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Non-risk-adapted surveillance for patients with stage I nonseminomatous testicular germ-cell tumors: diminishing treatment-related morbidity while maintaining efficacy

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Background: With treatment leading to nearly uniform cure in clinical stage I nonseminomatous testicular cancer (CSI-NSGCT), diminishing treatment-related morbidity has become the primary concern. This study examined feasibility and outcome of active surveillance as treatment in an unselected CSI patient population.

Materials and methods: All patients with CSI-NSGCT referred from 1998 to 2007 to the British Columbia Cancer Agency and the Oregon Testis Cancer Program were retrospectively reviewed. A total of 233 patients were identified, of which 223 chose active surveillance.

Results: Vascular invasion (VI) was absent, present and unknown in 66%, 27% and 7% of cases, respectively. Overall, 49% of patients had embryonal predominant disease. Fifty-nine patients (26%) relapsed, all but one with good prognosis disease. VI was present in 30 relapsed patients. Most patients relapsed within 2 years (88%). Only 7 of 223 patients (3%) relapsed beyond 2 years. All relapses were in long-term remission following chemotherapy with or without retroperitoneal lymph node dissection (RPLND). Only 17 of 223 patients (8%) required postorchiectomy surgery. Disease-specific survival is 100% after a median follow-up of 52 months (3–136). No patient has required second-line chemotherapy.

Conclusions: Active surveillance for all CSI-NSGCT patients is associated with excellent outcomes comparable with the best results reported with primary RPLND or adjuvant chemotherapy. Nearly 75% of patients are spared any therapy after orchiectomy.

Key words: nonseminomatous testicular cancer, stage I, surveillance, testis cancer

introduction

An increasing number of patients with nonseminomatous testicular cancer (NSGCT) present as clinical stage I nonseminomatous testicular cancer (CSI-NSGCT) with normalization of tumor markers (TUM) and without clinical, serological or radiographic evidence of regional or distant dissemination after radical orchiectomy [1, 2]. Most patients with CSI-NSGCT can be cured by orchiectomy alone [3, 4]. Long-term survival is expected and has approached 100% for the last three decades irrespective of the postorchiectomy management strategy employed.

The most valid predictor of occult metastatic disease and subsequent disease progression in CSI-NSGCT is the presence of vascular invasion (VI) in the primary tumor, which is present in ~30% of CSI patients [5–7]. VI is most often used in risk-adapted studies to assign therapy for those deemed 'high risk'. The presence and percentage of embryonal elements, the size of the primary tumor, absence of yolk sac elements as well as MIB-1 staining measuring proliferative activity are other factors with predictive value although these factors are clearly dominated by VI in multivariate analyses [5]. The risk of subsequent metastases without any further treatment is ~50% for CSI patients with VI (high-risk group) and 15%–20% for CSI patients without VI (low-risk group) [5, 8].

Three different postorchiectomy management strategies, namely surveillance, primary retroperitoneal lymph node dissection (RPLND) and adjuvant chemotherapy with two cycles

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of bleomycin, etoposide and cisplatin (BEP), have been used in these patients, all of which lead to an excellent outcome of almost 100% long-term cure rate [4]. In the United States, a standard approach has been RPLND, while in Europe and Canada, primary surgical approaches have fallen out of favor and nonsurgical approaches now predominate. Recent European consensus guidelines recommend active surveillance for low-risk CSI-NSGCT patients and adjuvant chemotherapy with two cycles of BEP for high-risk CSI-NSGCT [9]. Across Canada, active surveillance is recommended for all CSI-NSGCT patients (Canadian Germ Cell Cancer Consensus Conference, King City, Ontario, October 19–20, 2007).

Given that all current strategies for CSI-NSGCT, when well carried out, lead to nearly uniform cure, diminishing treatment-related morbidity has become the primary concern.

Few large European or USA series of non-risk-adapted treatment have been reported. In this article, we report the outcomes of a large North American series utilizing primary active surveillance for all patients with CSI-NSGCT irrespective of risk profile.

materials and methods

All patients with histologically confirmed CSI-NSGCT referred from 1998 to 2007 to the British Columbia Cancer Agency (BCCA), British Columbia, Canada, as well as through the Oregon Testis Cancer Program, Portland, OR, were retrospectively reviewed.

Patients treated before this time period were excluded to allow for an unselected homogenous patient population diagnosed and followed with adequate imaging methods and, if necessary, treatment according to modern standards.

The BCCA with its four cancer centers manages ~90% of all testicular cancer cases in British Columbia. Since 1998, active surveillance has been the preferred treatment option for all patients with CSI-NSGCT irrespective of risk status. Over 80% of Oregon state's testicular cancer patients are seen and managed by a single provider.

After diagnosis of NSGCT, patients were initially staged using computed tomographic (CT) scans of the abdomen, CT scan or X-ray of the chest and TUM α-fetoprotein (AFP), human chorionic gonadotropin (HCG) and lactate dehydrogenase. Following orchiectomy, normal levels of HCG and AFP as well as normal chest X-ray/CT scan of the abdomen and pelvis were defined as the criteria of CSI. Elevated preorchiectomy TUM were followed after orchiectomy until normalization before patients were classified as CSI. Pathology was reviewed for tumor subtype and presence of VI at the respective cancer centers by experienced genitourinary pathologists.

All CSI-NSGCT patients were thoroughly informed about their estimated risk of recurrence and all three treatment options, primary RPLND, adjuvant chemotherapy and active surveillance, before choosing their treatment strategy. All patients receive the recommendation for active surveillance after this detailed discussion.

Since the institution of the non-risk-adapted surveillance policy in 1998, a total of 233 CSI-NSGCT patients have been identified, of which 9 (4%) underwent adjuvant chemotherapy, 1 primary RPLND (0.4%) and 223 patients chose active surveillance. Patient data on the primary tumor, relapse, treatment and follow-up were abstracted from the charts. If patients had been discharged from the center, current status was obtained through contact with the family physician or local oncologist. Embryonal predominant subtype was defined as ≥50% embryonal carcinoma in the primary tumor.

Surveillance procedures after orchiectomy varied slightly but consisted of frequent observations in the first year, less frequent in the second and rarely thereafter (Table 1).

Table 1. Frequency of follow-up investigations for CSI patients

Follow-up procedures	Frequency of examination (time interval in months)					
	1 year	2 years	3 years	4 years	5 years	5–10 years
BCCA						
LDH, AFP, HCG and clinical examination	2/3[a]	2	3	3	3	12
X-ray of the chest	3	3	6	6	6	12
CT scan of the abdomen/pelvis	3	3	6	6	6	–
Oregon Testis Cancer Program						
LDH, AFP, HCG and clinical examination	1.5	2	6	6	6	12
X-ray of the chest	1.5	2	6	6	6	12
CT scan of the abdomen/pelvis	3	4	–	–	–	–

[a]During the first year: visit every 4 weeks during the first 6 months, then every 6 weeks.

CSI, clinical stage I; BCCA, British Columbia Cancer Agency; LDH, lactate dehydrogenase; AFP, α-fetoprotein; HCG, human chorionic gonadotropin; CT, computed tomography.

Relapsing disease was classified according to the International Germ Cell Cancer Collaborative Group (IGCCCG) classification [10] and relapses were treated according to their IGCCCG class with three to four cycles of BEP in the majority of patients with four cycles of etoposide/cisplatin being primarily reserved for those good prognosis patients with contraindications to bleomycin. Subsequent follow-up was done as per institutional policy.

All patients were included into the analysis independent from their adherence and compliance with the surveillance schedule. Relapse-free as well as disease-specific survival intervals were measured from the date of orchiectomy to the date of relapse and date of death or last contact, respectively. Median follow-up was calculated from the date of orchiectomy to the date of death or last follow-up.

The study was approved by the respective ethics boards of BCCA, Vancouver, Canada, and the Providence Cancer Center, Portland, OR.

results

A total of 223 patients treated with active surveillance from 1998 to 2007 were identified and included in this analysis (Table 2). Median follow-up was 52 (range 3–136) months with 181 patients (81%) having been followed for ≥2 years.

VI was present in 27% of all patients and unknown in 7%. Forty-nine percent of all patients had embryonal predominant carcinoma.

Relapses occurred in 59 (26%) patients, of which 30 (30 of 59; 51%) had VI (Table 3). Median time to relapse was 4 months (range 2–49) with 50 of 59 (85%) patients relapsing within the first year after diagnosis, 52 of 59 (88%) relapsing within the first 2 years and 58 of 59 relapsing within the 3 years. Only seven (3%) of all 223 patients relapsed beyond 2 years: at 25, 26, 28, 32, 34, 35 and 49 months. Five of these patients relapsed with retroperitoneal lymphadenopathy, one patient with left supraclavicular lymph nodes and one patient relapsed

Table 2. Patient characteristics

Factor	Number of patients	%
Patients		
BCCA	159	
OR	64	
Median age	29 (15–63)	
VI		
Present	60	27
Absent	146	66
Unknown	17	7
Embryonal predominant		
Yes	109	49
No	112	50
Unknown		1
Embryonal predominant and VI		
All patients	40	17
VI-positive patients	40	67
Tumor marker elevation at initial diagnosis		
Yes	154	69
No	69	31
Median follow-up (months)	52 (3–136)	

BCCA, British Columbia Cancer Agency; VI, vascular invasion.

with lung metastases. None of these patients exhibited the chemotherapy resistance typical for late recurrences reported after primary chemotherapy: all seven patients responded well to chemotherapy with four patients achieving a clinical complete and three patients a marker-negative partial remission. Only two of these patients went on to an RPLND showing residual teratoma in one and necrosis in the other. All seven patients are recurrence and disease free at 5-, 11-, 13-, 29-, 45-, 73- and 75-month follow-ups calculated from the time of relapse.

Most importantly, all but one of the 59 relapsed patients were classified by IGCCCG criteria as good risk disease. The majority of patients developed retroperitoneal lymph node metastases ≤5 cm or rising TUM only, while lung metastases were rare (Table 3). Treatment consisted of chemotherapy in 98% of relapses with 78% of patients achieving a clinical complete remission not requiring postchemotherapy RPLND for residual disease.

Only 12 of 223 patients (5%) required a postchemotherapy RPLND for residual radiographic abnormalities, while one patient underwent an RPLND as primary recurrence treatment resulting in a 6% overall initial postchemotherapy RPLND rate for all 223 patients (13 of 223). Ten of the 12 patients had teratoma, one had necrosis and only one patient had viable cancer.

Four of the 59 relapsed patients required additional therapy. These four patients developed retroperitoneal radiographic abnormalities at 6, 10, 15 and 22 months. All these patients were successfully treated with surgical resection only, with all showing mature teratoma on pathology. No patient has required second-line chemotherapy. The latest recurrence of teratoma in this series has been 32 months and all four patients relapsing after primary therapy for recurrent disease had recurrent teratoma discovered at an easily resectable volume. Taking these patients into account, the overall requirement for any type of postorchiectomy surgery for the total population was 8% (17 of 223) only.

Table 3. Recurrences and final outcome for 223 unselected CSI-NSGCT patients on active surveillance

	Number of patients	%
Relapse		
Yes	59	26
No	163	73
Unknown	1	1
Distribution of risk factors		
VI positive only	8	14
VI plus embryonal predominant	22	37
Embryonal predominant and VI negative	11	18
Embryonal predominant and VI unknown	3	5
Embryonal negative and VI unknown	7	12
Embryonal negative and VI negative	8	14
Median time to relapse (months)	4 (1–49)	
Method of first relapse detection		
CT	27	46
TUM	31	53
Chest X-ray	0	0
Clinical examination	0	0
Other	1	1
IGCCCG stage at relapse		
Good	58	98
Intermediate	1	2
Poor	0	
Extent of disease at relapse		
RP LN (nfs)	16	27
RP LN ≤2 cm	14	24
RP LN >2 and ≤5 cm	13	22
RP LN >5 cm	1	2
RP LN and/or lung metastases	8	13
Marker increase only	7	12

CSI-NSGCT, clinical stage I nonseminomatous testicular cancer; VI, vascular invasion; CT, computed tomography; TUM, tumor markers; IGCCCG, International Germ Cell Cancer Consensus; RP LN, retroperitoneal lymph nodes; nfs, not further specified.

Disease-specific survival after a median follow-up of 52 months (range 3–136 months) is 100% with all but one patient being alive without disease. One patient died free of disease from a gunshot wound.

discussion

Our results represent a large modern North American series of unselected application of active surveillance as primary management for all patients with CSI-NSGCT. Several observations from our series bear emphasis. Our experience closely mirrors other large series of active surveillance with

~30% of patients recurring after orchiectomy [3,11–13]. In long-term follow-up, there have been no deaths in our series related to testicular cancer or complications of treatment. After a thorough discussion, almost all our patients choose active surveillance over adjuvant chemotherapy or RPLND and compliance has been sufficient such that recurring patients almost uniformly relapsed with good risk disease and were cured with chemotherapy. No patient has exhibited the late-relapsing, chemotherapy-resistant, germ-cell tumor phenotype typically seen at relapse after primary chemotherapy. Overall, only 8% of patients required any postorchiectomy surgery for management of their testicular cancer; 74% of patients required no interventions other than active surveillance after orchiectomy. The vast majority of the 26% of patients who required additional therapy were cured with standard outpatient chemotherapy alone with only 20% (8% of total population) requiring postchemotherapy surgery.

The results obtained in this series represent the combined efforts of experienced centers with formal germ-cell tumor programs utilizing expert radiologists, urologists and committed medical oncologists. A reasonable question is 'Can similar results be obtained in a community setting where non-subspecialized physicians are seeing unselected, potentially less motivated patients?' We feel that the answer would be yes. First, in our series, both centers managed large populations in their respective geographies and respective health care delivery systems. The large percentage of the total testicular cancer population seen and managed by the program mitigates concerns that these patients were highly selected, better insured and more motivated than the average patients. In addition, our patient population with ~30% high-risk and 70% low-risk patients is consistent with the known profile of an unselected CSI patient population [3, 13, 14].

Secondly, patients were managed over very large often vast geographies with patients commonly managed over distances requiring long drives or even air transportation. Thirdly, and most importantly, our results are very similar to other larger experiences with nonsurgical management of unselected CSI-NSGCT patients managed over a large geography [12, 13, 15, 16]. Our results also largely confirm the results of the Swedish-Norwegian Testicular Cancer Group who recently reported 745 patients with CSI-NSGCT treated according to uniform guidelines and managed in the community with active surveillance for low-risk patients and one or two cycles of chemotherapy for high-risk patients [14]. The majority of patients received no therapy after orchiectomy, and no cancer-related deaths, late relapses or recurrent teratoma were reported. These data and that of others as well as our series strongly indicate that, with appropriate, well-thought-out and detailed guidelines, moderate coordinating activities and collaboration of an experienced center as well as appropriate education and committed physician teams, CSI-NSGCT patients can be managed with primary active surveillance after orchiectomy in the community [14, 17]. Results are predictable and excellent in both academic centers and in the community.

Common arguments for retaining primary surgery are that when done in one of the few high-volume centers in the United States or elsewhere, results are excellent, infertility and complication rates are very low and such an approach essentially eliminates the abdomen as a source of relapse making abdominal imaging unnecessary in follow-up. While all these arguments are true, several poignant facts are also true. Even in high-volume centers, preoperative evaluations routinely fail to reliably identify the large number of patients who are pathological stage I thus subjecting the majority of patients to major surgery without therapeutic benefit. Patients with substantial abdominal disease appropriate for primary chemotherapy are not always identified preoperatively thus necessitating adjuvant chemotherapy in addition to primary RPLND. Optimal management strategy of CSI-NSGCT should cure virtually all the patients with the minimum number of treatment modalities. Any argument that evokes center-based care as the standard is not germane since the vast majority of patients in the United States, Europe, Canada and the rest of the world as a whole will never find their way to a center of excellence in testicular cancer.

The results of community level primary surgical management of CSI-NSGCT have been tested and recently reported by Albers et al. [18]. This ambitious, large and very important study of primary RPLND versus a single cycle of BEP was community based and thus represented the skills of local urologists and medical oncologists throughout Germany. In addition to numerically greater relapses in the surgical arm, there were an unexpected number of patients experiencing both scrotal and abdominal relapses strongly indicating that the technical demands of even primary RPLND are substantial and the excellent abdominal control rates seen at expert centers are not duplicated in the community where the majority of patients receive care. In addition, when analyzed using a firm denominator, the primary concerns about the undissected retroperitoneum leading to a significant number of late refractory cancers or late recurrences of teratoma have not been realized in this and other studies [4, 12, 13, 15].

Adjuvant chemotherapy, in particular for high-risk disease, is considered a standard of care in many countries. As with RPLND, adjuvant chemotherapy will result in overtreatment in at least 50% of patients. All these patients will experience hair loss, significant disruption of life, exposure to significant neutropenia with the rare risk of fatal complications, risk of vascular complications, at least temporary effects on fertility and the anxiety and fears that all patients receiving chemotherapy face. The potential long-term complications of one to two cycles of chemotherapy, although thought to be low, are currently unknown, but excess cardiovascular and renal toxicity, metabolic syndrome and other toxic effects have been described after a higher number of cycles [19–22]. No safe lower limit appears to exist for BEP chemotherapy. A low level of recurrences still happens and most are seen in the abdomen [14, 18]. Thus, patients treated with adjuvant chemotherapy are fully spared neither the fear of relapse nor the inconvenience of ongoing imaging.

Recently, one cycle of BEP has been tested as adjuvant treatment of CSI-NSGCT. A higher number of relapses are seen as compared with two cycles and although the overall treatment burden is reduced, a significant number of patients continue to be overtreated and unnecessarily exposed to the risk of short- and long-term toxicity [14].

Applying active surveillance to all CSI-NSGCT patients results in treatment of only those who require it. Treatment of these patients will be slightly longer than adjuvant BEP × 2 (6 versus 9 weeks). However, the overall impact on the entire patient population is lower with chemotherapy only for patients requiring treatment (Table 4). Active surveillance for all risk categories completely spares 70%–75% of all patients the burden of any active treatment and 50% of the high-risk population and thus minimizes treatment-related morbidity for the entire patient population.

Concerns regarding the lack of compliance and intense follow-up with a high number of CT scans always serve as an argument against active surveillance, in particular in high-risk CSI-NSGCT patients. Little research has been done to address the issue of compliance and its potential impact on overall outcome of CSI-NSGCT patients [4]. While reported compliance with active surveillance visits range from poor to adequate, there is no clear evidence that the level of compliance across varying geographies materially impacts survival [4, 13, 23]. Survival rates consistently approach 100% even in series with reported 'unsatisfactory' compliance [4]. Nevertheless, the necessity of strict compliance with the surveillance schedule and testing in order to minimize morbidity and mortality should be clearly emphasized. In our series, almost all patients recurred with good risk disease independent of their degree of compliance. Obviously, educating patients about the risk of recurrence, the importance of reporting suspicious symptoms and the importance of adherence to recommended testing guidelines is crucial and emphasizing that later identification of disease might well lead to more complicated and complex therapies is fully warranted.

Table 4. Estimate of treatment burden with different treatment strategies for VASC+ patients (on the basis of $n = 60$)

VASC+	Surveillance	BEP × 2	RPLND
No. of adjuvant cycles of BEP	0	120 (100%)	0
No. of relapses	30 (50%)	1 (2%)	6 (10%)
No. of cycles of BEP for relapse	90	3	18
No. of patients receiving three or more cycles	30 (50%)	1	6 (10%)
No. of patients requiring RPLND	2 (3%)	0	60 (100%)
No. of patients receiving no treatment	30 (50%)	0	0
No. of patients with disruption of life	30 (50%)	60 (100%)	60 (100%)
Ongoing imaging	Yes	Yes	Yes[a]
No. of patients with potential risk of long-term toxicity	30 (50%)	60 (100%)	60 (100%)
Total no. of BEP cycles administered	90	123	18

[a]May be simpler after an expert RPLND than after chemotherapy or active surveillance.

VASC+, vascular invasion positive; BEP, bleomycin, etoposide and cisplatin; RPLND, retroperitoneal lymph node dissection.

Discussions whether frequent CT scans during follow-up are associated with a potentially increased secondary malignancy rate remain very controversial and further epidemiologic and radiobiology studies are needed to fully address this issue [24–29].

Two different follow-up strategies were utilized in our patient population (Table 1). No obvious difference in outcome was observed, indicating that less frequent CT scanning may result in similar outcomes. The follow-up at BCCA has since been revised with less frequent CT scans for low-risk disease in order to minimize CT scanning for these patients [30]. No relapse was detected by chest X-ray in our study questioning their usefulness, in particular in TUM-positive patients. Ongoing investigations are exploring safe modifications of frequency, timing and extent of surveillance strategies as well as alternative imaging methods such as magnetic resonance imaging scanning or ultrasound.

In conclusion, our results reported in this article are complementary to other nonsurgical approaches recently reported from Europe. Primary management of CSI-NSGCT with close surveillance results in superb outcomes in the modern era while at the same time minimizes treatment-related toxicity for the entire patient population. None of the 223 patients in our series have died of testicular cancer or complications of treatment and the majority of patients (74%) required no active therapy after orchiectomy.

Importantly, with careful attention to physician education, guideline development and implementation as well as collaboration with an experienced center, we believe such an approach has a less technical component and can be safely implemented in community-based practices where in many countries the majority of patients receive care. Active surveillance should therefore serve as the preferred treatment strategy for all CSI-NSGCT patients. 'Primum non nocere'.

references

1. Sonneveld DJ, Hoekstra HJ, Van Der Graaf WT et al. The changing distribution of stage in nonseminomatous testicular germ cell tumours, from 1977 to 1996. BJU Int 1999; 84: 68–74.
2. Powles TB, Bhardwa J, Shamash J et al. The changing presentation of germ cell tumours of the testis between 1983 and 2002. BJU Int 2005; 95: 1197–1200.
3. Read G, Stenning SP, Cullen MH et al. Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. J Clin Oncol 1992; 10: 1762–1768.
4. Groll RJ, Warde P, Jewett MA. A comprehensive systematic review of testicular germ cell tumor surveillance. Crit Rev Oncol Hematol 2007; 64: 182–197.
5. Vergouwe Y, Steyerberg EW, Eijkemans MJ et al. Predictors of occult metastasis in clinical stage I nonseminoma: a systematic review. J Clin Oncol 2003; 21: 4092–4099.
6. Pizzocaro G, Zanoni F, Salvioni R et al. Surveillance or lymph node dissection in clinical stage I non-seminomatous germinal testis cancer? Br J Urol 1985; 57: 759–762.
7. Peckham MJ, Brada M. Surveillance following orchidectomy for stage I testicular cancer. Int J Androl 1987; 10: 247–254.
8. Klepp O, Olsson AM, Henrikson H et al. Prognostic factors in clinical stage I nonseminomatous germ cell tumors of the testis: multivariate analysis of a prospective multicenter study. Swedish-Norwegian Testicular Cancer Group. J Clin Oncol 1990; 8: 509–518.
9. Krege S, Beyer J, Souchon R et al. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): part II. Eur Urol 2008; 53: 497–513.

10. Mead G. Group ftIGCCC. International Germ Cell Collaborative Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 1997; 15: 594–603.
11. Oliver RT, Ong J, Shamash J et al. Long-term follow-up of Anglian Germ Cell Cancer Group surveillance versus patients with Stage 1 nonseminoma treated with adjuvant chemotherapy. Urology 2004; 63: 556–561.
12. Daugaard G, Petersen PM, Rorth M. Surveillance in stage I testicular cancer. APMIS 2003; 111: 76–83.
13. Colls BM, Harvey VJ, Skelton L et al. Late results of surveillance of clinical stage I nonseminoma germ cell testicular tumours: 17 years' experience in a national study in New Zealand. BJU Int 1999; 83: 76–82.
14. Tandstad T, Dahl O, Cohn-Cedermark G et al. Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. J Clin Oncol 2009; 27: 2122–2128.
15. Francis R, Bower M, Brunstrom G et al. Surveillance for stage I testicular germ cell tumours: results and cost benefit analysis of management options. Eur J Cancer 2000; 36: 1925–1932.
16. Duran I, Sturgeon JF, Jewett MA et al. Initial versus recent outcomes with a non-risk adapted surveillance policy in stage I non-seminomatous germ cell tumors (NSGCT). J Clin Oncol 2007; 25(18S): (Abstr 5021).
17. Maroto P, Garcia del Muro X, Aparicio J et al. Multicentre risk-adapted management for stage I non-seminomatous germ cell tumours. Ann Oncol 2005; 16: 1915–1920.
18. Albers P, Siener R, Krege S et al. Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I nonseminomatous testicular germ cell tumors: AUO trial AH 01/94 by the German Testicular Cancer Study Group. J Clin Oncol 2008; 26: 2966–2972.
19. Meinardi MT, Gietema JA, van der Graaf WT et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. J Clin Oncol 2000; 18: 1725–1732.
20. Fossa SD, Lehne G, Heimdal K, Theodorsen L. Clinical and biochemical long-term toxicity after postoperative cisplatin-based chemotherapy in patients with low-stage testicular cancer. Oncology 1995; 52: 300–305.
21. Fossa SD, Aass N, Winderen M et al. Long-term renal function after treatment for malignant germ-cell tumours. Ann Oncol 2002; 13: 222–228.
22. Haugnes HS, Aass N, Fossa SD et al. Components of the metabolic syndrome in long-term survivors of testicular cancer. Ann Oncol 2007; 18: 241–248.
23. Hao D, Seidel J, Brant R et al. Compliance of clinical stage I nonseminomatous germ cell tumor patients with surveillance. J Urol 1998; 160: 768–771.
24. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. N Engl J Med 2007; 357: 2277–2284.
25. Tarin TV, Sonn G, Shinghal R. Estimating the risk of cancer associated with imaging related radiation during surveillance for stage I testicular cancer using computerized tomography. J Urol 2009; 181: 627–632.
26. Tubiana M, Aurengo A, Averbeck D, Masse R. The debate on the use of linear no threshold for assessing the effects of low doses. J Radiol Prot 2006; 26: 317–324.
27. Tubiana M, Aurengo A, Averbeck D, Masse R. Recent reports on the effect of low doses of ionizing radiation and its dose-effect relationship. Radiat Environ Biophys 2006; 44: 245–251.
28. Aurengo A, Averbeck D, Bonnin A et al. Dose-Effect Relationships and the Estimation of the Carcinogenic Effects of Low Doses of Ionizing Radiation. Paris, France: National Academy of Medicine 2005 http://www.radscihealth.org/rsh/Papers/FrenchAcadsFinal2007_2004_2005.pdf (20 May 2009, date last accessed).
29. Tubiana M. Computed tomography and radiation exposure. N Engl J Med 2008; 358: 850 author reply 852–853.
30. Rustin GJ, Mead GM, Stenning SP et al. Randomized trial of two or five computed tomography scans in the surveillance of patients with stage I nonseminomatous germ cell tumors of the testis: Medical Research Council Trial TE08, ISRCTN56475197—the National Cancer Research Institute Testis Cancer Clinical Studies Group. J Clin Oncol 2007; 25: 1310–1315.