSH												x
Ultrasound contralateral testis[1]												x

Abbreviations: BP = blood pressure, BMI = Body Mass Index, Creat = serum creatinine
[1] ultrasound of contralateral testis in patients without biopsy of contralateral testis

lent outcome of close to 100% disease-specific survival for the whole population.

In 20–25% of patients, tumour markers are negative and imaging is the only possibility to diagnose recurrence in these patients. The best evidence regarding the frequency of imaging for active surveillance in low-risk stage I non-seminoma patients comes from a large randomised phase III trial [31] [Level I, A]. This trial showed that 2 CT scans within the first year of follow-up (at 3 and 12 months) are equal to 5 CT scans, in terms of detection of recurrence in the low-risk group. For low-risk patients, the frequency of CT scans can therefore be safely reduced accordingly (table 6). However, the same tight follow-up schedule for clinical visits and tumour markers as in the trial should also be pursued in daily clinical practice. For high-risk patients, this trial does not provide enough evidence. Therefore we recommend a total of six imaging procedures during the first two years in this patient group (table 7).

Patients with metastatic non-seminoma in the good prognosis group who achieve complete remission with chemotherapy only or by additional complete resection of residual disease have recurrence rates that are below 10% [32]. Follow-up procedures, including imaging, can therefore be largely reduced especially in cases where a retroperitoneal lymph node dissection (RPLND) has been performed. For patients without RPLND, two additional CT scans of the abdomen are recommended. When RPLND was performed in pa-

Table 7

Non-seminoma stage I high risk: active surveillance.

YEAR 1												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI	x	x	x	x	x	x	x	x	x	x	x	x
HCG, AFP, LDH	x	x	x	x	x	x	x	x	x	x	x	x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray		x		x		x		x		x		x
CT chest						x						x
CT abdomen			x			x			x			x
Ultrasound contralateral testis[1]												x

YEAR 2												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI		x		x		x		x		x		x
HCG, AFP, LDH		x		x		x		x		x		x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray		x		x		x		x		x		x
CT chest												x
CT abdomen						x						x
Ultrasound contralateral testis[1]												x

YEAR 3												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
Ultrasound abdomen						x						x
Ultrasound contralateral testis[1]												x

YEARS 4 and 5												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 6 - 10												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI												x
HCG, AFP, LDH												x
Creat, lipids, Testosterone, LH, FSH												x
Ultrasound contralateral testis[1]												x

Abbreviations: BP = blood pressure, BMI = Body Mass Index, Creat = serum creatinine
[1] ultrasound of contralateral testis in patients without biopsy of contralateral testis

tients with complete resolution of retroperitoneal lymph nodes, it was demonstrated that mature teratoma or even viable tumours can be found in 10–20% of these cases [33, 34]. Therefore we recommend annual ultrasound of the retroperitoneum to rule out growing teratoma in these patients (table 9).

Again in all cases, we generally recommend to continue clinical follow-up (see general recommendations) for up to 10 years.

Conclusions

These recommendations are meant to serve as guidance and to help making decisions in the follow-up of testicular cancer patients. Most clinical situations are covered here. Recommendations, however, cannot address individual questions and needs. Therefore it is very important and in the patients' best interest to discuss special cases in a multidisciplinary team of an experienced centre.

Table 8

Non-seminoma stage I high risk: after adjuvant chemotherapy.

YEAR 1												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
CT abdomen												x
Ultrasound abdomen						x						
Ultrasound contraleral testis[1]												x

YEAR 2												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
CT abdomen												x
Ultrasound abdomen						x						
Ultrasound contralateral testis[1]												x

YEAR 3												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 4 and 5												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 6 - 10												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI												x
HCG, AFP, LDH												x
Creat, lipids, Testosterone, LH, FSH												x
Ultrasound contralateral testis[1]												x

Abbreviations: BP = blood pressure, BMI = Body Mass Index, Creat = serum creatinine
[1] ultrasound of contralateral testis in patients without biopsy of contralateral testis

This is even more important as, due to the lack of data, some of the recommendations are not based on published evidence.

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Table 9

Non-seminoma stage II–III good prognosis group: CR after chemotherapy alone or CR after chemotherapy followed by resection of residual masses.

YEAR 1												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						(x)						(x)
CT abdomen						x[3]						x
CT chest						x[2]						x[2]
Ultrasound contralateral testis[1]												x

YEAR 2												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI			x			x			x			x
HCG, AFP, LDH			x			x			x			x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray						x						x
CT abdomen												x[3]
Ultrasound abdomen						x						x
Ultrasound contralateral testis[1]												x

YEAR 3												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 4 and 5												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI						x						x
HCG, AFP, LDH						x						x
Creat, lipids, Testosterone, LH, FSH												x
Chest x-ray												x
Ultrasound abdomen												x
Ultrasound contralateral testis[1]												x

YEARS 6 - 10												
Date												
Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
History, clinical exam, BP, BMI												x
HCG, AFP, LDH												x
Creat, lipids, Testosterone, LH, FSH												x
Ultrasound contralateral testis[1]												x

Abbreviations: BP = blood pressure, BMI = Body Mass Index, Creat = serum creatinine
[1] ultrasound of contralateral testis in patients without biopsy of contralateral testis
[2] only if presence of supradiaphragmal disease at presentation
[3] if patient has not undergone retroperitoneal resection

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Appendix A

Levels of evidence and grading of recommendation

Level	Type of Evidence
I	Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies or from randomised trials with low false-positive and low false-negative errors (high power).
II	Evidence is obtained from at least one well-designed experimental study or from randomised trials with high false-positive and/or negative errors (low power).
III	Evidence is obtained from well-designed quasi-experimental studies such as non-randomised, controlled single-group, pre-post, cohort, time or matched case-control series.
IV	Evidence is from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies.
V	Evidence is from case reports and clinical examples.

Grade	Grading of recommendation
A	There is evidence of type I or consistent findings from multiple studies of types II, III or IV.
B	There is evidence of types II, III or IV and findings are generally consistent.
C	There is evidence of types II, III and IV but findings are inconsistent.
D	There is little or no systematic empirical evidence.