

CHAPTER II

DETECTION OF RECURRENCE IN PATIENTS WITH CLINICAL STAGE I NONSEMINOMATOUS TESTICULAR GERM CELL TUMORS AND CONSEQUENCES FOR FURTHER FOLLOW-UP: A SINGLE CENTER 10-YEAR EXPERIENCE

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ABSTRACT

A wait-and-see policy for patients with stage I nonseminomatous testicular germ cell tumors (NSTGCT) was evaluated in a prospective study. The frequency and time of recurrence, detection of recurrence and presence of unfavourable prognostic factors were investigated. During the period 1982 to 1992, 154 patients with stage I NSTGCT (median age 29 years) underwent orchidectomy and were monitored at follow-up evaluation with physical examinations, alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) levels, chest X-rays (CXR) and computed tomography (CT) scans of the abdomen and chest. Multivariate logistic regression analyses were performed to identify prognostic factors. During a median follow-up period of 7 years (range 2-12), recurrence was found in 42 patients (27.3%). All cases of recurrence were detected within two years, 90% in the first year after orchidectomy. In 29 patients (69.0%), recurrence was detected in the abdominal lymph nodes. Nine patients (21.4%) had metastases in the retroperitoneum and the mediastinum and/or the lungs and four patients (9.6%) had metastases only in the mediastinum or lungs. The majority of recurrences (97.6%) were detected by tumor markers and CT scans. Recurrence was related to the presence of vascular invasion, embryonal carcinoma (E), an elevated preoperative hCG level and the absence of mature teratoma (M). Only vascular invasion was an independent risk factor. After polychemotherapy treatment for recurrence, the survival rate in the total group was 98.7%. The wait-and-see policy is a reliable method for follow-up monitoring of patients with stage I NSTGCT. Even in patients with unfavourable prognostic factors, it is justified to await the possible appearance of metastases. For the future it is recommended that CXR be omitted from the schedule, and it might be feasible to discontinue the follow-up evaluations after five years.

INTRODUCTION

In the 1970s, cisplatin became available in various chemotherapy combinations. This considerably improved the prognosis of patients with disseminated nonseminomatous testicular germ cell tumors (NSTGCT), especially in the lower stages.^{1,2} In addition, the introduction of computed tomography (CT) scanning of

the abdomen and chest enabled more accurate clinical staging than could be achieved with the former diagnostic procedures: lymphangiography and lung tomography.^{3,4} Before the introduction of cisplatin patients with stage I NSTGCT were treated with radical retroperitoneal lymph node dissection (RPLND)^{5,6} or external beam radiotherapy (EBRT) of the para-aortic and ipsilateral pelvic lymph nodes.⁷ A major complication from RPLND had been retrograde ejaculation and EBRT may induce a radiation enteritis. The high cure rates obtainable with cisplatin-based chemotherapy, especially in patients with low stage disease, the availability of serum tumor markers for NSTGCT and the increased accuracy of the CT scanning, as well as the adverse effects associated with RPLND and EBRT, led to the initiation of a number of studies to assess the utility of surveillance for stage I disease. Peckham and colleagues introduced in 1979 this management policy.⁸ They found a recurrence rate of 17% in 53 patients after a median follow-up of 15 months. They argued that the proportion of patients curable with orchidectomy alone should be 60-80%, and that if recurrence occurred, effective chemotherapy was available.

After orchidectomy for patients with a clinical stage I NSTGCT without any evidence of metastases the wait-and-see policy was commenced. At the regular outpatient check-ups, the patients underwent a physical examination, evaluation of the serum tumor markers alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) and a chest X-ray. At various intervals, CT scans were taken of the abdomen and chest. In this way, any retroperitoneal, mediastinal and/or lung metastases could be detected early. Also several other groups have reported their preliminary or mature data. Recurrences occurred at a rate of 16% to 35.2%⁹⁻¹⁵ after a median follow-up varying between 10 and 64 months. Most recurrences, however, occurred within 12 months. Among the patients who recurred, disease-free survival after treatment is 92% to 100%. Later on, efforts have been directed toward the identification of prognostic factors that may predict the likelihood of recurrence. The unfavourable significance of vascular or lymphatic invasion,^{12,13,15-18} histology^{13,16,18} and local tumor extension^{13,19} has been generally accepted.²⁰ This had led to the institution of trials using adjuvant chemotherapy in patients with high risk stage I disease.^{12,21}

In the Netherlands, the University Hospital Groningen has been employing the wait-and-see policy since 1982.^{22,23} This prospective study describes the ten years of experience with this policy in patients with stage I NSTGCT. The number of patients with recurrence was evaluated, how this recurrence was detected was

described and the number of months until recurrence was determined. Also, the presence of any unfavourable prognostic factors which might be related to recurrence were investigated. The aim of the study was to examine the adequacy of a wait-and-see policy for patients with a stage I NSTGCT. Advice and recommendations regarding follow-up evaluation are given.

PATIENTS AND METHODS

In the period 1982 to 1992, 154 patients with clinical stage I NSTGCT (median age 29 years; range 15-66) were treated at the University Hospital Groningen, the Netherlands. All of the patients underwent orchidectomy and at staging there was no evidence of regional and/or distant metastases. Clinical staging was performed as described by Peckham et al²⁴ with the aid of physical examination, chest X-ray, serum tumor markers AFP and hCG, and CT scanning of the chest and abdomen. Values for AFP of $>10 \mu\text{g/l}$ and for hCG of $\geq 2.0 \mu\text{g/l}$ were considered to be elevated. If the serum tumor markers were elevated before the orchidectomy, they were expected to normalize postoperatively in accordance with the half-life times. The half-life times for AFP and hCG are six days and two days, respectively. In the initial years of the study period, bilateral lymphangiography also formed part of the staging procedure. Since 1986, only CT scanning has been performed owing to the limited reliability of lymphangiography and its complicated interpretation.^{3,25}

In the period 1982-1983, an explorative laparotomy was carried out in conjunction with the orchidectomy to make a definite diagnosis regarding the presence or absence of retroperitoneal lymph node metastases. On the basis of an interim analysis, it was decided from 1984 on to perform this laparotomy only if radiologic findings were inconclusive. If there were no palpable pathologic retroperitoneal lymph nodes these patients were classified as stage I and still entered the study.²³

The tumors were classified in accordance with the nomenclature of the World Health Organisation (WHO),²⁶ which distinguishes the following histological components in nonseminomatous testicular tumors: embryonal carcinoma (E), choriocarcinoma (C), yolk sac tumor (Y) and teratoma. Teratomas can contain

mature or immature components: mature teratoma (M) and immature teratoma (I). The nonseminomas are usually composed of more than one histological subgroup, sometimes with a seminoma (S) component.²⁷ Data on the diameter of the primary tumor and the presence or absence of vascular invasion were obtained from the surgical specimens. pT stage was determined according to the International Union Against Cancer (UICC) 1978 edition.²⁸

Outpatient check-ups were performed according to a strict schedule (Table 1). Physical examination and serum AFP and hCG determinations were performed at each visit. A chest X-ray and CT scanning of the chest and abdomen were carried out at regular intervals. After ten years, the follow-up was considered to be complete and the patients were discharged from further evaluations. The patients with recurrence were treated with cisplatin-based combination chemotherapy.

Table 1. Follow-up schedule of the wait-and-see policy for patients with stage I NSTGCT (1982-1992)

Year 1	Every 4 weeks: PE, TM Every 8 weeks: PE, TM, CXR
Year 2	Every 3 months: PE, TM, CTa, CTc Every 8 weeks: PE, TM Every 3 months: PE, TM, CXR
Year 3	Every 6 months: PE, TM, CTa, CTc Every 3 months: PE, TM, CXR
Years 4 and 5	Every 12 months: PE, TM, CTa, CTc Every 6 months: PE, TM, CXR
Years 6, 7, 8, 9 and 10	Every 12 months: PE, TM, CXR

Abbreviations: PE, physical examination; TM, tumor markers AFP and hCG; CXR, chest X-ray; CTa, computed tomogram of the abdomen; CTc, computed tomogram of the chest.

Statistical analysis

Univariate analyses were performed on differences in clinical characteristics between the two subgroups 'recurrence' and 'no-recurrence' with Student's *t* test for continuous variables and by means of the Chi-square test for categorical variables. Fisher's exact test was used in case of small numbers. Multivariate logistic regression analysis was used to examine correlations between variables with possible prognostic significance and the appearance of recurrence;²⁹ the dependent variable was recurrence within two years. Independent variables were age, tumor location (left or right), maximum diameter of the primary tumor, preoperative elevation of AFP and/or hCG, histological components of the primary tumor, the presence of vascular invasion in the primary tumor and pT stage. Age and maximum diameter of the primary tumor were continuous variables, while the remaining variables were dichotomous (0=absent, 1=present).

By including all of the independent variables simultaneously in the regression model, we could establish the relationship between each separate variable and the appearance of recurrence. No-recurrence acted as a reference for the dependent variables, while the absence of a particular characteristic acted as a reference for the independent variables. To obtain the best fitting regression model, the number of independent variables was reduced by means of the step-wise elimination of covariables, with the likelihood-ratio statistic as selection criterion.

Owing to the fact that the maximum diameter of the primary tumor was unknown in 19 patients, the regression analysis was also carried out without this variable. The statistical analyses were conducted using the SPSS-PC+ (V4.0) software package (SPSS inc., Chicago, Ill., USA.). Test statistics and odds ratios were considered to be statistically significant at $P \leq 0.05$.

RESULTS

Between January 1982 and December 1991, 154 patients with clinical stage I NSTGCT were treated at the University Hospital Groningen. Before 1984 all patients who entered the study had undergone an explorative laparotomy. Since 1984, four patients have undergone laparotomy because the findings on CT-scans were inconclusive: i.e. no palpable abnormalities were found during laparotomy. The median follow-up was seven years (range 2-12 years). The frequencies of the

various separate histological basic components in the primary tumors are shown in Table 2. These results resemble the results of other authors also using the WHO-classification.³⁰ Choriocarcinoma (C) was present in 22 patients (14.3%), embryonal carcinoma (E) in 132 patients (85.7%), immature teratoma (I) in 56 patients (36.4%), mature teratoma (M) in 101 patients (65.6%), seminoma (S) in 49 patients (31.8%) and yolk sac tumor (Y) in 60 patients (39.0%). The most frequent mixed tumors were composed of S plus E with or without Y and/or M and/or I (41 patients), E plus M with or without I (27 patients) and E plus Y with or without M and/or I (26 patients). In 25 patients, the orchidectomy specimen consisted of one single tumor component: embryonal carcinoma in 16 patients (10.4%) and mature teratoma in 9 patients (5.8%).

During the course of follow-up, metastases were found in 42 patients (27.3%). Recurrence was diagnosed after a median duration of four months (average 5.7 months, range 2-24 months). Ninety per cent of the recurrences, i.e. 38 out of 42, were detected within one year. All of the cases of recurrence were discovered within two years of the orchidectomy.

After orchidectomy, 27 patients (64.2%) developed retroperitoneal lymph node metastases (stage II) and two patients (4.8%) developed inguinal lymph node metastases. One of the latter patients was later also found to have retroperitoneal lymph node metastases. Also, of the 42 patients with recurrence, 29 had stage II disease at the time of detection. In nine patients (21.4%), metastases had developed in the retroperitoneum as well as in the mediastinum and/or lungs (stage III or IV). In two patients (4.8%), metastases were only found in the mediastinal lymph nodes (stage III) and in two other patients (4.8%) only in the lungs (stage IV). Of the four patients who developed recurrence in the second year after orchidectomy, three had retroperitoneal metastases (stage IIb, IIc and IIc, respectively) and one had mediastinal metastases (stage III).

In 17 patients, the CT scans showed abnormalities at the same time as the tumor markers became elevated (40.5%), while in eight patients (19.0%) the diagnosis of recurrence was made on the basis of elevated serum tumor markers only. In all these patients elevated markerlevels were confirmed repeatedly. In one patient (2.4%) the only expression of recurrence was a histologically proven inguinal lymph node metastasis found during physical examination. In 16 patients recurrence was detected by radiological abnormalities on the CT scans (38.1%).

Table 2. Histological findings in the primary tumor

Follow-up in Stage I NSTGCT

Components	Total (n=154)	No Rec.(n=112)	Rec.(n=42)
S+E	16 (10%)	10	6
S+E+C+Y+M	1 (0.6%)	0	1
S+E+C+M+I	1 (0.6%)	1	0
S+E+Y	4 (2.6%)	2	2
S+E+Y+M	4 (2.6%)	4	0
S+E+Y+M+I	7 (4.5%)	5	2
S+E+M	1 (0.6%)	1	0
S+E+M+I	7 (4.5%)	5	2
S+E+Y+I	1 (0.6%)	0	1
S+E+I	1 (0.6%)	1	0
S+C	1 (0.6%)	1	0
S+Y	1 (0.6%)	1	0
S+Y+M+I	1 (0.6%)	1	0
S+M	1 (0.6%)	1	0
S+M+I	2 (1.3%)	2	0
E	16 (10%)	11	5
E+C	1 (0.6%)	1	0
E+C+Y	1 (0.6%)	1	0
E+C+Y+M	4 (2.6%)	4	0
E+C+Y+I	2 (1.3%)	2	0
E+C+Y+M+I	5 (3.2%)	3	2
E+C+M	4 (2.6%)	3	1
E+C+M+I	2 (1.3%)	0	2
E+Y	8 (5.2%)	3	5
E+Y+M	8 (5.2%)	6	2
E+Y+M+I	10 (6.5%)	8	2
E+M	16 (10%)	13	3
E+M+I	11 (7.1%)	7	4
E+I	1 (0.6%)	1	0
Y+M+I	1 (0.6%)	1	0
Y+M	2 (1.3%)	1	1
M	9 (5.8%)	8	1
M+I	4 (2.6%)	4	0

Abbreviations: Rec., recurrence; C, choriocarcinoma; E, embryonal carcinoma; I, immature teratoma; M, mature teratoma; S, seminoma; Y, yolk sac tumor

In one patient lung metastases were histologically proven. None of the cases of recurrence were found by means of the chest X-ray. Fourteen patients who developed radiological changes on CT-scans of abdomen, but without marker elevation, underwent an exploratory laparotomy before remission induction chemotherapy was started. Three of these patients also had signs of metastases on CT-scan of the chest. All fourteen patients had palpable pathologic para-aortic lymph nodes. In one patient retroperitoneal lymph node metastases caused hydronephrosis of the left kidney, in this patient no exploratory laparotomy was done because the clinical appearance and CT-scan of the abdomen were thought to be conclusive for metastases. This patient and seven out of the fourteen patients with retroperitoneal recurrence detected only on CT scan, were relaparotomized after four remission-induction courses with cisplatin based polychemotherapy. In one case no palpable abnormalities were found and in seven cases residual tumor was found, and resected. Histologic examination of the resected specimen revealed necrosis and fibrosis in three cases and mature teratoma in the other four. Because in the other seven patients radiologically documented recurrences disappeared completely, surgical evaluation was not performed.

Table 3 shows a comparison of the characteristics present in the recurrence group and the no-recurrence group. Univariate comparison of the clinical characteristics between the group with and the group without recurrence did not reveal any significant differences in the average age, tumor location, average maximum diameter of the primary tumor and pT stage ≥ 2 . Of the tumor markers, particularly the serum hCG level was elevated more frequently in the patients with recurrence than in those without recurrence; this difference was not statistically significant ($P=.085$). Of the histological characteristics of the primary tumor, embryonal carcinoma was present significantly more often in the patients with recurrence, whereas mature teratoma was present more often (not significant) in the patients without recurrence ($P=.083$). Vascular invasion was present significantly more often in the recurrence group than in the no-recurrence group: 45.2% versus 15.2%. Multivariate logistic regression analysis was carried out on all the possible risk factors ($n=135$; Table 4) and repeated after the only variable with missing values, i.e. the maximum diameter of the primary tumor, had been omitted. The exclusion of this variable which was not found to be associated with the appearance of recurrence using univariate or multivariate analysis, meant that all the patients could be included in the analyses ($n=154$; Table 5).

Table 3. Population characteristics by recurrence status

	No Recurrence (n = 112)	Recurrence (n = 42)	P
Age, in years (mean±SD)	30±10	29±7	.648
Primary tumor			
Location: Left	50 (44.6%)	17 (40.5%)	.642
Right	62 (55.4%)	25 (59.5%)	
Max. diameter, mm (mean±SD)	39.0±19	41.4±18	.505
Preoperative elevated AFP	53 (47.3%)	23 (54.8%)	.411
Preoperative elevated hCG	39 (34.8%)	21 (50.0%)	.085
Histological findings:			
Seminoma	35 (31.3%)	14 (33.3%)	.805
Embryonal carcinoma	92 (82.1%)	40 (95.2%)	.039
Choriocarcinoma	16 (14.3%)	6 (14.3%)	1.000
Yolk sac tumor	42 (37.5%)	18 (42.9%)	.544
Mature teratoma	78 (69.6%)	23 (54.8%)	.083
Immature teratoma	41 (36.6%)	15 (35.7%)	.918
Vascular invasion present	17 (15.2%)	19 (45.2%)	.000
Histologic staging pT≥2	6 (5.4%)	4 (9.5%)	.462

In both cases, vascular invasion was the only significant independent risk factor for the manifestation of recurrence (Odds Ratios 4.28 and 4.06, respectively). In the patients who were included in the second regression analysis (and not the first), mature teratoma occurred more frequently, while embryonal carcinoma, an elevated AFP and an elevated hCG occurred less frequently. In this way, the step-wise elimination of covariables led to two slightly different models. Logistic regression analysis with step-wise elimination of covariables in the first case (n=135) gave rise to the following regression model: $y = -1.275 + 0.808 \times \text{hCG} - 0.793 \times \text{mature teratoma} + 1.534 \times \text{vascular invasion}$. In the second case (n=154), the regression model was: $y = -2.519 + 1.250 \times \text{embryonal carcinoma} + 1.445 \times \text{vascular invasion}$. The two models indicate that recurrence is related to the presence of vascular invasion (Odds Ratios 4.63 and 4.24, respectively), a preoperative elevated hCG value (Odds Ratio 2.24), the absence

of mature teratoma (Odds Ratio 0.45) and the presence of embryonal carcinoma (Odds Ratio 3.49). The only independent prognostic factor was the presence of vascular invasion.

Table 4. Multivariate logistic regression analysis of risk factors for recurrence (n=135)

Independent variable	Odds Ratio	P
All potential risk factors simultaneously in the model		
Age	1.00	.940
Tumor location (Left vs Right)	0.82	.657
Maximum diameter primary tumor	1.01	.517
Preoperative elevated AFP	1.44	.514
Preoperative elevated hCG	2.23	.105
Seminoma present	0.70	.471
Embryonal carcinoma present	2.10	.386
Choriocarcinoma present	0.58	.393
Yolk sac tumor present	1.10	.841
Mature teratoma present	0.38	.082
Immature teratoma present	0.96	.940
Vascular invasion present	4.28	.001
Histologic staging pT \geq 2	2.34	.321
Model after backward elimination of covariates		
Vascular invasion present	4.63	.001
Preoperative elevated hCG	2.24	.062
Mature teratoma present	0.45	.069

Owing to the fact that we found relationships between an elevated AFP and the presence of choriocarcinoma, yolk sac tumor and mature teratoma, and between an elevated hCG and the presence of choriocarcinoma, the regression analyses were also carried out with interaction terms for these variables. However, the addition of these interaction terms did not produce any significant improvement in the regression models.

Table 5. Multivariate logistic regression analysis of risk factors for recurrence (n=154)*

Independent variable	Odds Ratio	P
All potential risk factors simultaneously in the model		
Age	1.00	.932
Tumor location (Left vs Right)	0.89	.767
Preoperative elevated AFP	1.54	.395
Preoperative elevated hCG	1.84	.178
Seminoma present	0.98	.965
Embryonal carcinoma present	2.67	.228
Choriocarcinoma present	0.60	.403
Yolk sac tumor present	0.97	.949
Mature teratoma present	0.46	.136
Immature teratoma present	1.20	.701
Vascular invasion present	4.06	.001
Histologic staging pT \geq 2	1.54	.576
Model after backward elimination of covariates		
Vascular invasion present	4.24	.000
Embryonal carcinoma present	3.49	.110

* Maximum diameter of primary tumor not included because of missing values

Of the 42 patients with metastases, 40 went into complete remission after treatment with cisplatin-based polychemotherapy, with or without explorative surgery for resection and histological examination. Those patients in which no viable cancer was found in resected specimens, were classified as complete responders. One patient refused to be treated with chemotherapy. The other patient only had a local inguinal lymph node metastasis on the left side. After excision of this small metastasis, no further evidence could be found of distant metastases, so there was no longer any indication for chemotherapy.

Two of the patients with recurrence died. One of these patients was the one who had refused chemotherapy; he died 41 months after the orchidectomy. The other

patient went into complete remission after cisplatin-based polychemotherapy for inguinal, retroperitoneal and lung metastases, but he developed a second recurrence eleven months later. The second recurrence was also accompanied by lung metastases, for which he received second line polychemotherapy. He died twenty months after the orchidectomy. The ultimate disease-free survival of the 154 patients with stage I NSTGCT who were monitored with the wait-and-see follow-up policy was 98.7%; two out of the 154 patients (1.3%) died.

DISCUSSION

Over a 10-year period (median follow-up time 7 years), this study group comprised 154 patients with a clinical stage I nonseminomatous testicular germ cell tumor. A total of 42 patients (27.3%) developed recurrence after a median follow-up of 4 months (range 2-24 months). At the time of detection of recurrence, the majority of patients (69.0%) had stage II disease, i.e. the metastases were located in the abdominal lymph nodes: in the retroperitoneal and/or inguinal lymph nodes. In this series, all the cases of recurrence were found within two years after the orchidectomy. Other authors have reported cases of dissemination after two years,^{14,31} with rates of up to 7%. After five years, the appearance of recurrence is extremely rare. In such cases, if the histology of the recurrence does not exactly match that of the primary tumor, it is worth considering whether the second tumor is a new primary extragonadal germ cell carcinoma.³² Forty patients had to be treated with cisplatin-based polychemotherapy during the course of the follow-up. With a median follow-up duration of seven years, a disease-free survival of 98.7% was achieved.

Serum tumor markers as well as CT scanning of the abdomen and chest played a major role in the detection of recurrence. Both were indispensable for the early detection of metastases, so that treatment with polychemotherapy could be started at an early stage. In eight patients, the diagnosis of recurrence was made purely on the basis of elevation of one or both serum tumor markers. In one of these patients, palpable inguinal lymph nodes were found shortly afterwards and in the other seven, the CT scans became abnormal after 2, 2, 3, 3, 4, 5 and 20 months, respectively. These patients received polychemotherapy after the metastases had been confirmed radiologically using CT. Prior to the orchidectomy, elevated

values of one or both serum tumor markers were found in 93 patients (60.4%). Nine of these patients developed recurrence (21.4%), however the tumor markers were not elevated when the recurrence was found. The opposite was observed in six patients (14.3%) who had normal serum tumor marker values before orchidectomy but elevated values at the time of recurrence. This discordance in the behaviour of tumor markers has been described by other authors^{14,15,31,33,34} and has been reviewed.³⁵ In cases where the primary tumor had exclusively produced AFP (6 patients), the metastases caused either an elevation in the AFP values (3 patients) or no increase in tumor marker values. The same was valid for the tumors which had exclusively produced hCG (4 patients): if the metastases had produced a tumor marker (3 patients) it was always exclusively hCG.

CT scanning was also very helpful in the detection of recurrence. In only four patients CT scans were inconclusive during follow-up. Because a recurrence could not be excluded completely, these four patients underwent diagnostic laparotomy. However, no palpable abnormalities were found at laparotomy and none of these patients developed recurrence during follow-up.

The chest X-ray was not found to have much value in this series. Abnormalities on the chest X-ray never formed the first indication of recurrence. Of the 13 patients with lung metastases, abnormalities were only visible on the relevant chest X-ray in two cases. Therefore, it seems to be not worthwhile to take regular chest X-rays in the follow-up of patients with stage I NSTGCT.

This study and others have shown that the presence of vascular invasion is an unfavourable prognostic factor.^{12,13,15-18,21,36} pT stage has also been identified as a prognostic factor by several authors, especially tumor invading into the tunica albuginea, rete epididymis or spermatic cord: pT \geq 2.^{13,35,37} However this prognostic factor was found in univariate analyses. In this study pT-stage was not found to be predictive of subsequent recurrence, in multivariate nor in univariate comparison. An embryonal carcinoma component in the primary tumor has also often been mentioned as an independent risk factor for the development of recurrence.^{18,30,36} In this study, only univariate comparison of the clinical characteristics between the recurrence group and the no-recurrence group showed that embryonal carcinoma occurred significantly more often in the recurrence group. In the literature, other unfavourable prognostic factors include: the absence of yolk sac tumor,²¹ lymphatic invasion^{12,21,30,38,39} and the absence of teratomatous elements.¹⁶ In this study we found that the development of recurrence was related to the presence of vascular invasion, embryonal carcinoma, a pre-orchidectomy

elevated serum hCG value, and the absence of mature teratoma. On the basis of the list of unfavourable prognostic factors, it is possible to select a group of patients from those with stage I NSTGCT who are at increased risk for recurrence. Some authors have recommended adjuvant treatment for these patients.^{12,21} However, retroperitoneal lymph node dissection,⁴⁰ adjuvant chemotherapy⁴¹ or radiotherapy¹⁴ cannot prevent the development of recurrence in all cases. In this series of patients, the administration of adjuvant polychemotherapy to for example all the patients with vascular invasion in the primary tumor would have meant the 'overtreatment' of 17 out of the 36 patients.

The wait-and-see policy for patients with stage I NSTGCT is a safe and suitable follow-up method. With this approach, about three quarters of the patients could be spared RPLND or EBRT. On the basis of the results of this study, we are of the opinion that it is justified to follow a wait-and-see policy even in patients with stage I NSTGCT who are at increased risk for developing recurrence. The compilation of these results has led to the new wait-and-see follow-up schedule for patients with stage I NSTGCT shown in Table 6.

Table 6. Recommendations for future follow-up schedule of patients with stage I NSTGCT

Year 1	Every 4 weeks: PE, TM Every 3 months: PE, TM, CTa, CTc
Year 2	Every 8 weeks: PE, TM Every 6 months: PE, TM, CTa, CTc
Year 3	Every 3 months: PE, TM Every 12 months: PE, TM, CTa, CTc
Years 4 and 5	Every 6 months: PE, TM Every 12 months: PE, TM, CTa, CTc

Abbreviations: PE, physical examination; TM, tumor markers AFP and hCG; CTa, computed tomogram of the abdomen; CTc, computed tomogram of the chest.

The chest X-ray has been omitted from this schedule because the relevance for the detection of recurrence was questionable. Furthermore, it is our view that it

is accountable to discontinue the follow-up evaluations after five years because no cases of recurrence were found after two years. Other changes to the schedule, for example, lengthening the interval between two follow-up visits, would not be wise, particularly in the first two years, because in our experience, dissemination can be rapidly progressive. This would involve the risk of detecting recurrence at a later stage, with a decreasing chance of being able to cure the patient with polychemotherapy.⁴²

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