Paternity Following Treatment for Testicular Cancer

Marianne Brydøy, Sophie D. Fosså, Olbjørn Klepp, Roy M. Bremnes, Erik A. Wist, Tore Wentzel-Larsen, Olav Dahl

Background: **Studies of fertility in men treated for testicular cancer have mainly addressed serum follicle-stimulating hormone levels and sperm parameters. We assessed post-treatment paternity among long-term survivors of testicular cancer.** ***Methods:*** **Men (n = 1814) who had been treated for unilateral testicular cancer in Norway during 1980 through 1994 were invited to participate in a national multi-center follow-up survey in 1998 through 2002. The participants were allocated to five groups according to the treatment received after orchiectomy, including treatment at relapse (surveillance, retroperitoneal lymph node dissection, radiotherapy, low-dose chemotherapy [i.e., ≤850 mg cisplatin], and high-dose chemotherapy [i.e., >850 mg cisplatin]). Cox proportional hazards analysis was used to assess predictive factors for post-treatment paternity. Statistical tests were two-sided.** ***Results:*** **A total of 1433 men were assessable, of whom 827 were fathers at diagnosis. Post-treatment conception was attempted by 554 men, among whom the overall 15-year actuarial post-treatment paternity rate was 71% (95% confidence interval [CI] = 66% to 75%) without the use of cryopreserved semen. This rate ranged from 48% (95% CI = 30% to 69%) in the high-dose chemotherapy group to 92% (95% CI = 78% to 98%) in the surveillance group (*P*<.001). The median actuarial time from diagnosis to the birth of the first child after treatment was 6.6 years overall but varied according to treatment. Assisted reproductive technologies were used by 22% of the couples who attempted conception after treatment. Dry ejaculation, treatment group, pretreatment fatherhood, and marital status were statistically significant independent predictors for post-treatment fatherhood, with dry ejaculation as the most important negative factor.** ***Conclusions:*** **Although the overall paternity rate after treatment for testicular cancer was high, the ability to conceive and the time to conception reflected the intensity of treatment. These data may help inform patients about their future ability to father biological children. [J Natl Cancer Inst 2005;97:1580–8]**

Germ-cell testicular cancer is the most common cancer among 20- to 40-year-old men, and the incidence is increasing *(1,2)*. The introduction of cisplatin-based chemotherapy in the late 1970s, more reliable radiologic staging, and the ability to monitor disease activity by tumor markers have led to substantial improvements in the outcome of testicular cancer patients during the last two decades, and the current cure rate exceeds 95% *(1)*. As a result, a considerable number of testicular cancer patients have an almost normal life expectancy.

Many testicular cancer patients are diagnosed at an age at which they are starting a family, and the ability to father children in the future is an important issue for approximately 60% of newly diagnosed patients *(3,4)*. Subfertility or infertility can be associated with the disease itself or with its treatment *(5,6)*. Approximately half of all testicular cancer patients have defective spermatogenesis at diagnosis, even before orchiectomy *(7,8)*. Radiation therapy and chemotherapy impair spermatogenesis at least temporarily *(9–12)*, and retroperitoneal lymph node dissection (RPLND) may be followed by "dry ejaculation," in which surgical injury to sympathetic nerves and ganglia may cause loss of seminal emission into the posterior urethra or true retrograde ejaculation *(13)*. The introduction of modified unilateral and/or nerve-sparing RPLND *(14)* and surveillance as a primary therapy option after orchiectomy *(15)* are important treatment modifications for preserving fertility. Other possible strategies for preserving fertility include limiting the radiation fields to the para-aortic area *(16)*, lower radiation doses *(17)*, and less chemotherapy *(18)*. Pretreatment cryopreservation of semen and assisted reproductive technologies can also decrease the rate of involuntary infertility.

Most previous reports on post-treatment fertility in men treated for testicular cancer have used semen parameters and serum follicle-stimulating hormone (s-FSH) levels as endpoints. Reports on paternity *(19–25)* are few, are often based on small series, and are rarely suitable for comparing different treatment modalities. Thus, reliable data for guiding these men on their future ability of having children without the use of cryopreserved semen are needed. The aim of the present study was to assess long-term post-treatment paternity in a large cohort of unselected testicular cancer survivors whose treatment has followed a modern management approach *(26)*.

Patients and Methods

Population and Study Design

In 1998 through 2002, the five national academic oncology units in Norway conducted a national multi-center follow-up survey to assess the long-term physical and psychological morbidity in testicular cancer survivors. All surviving unilateral germ-cell testicular cancer patients treated in Norway in 1980

Affiliations of authors: Department of Oncology (MB, OD) and Centre for Clinical Research (TW-L), Haukeland University Hospital, and Section of Oncology, Institute of Medicine, University of Bergen (MB, OD), Bergen, Norway; St. Olav University Hospital and Norwegian University of Science and Technology, Trondheim, Norway (OK); University of Tromsø and University Hospital of Northern Norway, Tromsø, Norway (RMB); Norwegian Radium Hospital (SDF), Ullevål University Hospital (EAW), and University of Oslo Medical Faculty (EAW, SDF), Oslo, Norway.

Correspondence to: Marianne Brydøy, MD, Department of Oncology and Medical Physics, Haukeland University Hospital, N-5021 Bergen, Norway (e-mail: marianne.brydoy@helse-bergen.no).

See "Notes" following "References."

DOI: 10.1093/jnci/dji339

through 1994 were identified through the Cancer Registry of Norway and the regional university hospitals. Former patients currently aged 18–75 years were invited to participate in the survey, which consisted of a mailed questionnaire and an outpatient clinical examination that included laboratory tests, spirometry, audiometry, and an optional semen analysis at one of the five collaborating oncology units. Exclusion criteria included bilateral orchiectomy for any reason, extragonadal germ cell cancer, other malignancies except skin cancer, and mental retardation.

A total of 1814 men were invited to participate in the national survey. Ten patients were untraceable, 340 did not respond, and one had died, leaving 1463 (80.6%) participants. Of these, 1272 answered the questionnaire and underwent the outpatient examination, 166 answered the questionnaire but did not have the examination, and 25 had the examination but did not answer the questionnaire. Of the 1438 men who answered the questionnaire, five were excluded due to missing paternity data both before and after treatment. Men who provided paternity data for only one of the two periods were included. Thus, the remaining 1433 patients (79%) constitute the study sample. Primary data regarding histology (seminoma or nonseminoma), Royal Marsden Hospital system staging *(27)*, treatment, and relapse were retrieved from the patients' medical records. The Committee for Medical Research Ethics of the Southern Health Region of Norway approved the study.

Following invitations to participate in the study and our receipt of written informed consent, the study population received the mailed questionnaire, which included 14 questions assessing pre- and post-treatment fertility (see Supplementary Information available at http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol97/issue21). Men who indicated that they had not attempted to father a child but who reported paternity were categorized in the analyses as having an intention of fatherhood.

Men whose children were born after treatment were categorized as pretreatment fathers if conception appeared to have taken place before or during treatment. Five men whose partners were at least 12 weeks pregnant at the time of the survey were considered to be post-treatment fathers. Because the main aim of this study was to assess paternity after treatment for testicular cancer, men who fathered a child by the use of cryopreserved semen are discussed separately and not included as paternity cases in the analyses. Similarly, couples who used donor insemination or who adopted children were categorized as nonpaternity cases. However, men who fathered children with their own post-treatment semen following assisted reproductive technologies were considered paternity cases.

Treatment Principles, 1980–1994

The patients in the study were treated either within the Swenoteca collaboration *(28–30)* or according to the EORTC and MRC protocols *(31–36)*. Among patients who received chemotherapy, most received cisplatin in combination with vinblastine and bleomycin (CVB) or in combination with bleomycin and etoposide (BEP), with the addition of ifosfamide as salvage therapy. In addition, 32 patients participating in research protocols *(34–36)* were treated with carboplatin-based chemotherapy. These patients were included because their paternity did not differ from that of those who received up to four cycles of cisplatin-based chemotherapy (data not shown).

Seminomas. Most early-stage (I-IIA) seminoma patients were treated with infradiaphragmatic radiotherapy. Radiotherapy was generally given by the L-field or dogleg technique, which involves opposing anterior and posterior fields covering the para-aortic and ipsilateral iliac nodes *(16,37)*. However, radiation limited to the para-aortic area was introduced at one institution in 1989, and 44 of the patients in our study therefore received radiotherapy by this technique (16). Testicular shielding was routinely used when the iliac nodes were irradiated. The standard target dose according to stage of the early 1980s, 36–40 Gy, was gradually reduced to 25.2–27 Gy by the mid-1990s. Only eight seminoma patients received surveillance. Patients with more advanced seminomas were treated with cisplatin-based chemotherapy (one received carboplatin monotherapy); in some patients, chemotherapy was followed by RPLND or more limited retroperitoneal surgery or radiotherapy.

Nonseminomas. Until approximately 1990, patients with early-stage (I or IIA) nonseminomas were usually treated with a primary modified bilateral or ipsilateral template RPLND, followed by adjuvant chemotherapy if lymph node metastases were present. After 1990, stage I patients were generally untreated after orchiectomy (i.e., subject to surveillance) or treated with one to three cycles of adjuvant chemotherapy. However, a few stage I patients, who were considered to have an intermediate risk of recurrence according to a Swenoteca research protocol *(28)*, were treated with unilateral RPLND. Nerve-sparing RPLND was introduced around 1989. Patients with advanced-stage nonseminomas (i.e., stage IIB–IV) generally received four to six cycles of cisplatin-based chemotherapy, followed by RPLND or more limited retroperitoneal surgery and further chemotherapy if malignant cells were present on histologic examination.

Treatment groups. The total cisplatin dose was reported for all patients, but the number of cycles was not. Therefore, a cutoff of 850 mg of total cisplatin was used to separate men into low-dose and high-dose chemotherapy groups. This cutoff point, which has been used in other publications from this group *(38,39)*, was chosen to separate those who received four or fewer cycles, which is regarded as standard therapy, from those who required more intense treatment. This cutoff point may have resulted in a few men (i.e., those with body surface areas less than 1.7 m^2) who were treated with five cycles being assigned to the low-dose group. However, men with a body surface area of 2.1 m^2 (which is common among Norwegian men) who were treated with four cycles would have been allocated to the low-dose group.

On the basis of these treatment principles, the testicular cancer survivors in the current study were allocated to five different groups according to the treatment administered after orchiectomy, including treatment at relapse: (1) surveillance; (2) RPLND only; (3) radiotherapy only; (4) chemotherapy with cumulative doses of cisplatin of ≤850 mg, with or without RPLND or more limited retroperitoneal surgery or radiotherapy, and including treatment with only carboplatin-based chemotherapy; and (5) chemotherapy with cumulative doses of cisplatin of >850 mg, with or without RPLND or more limited retroperitoneal surgery or radiotherapy.

Statistical Analysis

The data were analyzed with the SPSS 12.0 package (SPSS Inc., Chicago, IL) and with R (The R Foundation for Statistical Computing, Vienna, Austria). Student's *t* test or the Kruskal–Wallis test were used for continuous data, and the chi-square test was used for categorical data. Kaplan–Meier curves and the log-rank test were used to evaluate factors influencing paternity in univariate analyses, with post-hoc comparisons of the five treatment

groups using Bonferroni correction for multiple comparisons (for 10 post-hoc comparisons; the cutoff for statistical significance was .05/10 = .005). To assess predictive factors for post-treatment paternity, we applied a Cox regression model, in which all factors of interest were included: history of cryptorchism (no/yes); age at orchiectomy (<29, 29–35, or >35 years); marital status (single versus married or cohabiting); pretreatment fatherhood (no/yes), treatment group (surveillance, RPLND, radiotherapy, low-dose chemotherapy, or high-dose chemotherapy); and "dry ejaculation" (no/yes). Because histology almost always coincides with treatment, it was not included in the model. The marital status of men who were not married or cohabiting at the time of the survey and who had not been married at any time following treatment was defined as single; the status of men who were married or cohabiting at the time of the survey or who had been married at any time after treatment was defined as married/cohabiting.

The assumption of proportional hazards was investigated as recommended by Therneau and Grambsch *(40)* using diagnostic plots based on Schoenfeld residuals for each covariate. In case of deviations from the proportional hazards assumption, the original estimates were used as conservative estimates, and supplementary analyses were performed with emphasis on treatment comparisons, with separate analyses for portions of the time axis, and consecutive analyses up to and following a specified point of time.

Some analyses were performed in subsets of patients, including an analysis of the impact of dry ejaculation, in which only men treated with three or four cycles of standard cisplatin-based chemotherapy with no additional therapy other than RPLND were included.

Two-sided *P* values less than .05 were considered statistically significant.

Results

Study Population

Of the 1814 invited men, 1433 (79%) were assessable. The median interval between orchiectomy and survey for the assessable men was 10.6 years (range = 4–21 years). The clinical characteristics of the men according to treatment group are shown in Table 1. There were no statistically significant differences between the study sample and the 381 nonassessable men (data not shown; difference in marital status could not be tested). The median cisplatin doses were 738 mg (range = 185–850 mg) in the low-dose group and 1165 mg (range = 855–2455 mg) in the high-dose group. The median carboplatin dose was 2960 mg (range = 710–3710 mg).

Paternity

Of the 1433 assessable men, 918 men reported that they had attempted to conceive before their testicular cancer diagnosis, and 827 (90%) of these men had succeeded in fathering children

Table 1. Characteristics and attempts at post-treatment conception according to postorchiectomy treatment in 1433 testicular cancer survivors*

Characteristic	Surveillance (n = 119)	RPLND (n = 153)	RT (n = 610)	Cisplatin ≤850 mg† (n = 447)	Cisplatin >850 mg† (n = 104)	Total (N = 1433)	*P*‡
Age, y, median (range)							
At treatment	30 (17–64)	28 (16–58)	35 (18–64)	29 (15–64)	26 (15–62)	32 (15–64)	<.001§
At survey	39 (24–73)	42 (28–75)	47 (25–75)	42 (23–75)	36 (23–72)	43 (23–75)	<.001§
Marital status,‖ no. (%)							.003
Married	68 (57%)	97 (63%)	380 (62%)	258 (58%)	45 (43%)	848 (59%)	
Cohabiting	25 (21%)	29 (19%)	89 (15%)	82 (18%)	25 (24%)	250 (18%)	
Separated/divorced	11 (9%)	12 (8%)	65 (11%)	35 (8%)	5 (5%)	128 (9%)	
Never been married	14 (12%)	13 (9%)	68 (11%)	65 (15%)	29 (28%)	189 (13%)	
Widowed	1 (1%)	2 (1%)	7 (1%)	5 (1%)	0	15 (1%)	
Histology, no. (%)							<.001
Seminoma	8 (7%)	3 (2%)	608 (99%)	88 (20%)	11 (11%)	718 (50%)	
Nonseminoma	111 (93%)	150 (98%)	2 (1%)	359 (80%)	93 (89%)	715 (50%)	
Initial RMH stage,¶ no. (%)							<.001
I	119 (100%)	147 (96%)	579 (95%)	151 (34%)	12 (12%)	1008 (70%)	
IM				9 (2%)		9 (1%)	
II		6 (4%)	31 (5%)	208 (47%)	32 (30%)	277 (19%)	
III				20 (4%)	12 (12%)	32 (2%)	
IV				59 (13%)	48 (46%)	107 (8%)	
NED after relapse, no. (%)	1# (1%)		1 (0.2%)	69 (15%)	22 (21%)	93 (6%)	<.001
Additional treatment in chemotherapy groups, no. (%)							
RPLND				280 (63%)	85 (82%)		<.001
RT				50 (11%)	10 (10%)		.03
Post-treatment attempt at conception, no. (%)	52 (44%)	81 (53%)	201 (33%)	183 (41%)	37 (36%)	554 (39%)	<.001
Success at post-treatment conception**	42 (81%)	62 (77%)	130 (65%)	113 (62%)	14 (38%)	361 (65%)	<.001

*RPLND = retroperitoneal lymph node dissection; RT = radiotherapy; RMH = Royal Marsden Hospital; NED = no evidence of disease.

†Some men treated with cisplatin also received RT or RPLND, and some men in the low-dose cisplatin group were actually given carboplatin.

‡Two-sided chi-square test except where indicated.

§Two-sided Kruskal–Wallis test.

‖Data on marital status were not available for three participants.

¶According to Peckham et al. *(27)*.

#Local relapse treated by scrotal surgery only.

**Percentage of men, who, at follow-up (median of 10.6 years for all assessable men and 11.1 years for men who attempted conception), were successful in their attempt to conceive without the use of cryopreserved semen.

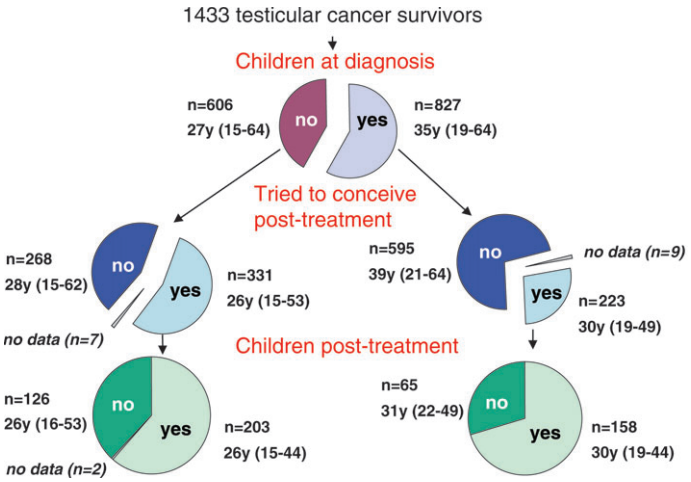

Fig. 1. Number (n) of patients attempting to conceive and the post-treatment outcome, without the use of cryopreserved semen, in relation to pretreatment fatherhood. The median age (range) in years (y) at orchiectomy is given.

(mean = 2 children; range = 1–7 children) (Fig. 1). Of the total cohort, 554 men (39%, 95% confidence interval [CI] = 37% to 42%) had tried to father a child following treatment for testicular cancer, including 32% (95% CI = 29% to 36%) of men with seminomas and 46% (95% CI = 42% to 50%) of men with nonseminomas ($P<.001$). At the time of follow-up, paternity data were missing for two of these men, and 361 of the remaining 552 (65%) had succeeded in fathering biological children after treatment (mean = 1.5 children; range = 1–7 children) without the use of cryopreserved semen. The paternity rate at follow-up (median of 10.6 years for all assessable men and 11.1 years for men who attempted conception) varied from 81% (95% CI = 68% to 90%) in the surveillance group to 38% (95% CI = 23% to 54%) in the high-dose chemotherapy group ($P<.001$) (Table 1). Conception was achieved by 69% (95% CI = 65% to 73%) of the men (383/552).

Overall, 373 (68%) of the 552 men actually became biological fathers, including 12 who used cryopreserved semen. Additionally, eight men had children by donor insemination of their partner, and 27 adopted children. In the total cohort, 25% were recorded as post-treatment biological fathers; a total of 72% had biological children either before or after treatment.

Cumulative paternity rate. The median actuarial time from orchiectomy to the birth of the first child after treatment was 6.6 years among all treatment groups combined, but it ranged from 3.6 years in the surveillance group to 6.9 years in the low-dose chemotherapy group; the median (not yet reached) in the high-dose group is at least 19 years (Fig. 2). The cumulative paternity rate at 15 years after orchiectomy was 71% in all treatment groups combined (95% CI = 66% to 75%), but it ranged from 92% (95% CI = 78% to 98%) in the surveillance group to 48% (95% CI = 30% to 69%) in the high-dose chemotherapy group ($P<.001$). The cumulative paternity rate at 20 years after orchiectomy was 76% (95% CI = 70% to 81%). The five treatment groups were compared in post-hoc log-rank tests with Bonferroni correction for multiple comparisons; all treatment groups, with the exception of RPLND ($P = .04$) had statistically significantly lower paternity rates ($P<.001$) than did the surveillance group (Fig. 2), but the paternity rates in the RPLND, radiotherapy, and low-dose chemotherapy groups were similar. The paternity rate in the high-dose chemotherapy group was (after Bonferroni correction) statistically significantly ($P<.002$) lower than that in all other groups except the low-dose chemotherapy group ($P = .01$). However, even among these most intensively treated patients, almost half were ultimately able to father children without the use of cryopreserved semen.

Assisted reproduction. Of the 554 men who tried to conceive after treatment, 459 responded to the question concerning medical assistance with reproduction. Of these, 100 (22%, 95% CI = 18% to 26%) reported that they had needed some form of assistance, with the rate of assistance ranging from 15% (95% CI = 7% to 28%) in the surveillance group to 44% (95% CI = 28% to 62%) in the high-dose chemotherapy group ($P = .004$). Fertility problems in the female partner were not specifically addressed in the questionnaire, and female infertility may have been an issue for some couples needing assistance (e.g., one man stated in answering an open question that the need for assistance was in part based on his partner). Thirty-six of the 100 couples who received some form of assistance had biological children without the use of cryopreserved semen, but further information about the type of assistance was available for only some couples; six couples used in vitro fertilization, and three men used α-sympathomimetic drugs (imipramine or phenylpropanolamine-hydrochloride [Rinexin]) to reverse retrograde ejaculation *(41,42)*. It is worth noting that 11 of the 36 couples who reported having consulted a doctor for fertility problems before the diagnosis of testicular cancer (and thus might have considered themselves infertile at diagnosis) succeeded in having children after treatment for testicular cancer. Eight of these couples did, however, need some kind of assistance following treatment.

Semen was cryopreserved before treatment by 326 of the men in our cohort. At follow-up, 197 of these men had tried to conceive a child, and 138 had succeeded without use of cryopreserved semen. Of the remaining 59 men, 18 reported that their partners had attempted to become pregnant with the use of cryopreserved semen, and 12 of those men became fathers by this route. Of the 18 men whose cryopreserved semen was used, 10 received

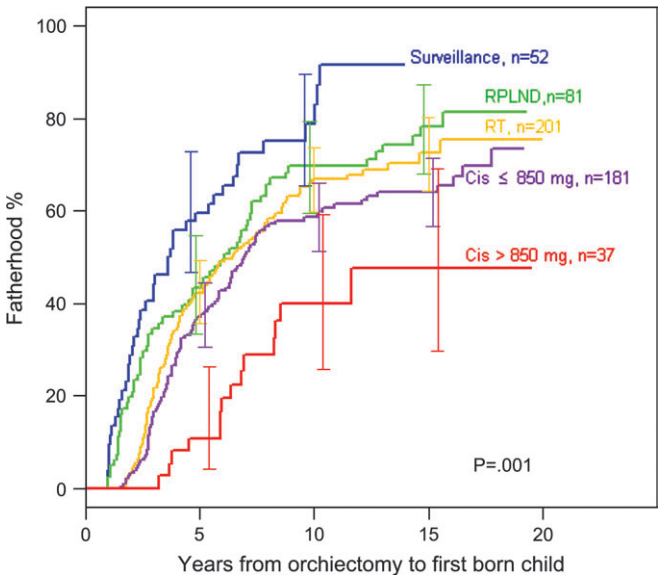

Fig. 2. Actuarial post-treatment paternity rates in each treatment group for patients who attempted conception without the use of cryopreserved semen. $P<.001$ from two-sided log-rank test. RPLND = retroperitoneal lymph node dissection; RT = radiotherapy; cis = cisplatin. Vertical bars indicate 95% confidence intervals.

low-dose chemotherapy, four received high-dose chemotherapy, three were in the RPLND group, and one was in the surveillance group.

Impact of ejaculation function on paternity. Among the 554 men who tried to conceive after treatment, 520 responded to the question about ejaculation function after treatment. Dry ejaculation was reported by 54 of these men, of whom 12 (22%) fathered children after treatment without the use of cryopreserved semen. In addition, three of these men fathered children with the use of cryopreserved semen, but overall 72% of the men with dry ejaculation were still unwillingly childless at the end of follow-up. The men who responded to the question about ejaculation function included 128 men in the low-dose chemotherapy group who were treated with three or four cycles of cisplatin-based chemotherapy (i.e., 480–850 mg), of whom 30 reported dry ejaculation. The actuarial paternity rate 15 years after treatment was only 10% (95% CI =3% to 29%) among the men with dry ejaculation, compared with 83% (95% CI = 74% to 91%) of the 98 men with normal (i.e., antegrade) ejaculation. After 19 years of follow-up, the actuarial paternity rates in these two groups of men were 31% (95% CI = 12% to 67%) and 91% (95% CI = 79% to 98%), respectively (P<.001, log-rank test [Fig. 3]).

Impact of specific therapies on paternity. We compared paternity rates by specific therapy among subsets of men who retained normal (i.e., antegrade) ejaculation. To identify a possible difference between the two chemotherapy regimens (BEP and CVB) that were the standard of care during the period under study, we defined a subset of men who were treated with cisplatin doses corresponding to four cycles (660–850 mg) of these regimens without additional chemotherapy or radiotherapy. We found no statistically significant difference in post-treatment paternity between men treated with BEP (32 of 47) and those treated with CVB (19 of 25) (P = .67). In another subset of men treated with more intense chemotherapy including the alkylating drug ifosfamide, 4 of 10 fathered children.

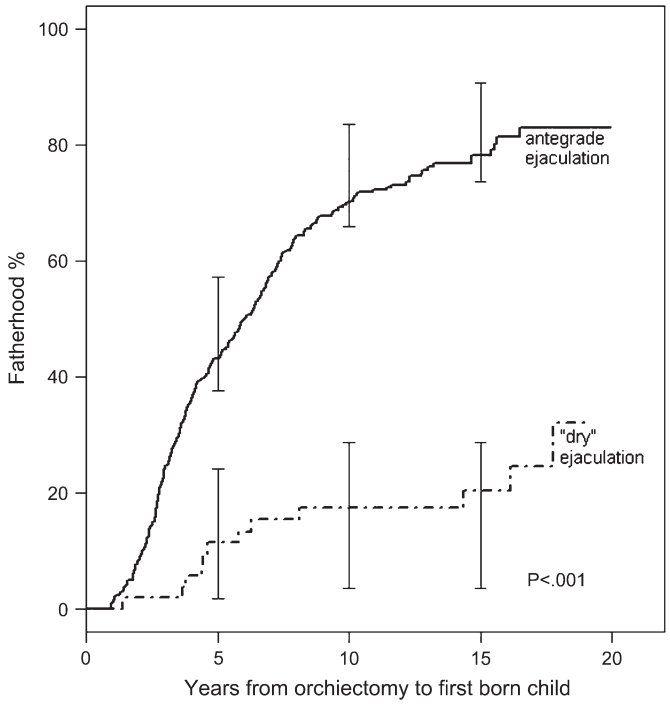

Fig. 3. Actuarial post-treatment paternity rates among men treated with three or four cycles of cisplatin-based chemotherapy (i.e., 480–850 mg of cisplatin) with or without retroperitoneal lymph node dissection in relation to ejaculation function. P<.001 from two-sided log-rank test. Vertical bars indicate 95% confidence intervals.

Of the 178 seminoma patients who were irradiated with the dogleg or L-field technique and attempted to conceive following treatment, 112 succeeded. We found no statistically significant difference in paternity according to radiation dose between the three dose groups (<31 Gy, 31–36 Gy, and >36 Gy) (P = .7) (data not shown). Eleven of the men who received radiation to the para-aortic area only attempted to conceive after treatment and nine of them fathered children, a success rate that was statistically significantly better than that of men in the dogleg- or L-field group (P = .006).

Nine (56%) of the 16 men who tried to conceive a child following treatment with combination of chemotherapy and infradiaphragmatic radiotherapy succeeded. The median cisplatin dose in these 16 men was 770 mg (range = 200–1240 mg), and the median radiation dose was 40 Gy (range = 31–44 Gy), with no difference in cisplatin and radiation doses between those who succeeded and those who did not (data not shown).

Overall, among the 465 men who retained antegrade ejaculation after treatment and who tried to conceive children, the fraction of post-treatment fathers at follow-up according to treatment group was surveillance, 80% (37/46; 95% CI = 67% to 90%); RPLND, 78% (53/68; 95% CI = 67% to 86%); radiotherapy, 64% (125/194; 95% CI = 57% to 71%); low-dose chemotherapy, 76% (100/132; 95% CI = 68% to 83%); and high-dose chemotherapy, 52% (13/25; 95% CI = 32% to 70%) (P = .01). When paternity rates among men with retained ejaculation were compared with those in all men (i.e., Table 1), the greatest differences were seen for the men in the two chemotherapy groups.

Predictive factors for post-treatment paternity. The factors listed in Table 2 were tested in Cox regression multivariable analysis as potential predictors for post-treatment fatherhood. Paternity in the surveillance group was statistically significantly better than that in all other treatment groups. The other statistically significant predictors were having children before treatment, ejaculatory function, and marital status (Table 2).

There were statistically significant deviations from the proportional hazards assumption for pretreatment fatherhood, for all treatment comparisons in the model except RPLND versus surveillance, and for age at orchiectomy greater than 35 versus less than 29 years. In the Schoenfeld residuals plots, the differences in paternity rate by treatment were strongest immediately after treatment and became much smaller after about 3 years. Consequently, the model was refitted for follow-up for the first 3 years after treatment and also for men who did not achieve fatherhood until after 3 years after treatment. The treatment differences were somewhat greater in the first 3 years than in the presented analysis for the whole study period, and treatment differences were not statistically significant in the period after 3 years (Table 2).

There were also statistically significant deviations from the proportional hazards assumptions the first 3 years for pretreatment fatherhood and for two treatment comparisons (radiotherapy versus surveillance and low-dose chemotherapy versus surveillance) and after 3 years for pretreatment fatherhood and the last age comparison. Therefore, the corresponding hazard ratios (HRs) from these analyses are likely to be conservative estimates.

Time trends in paternity rates. Some modifications to testicular cancer treatment were introduced in the late 1980s in an effort to reduce toxicity and better maintain fertility *(14,15,28,43)*. These included the surveillance policy (no treatment other than

Table 2. Independent predictors of fatherhood in testicular cancer survivors from a Cox model*

Predictor variable	HR (95% CI)	HR (95% CI) until 3 y	HR (95% CI) after 3 y
History of cryptorchism			
No	1 (referent)	1	1
Yes	0.79 (0.57 to 1.08)	0.99 (0.59 to 1.67)	0.70 (0.47 to 1.05)
	.14	.96	.09
Age at orchiectomy, y			
<29	1 (referent)	1	1
29–35	0.95 (0.74 to 1.23)	0.91 (0.59 to 1.39)	0.93 (0.68 to 1.28)
>35	0.59 (0.35 to 0.97)	0.88 (0.42 to 1.83)	0.43 (0.22 to 0.87)
	.11	.88	.03
Marital status			
Single	1 (referent)	1	1
Married/cohabitant	1.76 (1.00 to 3.08)	1.51 (0.55 to 4.15)	1.92 (0.98 to 3.78)
	.049	.42	.058
Pretreatment fatherhood			
No	1 (referent)	1	1
Yes	1.55 (1.23 to 1.96)	2.36 (1.57 to 3.55)	1.21 (0.90 to 1.62)
	<.001	<.001	.20
Treatment group			
Surveillance	1 (referent)	1	1
RPLND	0.61 (0.40 to 0.93)	0.64 (0.35 to 1.17)	0.65 (0.36 to 1.18)
RT	0.48 (0.33 to 0.70)	0.31 (0.18 to 0.53)	0.70 (0.41 to 1.19)
Cisplatin ≤ 850 mg	0.58 (0.40 to 0.85)	0.27 (0.15 to 0.50)	0.95 (0.56 to 1.60)
Cisplatin > 850 mg	0.31 (0.17 to 0.58)	0 (0 to 0.37)†	0.60 (0.30 to 1.22)
	.001	<.001	.15
Dry ejaculation			
No	1 (referent)	1	1
Yes	0.19 (0.10 to 0.34)	0.10 (0.01 to 0.76)	0.18 (0.10 to 0.34)
	<.001	.025	<.001

*Based on 507 of the 554 men attempting conception (data on some variables were missing for 47 of these men). Two-sided *P* values determined from Cox regression analysis are shown in the last row for each predictor variable. HR = hazard ratio; CI = confidence interval; RPLND = retroperitoneal lymph node dissection; RT = radiotherapy.

†Undefined HR because no men in this group achieved fatherhood within 3 years. The 95% CI is based on profile likelihood.

orchiectomy until clinical evidence of metastases is established), fewer chemotherapy cycles in early-stage nonseminomas, reduced radiation volume and doses, and modification of post-chemotherapy surgery by restriction to removal of involved lymph nodes only and use of nerve-sparing techniques.

To investigate whether these modifications were actually associated with increased fertility, we compared the 10-year actuarial paternity rate of patients diagnosed from 1980 through 1988 with that of patients diagnosed from 1989 through 1994. Men diagnosed during the more recent period had a statistically significantly greater chance of fathering children, with a 10-year actuarial paternity rate of 76% (95% CI = 69% to 83%), compared with 55% (95% CI = 50% to 61%) for men diagnosed during the earlier period ($P<.001$) (Fig. 4). To evaluate the effects of changes in the active therapies (surgery, radiotherapy, and chemotherapy), we repeated the analysis but omitted the men in the surveillance group. This analysis yielded 10-year actuarial paternity rates that were very close to those in the analysis that included men in the surveillance group: 75% (95% CI = 67% to 82%) for men diagnosed in the later period and 55% (95% CI = 49% to 61%) for men diagnosed in the earlier period.

Discussion

We present data on paternity rates from a large national cohort of testicular cancer survivors, of whom 554 attempted to conceive a child after treatment. The paternity rates among these men were 71% at 15 years and 76% at 20 years after orchiectomy. This study is, to our knowledge, the largest to address this issue and the first to show the impact of all commonly used treatment modalities compared with orchiectomy only (i.e., surveillance). Paternity was assessed in relation to those who actually tried to conceive a child and not to the overall group of testicular cancer survivors. Post-treatment paternity rates in all treatment groups were lower than those in the surveillance group. Patients treated with the higher chemotherapy dose (i.e., more than 850 mg of cisplatin) had the lowest chance of becoming fathers. However, even among these most intensively treated men, almost half were able to father children.

A potential limitation to this study is the possibility that some of the men recorded as fathers were not the actual biological fathers of the children they "fathered" after treatment. The previously much-quoted rate of nonbiological paternity cases in the general population of 10% is most likely exaggerated, although cultural and socioeconomic variations probably occur *(44)*. European data suggest a rate closer to 1%–2% *(44–46)*. Whether the frequency is higher among couples comprising subfertile testicular cancer survivors remains an open question.

This study is also limited by some aspects of the design of our questionnaire. No questions asked specifically about the length of time the couple had tried to conceive or whether unwillingly childless couples had tried to have children for longer than 1 year, which is generally considered the definition of infertility *(47)*. However, such a definition may not apply to men experiencing testicular cancer treatment–related infertility because spermatogenesis may still improve for many years following therapy *(9,48)*. For couples who needed assistance with reproduction, the extent of assistance that they actually needed is mostly unknown. Subfertility in the female partner was also not specifically addressed. In the general population, female factors are at least partly involved in 65% of couples consulting for infertility *(47)*.

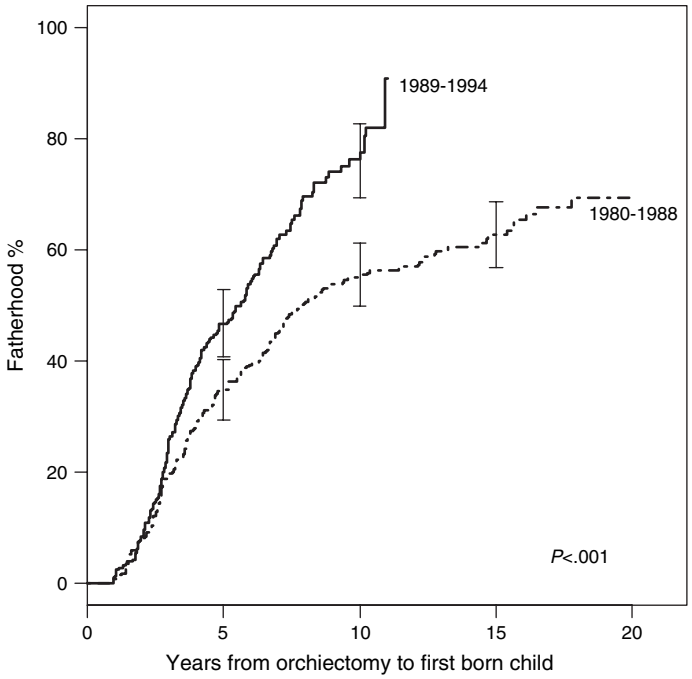

Fig. 4. Actuarial post-treatment paternity rates among men treated for testicular cancer in relation to period of treatment. $P<.001$ from two-sided log-rank test. Vertical bars indicate 95% confidence intervals.

However, for the present series we assumed that a history of testicular cancer, with subsequent orchiectomy and spermatotoxic therapy, was the main factor contributing to infertility.

Finally, our analysis of predictive factors was limited by deviations from the proportional hazards assumption. Such deviations are not surprising, considering the nature of these data. Chemotherapy and radiotherapy are well known to cause azoospermia or oligospermia following treatment, but in the majority of men there is at least some, and often good, recovery of spermatogenesis over the first few years after treatment *(9,10,11,12,48)*. Moreover, patients treated with chemotherapy or radiotherapy are often advised to postpone having children for at least 1 year following therapy to avoid potential teratogenicity. By contrast, surgery does not have the same impact on spermatogenesis, and there are no restrictions on these patients' attempts to conceive. Thus, the treatment differences were more pronounced during the first years following therapy. For the difference between men with and without children pretreatment, those who already had children at diagnosis may have been more likely to complete their family in the early period following treatment and less likely to have children many years later. The same principle may apply for the changes, over time, in the differences in paternity rates by age, because older men may be more eager to have their children at an early point following treatment than many years later. Consequently, the presented HRs are likely to be conservative estimates and should still be suitable for practical guidance.

Attempts at conception after treatment were recorded by 554 (39%) of the men. This intention rate is similar to or higher than that previously reported *(20,24)*, but it is lower than the stated intentions of testicular cancer patients when asked at diagnosis *(3,4)*. It is possible that this difference between future intentions stated at diagnosis and actual attempts prior to follow-up reflects psychological adjustments among infertile couples who might deny prior attempts at conceptions. If so, there would be a bias toward artificially low reported intention rates, which would lead to artificially high paternity rates (which are based on the intention rates). However, it is also likely that some men were not yet in the right life situation to have children, and the intention rate might thus have increased with even longer follow-up.

Attempts at conception were lowest in the radiotherapy and high-dose chemotherapy groups. Men in the radiotherapy group were generally older than men in the other groups and, thus, more likely to have completed their families before diagnosis. The low attempt rate in the high-chemotherapy group might be explained, in part, by the fact that more men in that group than in any of the other groups were single (Table 1). It is also possible that the low attempt rate among this group of men was influenced by their knowledge of their reduced fertility potential, because men who consider themselves infertile may not have attempted to conceive a child.

The post-treatment paternity rates we found—71% at 15 years and 76% at 20 years—were similar to or higher than rates that have previously been reported in groups of testicular cancer patients treated with more than one treatment modality *(20,21,24)*. Reasons for our higher rates may include the longer follow-up and the lower rates of dry ejaculation following RPLND, which was a strong predictor for post-treatment paternity. The proportions of patients receiving different treatment modalities may also have varied from those in other studies.

We found that the time from orchiectomy to birth of the first post-treatment child varied according to treatment (Fig. 2). Age may, however, be a confounder in this relationship, because it is likely that age to some extent determined when the men wanted children. Young men are more likely to wait to start a family, and the longer interval between orchiectomy and first child in the high-dose chemotherapy group, which was the youngest age group in our study, may thus to some extent be influenced by the age of the men in this group.

According to our multivariable analysis, age was not a statistically significant factor for paternity. However, one age comparison indicated that men older than 35 years were less successful at fathering children than those younger than 29 years. This difference may reflect the impact of age on the recovery of spermatogenesis following treatment, which has been reported to be better among younger men *(48,49)*. The man's age may also, to some extent, reflect that of his female partner, and female age is strongly related to fertility.

We found no statistically significant difference in paternity rates between the radiotherapy and low-dose chemotherapy groups (Fig. 2 and Table 2). This finding is in contrast to the results of Huyghe et al., who reported a statistically significantly more deleterious effect of radiotherapy than of two to four cycles of chemotherapy on pregnancy rates *(24)*. It is possible that this difference reflects differences in multivariable adjustment in the two studies. Huyghe et al. *(24)* note only that "various infertility risk factors" were tested and explicitly report only the statistically significant factors (history of cryptorchism and chemotherapy versus radiotherapy). By contrast, we adjusted for additional factors, including age. In Huyghe et al.'s study *(24)*, the median age of the seminoma patients (treated with radiotherapy) was 7 years higher than that of the nonseminoma patients (treated with chemotherapy), and this difference could account, at least in part, for the lower paternity rate in the radiotherapy group *(48,49)*. Alternatively, the different results could reflect differences in the chemotherapy groups between the two studies. The low-dose chemotherapy group in our study was more heterogeneous, with some of the patients having

been treated with additional radiotherapy or RPLND (the latter treatment being followed by dry ejaculation in some patients). In our univariate analysis comparing paternity rates only among patients with retained ejaculation, the radiotherapy and the high-dose chemotherapy groups had the lowest paternity rates, indicating that radiotherapy may have a more profound effect on paternity rates than low-dose chemotherapy. However, dry ejaculation was included as a factor in our multivariable analysis.

The finding that patients treated with the higher chemotherapy dose (i.e., more than 850 mg of cisplatin) had the lowest paternity rates among the five treatment groups is in accord with data on s-FSH and sperm count, which show long-lasting or irreversible impairment of spermatogenesis following cisplatin doses exceeding 400 mg/m^2 (i.e., more than four cycles, corresponding to our high-dose group) *(12)*.

In our analysis, dry ejaculation was the strongest negative predictive factor for post-treatment paternity. More than two-thirds of the men reporting this condition remained childless, even though they could have used cryopreserved semen or other treatment options, such as α-sympathomimetic drugs, which have been shown to reverse retrograde ejaculation in 50%–80% of cases *(41,42)*. Although only three men reported the use of such drugs, their use was probably underreported because type of assistance was stated by only some of the respondents in response to an open question. Transrectal electroejaculation and testis sperm extraction combined with assisted reproductive techniques have also been reported to be successful in assisting men with dry ejaculation to father children *(50,51)*. However, these methods were introduced relatively recently and were not available for most of the men in our study. In any event, dry ejaculation is now an infrequent complication of testicular cancer treatment due to reduced use of retroperitoneal dissections and increased use of nerve-sparing surgical techniques.

Men who were fathers before treatment were more likely to succeed in having children following treatment than those who had not had children before treatment. This difference may reflect the known association between infertility and testicular cancer *(5,6)*. The pretreatment fathers were, by definition, fertile, and the fraction of inherently infertile men is therefore higher among those who have not yet had children.

Results of our analysis of paternity rate according to radiation field imply that the pelvic part of the field influences paternity rates. In a small, preliminary subgroup analysis we found a highly statistically significant difference in favor of treatment with a para-aortic field, confirming previous data on the effect of radiation field on sperm count and s-FSH *(16,52,53)*. Although para-aortic radiation is used more frequently now than it was in the period of study, some institutions still use dogleg and L-fields to minimize the risk of pelvic relapse. Overall survival following both radiation fields as well as surveillance with salvage chemotherapy in stage I seminomas is considered to be equivalent. Therefore, the desire to have children in the future should be taken into consideration when treatment is discussed.

Among 191 men who were unwillingly childless after treatment, 12 (6.3%) became fathers by using cryopreserved semen. This rate is lower than the 12.7% (7/55) reported by Huyghe et al. *(24)*. The difference between the two studies may reflect different procedures for offering sperm banking, especially in the early period of this study, when sperm banking was less common in Norway than it is now *(54)*. It is also possible that there are cultural differences regarding use of assisted reproductive techniques between Norway and France, where Huyghe et al.'s study was performed. Economic issues should not be of major importance because there were no private costs attached to these procedures in Norway. In our cohort, none of the men in the radiotherapy group used cryopreserved semen. However, this was available for only 13 of the radiotherapy patients who were unsuccessful in their attempts to father children post-treatment, some of whom already had children born prior to diagnosis. It is possible that, despite wanting additional children, these men and their partners ultimately decided not to undergo assisted reproductive techniques to have more children.

There was a positive trend in preservation of fertility across the study period. That is, a larger percentage of men treated from 1989 through 1994 than from 1980 through 1988 fathered children. The difference was not affected when the surveillance patients were omitted from the analysis; thus, it probably reflects early introduction of modified retroperitoneal surgical techniques, reduction in number of chemotherapy cycles in early stages of nonseminomas, and reduction of radiation volume and dose in the late 1980s.

The comprehensive data presented in this article should serve as a reliable guide for physicians counseling new or prior testicular cancer patients for whom fertility is of major concern. With recent advances in assisted fertility techniques, more testicular cancer survivors may be helped to father children. However, because infertility cannot be predicted on an individual basis, it is important to continue the policy of offering sperm preservation prior to treatment.

References

(1) Dearnaley D, Huddart R, Horwich A. Regular review: managing testicular cancer. BMJ 2001;322:1583–8.

(2) Hansen S, Norstein J, Næss Å. Cancer in Norway 2001. Oslo (Norway): Cancer Registry of Norway, Institute of Population-Based Cancer Research; 2004.

(3) Fossa SD, Aass N, Ous S, Waehre H. Long-term morbidity and quality of life in testicular cancer patients. Scand J Urol Nephrol Suppl 1991;138:241–6.

(4) Aass N, Fossa SD. Paternity in young patients with testicular cancer—expectations and experience. Prog Clin Biol Res 1988;269:481–91.

(5) Turek PJ, Lowther DN, Carroll PR. Fertility issues and their management in men with testis cancer. Urol Clin N Am 1998;25:517–31.

(6) Petersen PM, Skakkebaek NE, Giwercman A. Gonadal function in men with testicular cancer: biological and clinical aspects. APMIS 1998;106:24–34; discussion 34–6.

(7) Carroll PR, Whitmore WF Jr, Herr HW, Morse MJ, Sogani PC, Bajorunas D, et al. Endocrine and exocrine profiles of men with testicular tumors before orchiectomy. J Urol 1987;137:420–3.

(8) Petersen PM, Skakkebaek NE, Vistisen K, Rorth M, Giwercman A. Semen quality and reproductive hormones before orchiectomy in men with testicular cancer. J Clin Oncol 1999;17:941–7.

(9) Lampe H, Horwich A, Norman A, Nicholls J, Dearnaley DP. Fertility after chemotherapy for testicular germ cell cancers. J Clin Oncol 1997;15:239–45.

(10) Fossa SD, Abyholm T, Normann N, Jetne V. Post-treatment fertility in patients with testicular cancer. III. Influence of radiotherapy in seminoma patients. Br J Urol 1986;58:315–9.

(11) Berthelsen JG. Sperm counts and serum follicle-stimulating hormone levels before and after radiotherapy and chemotherapy in men with testicular germ cell cancer. Fertil Steril 1984;41:281–6.

(12) Pont J, Albrecht W. Fertility after chemotherapy for testicular germ cell cancer. Fertil Steril 1997;68:1–5.

(13) Nijman JM, Schraffordt Koops H, Oldhoff J, Kremer J, Jager S. Sexual function after bilateral retroperitoneal lymph node dissection for nonseminomatous testicular cancer. Arch Androl 1987;18:255–67.

(14) Donohue JP, Thornhill JA, Foster RS, Rowland RG, Bihrle R. Retroperitoneal lymphadenectomy for clinical stage A testis cancer (1965 to 1989): modifications of technique and impact on ejaculation. J Urol 1993;149:237–43.

(15) Peckham MJ, Barrett A, Husband JE, Hendry WF. Orchidectomy alone in testicular stage I non-seminomatous germ-cell tumours. Lancet 1982;ii:678–80.

(16) Fossa SD, Horwich A, Russell JM, Roberts JT, Cullen MH, Hodson NJ, et al. Optimal planning target volume for stage I testicular seminoma: a Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. J Clin Oncol 1999;17:1146.
(17) Jones WG, Fossa SD, Mead GM, Roberts JT, Sokal M, Horwich A, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). J Clin Oncol 2005;23:1200–8.
(18) de Wit R, Roberts JT, Wilkinson PM, de Mulder PH, Mead GM, Fossa SD, et al. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol 2001;19:1629–40.
(19) Fossa SD, Almaas B, Jetne V, Bjerkedal T. Paternity after irradiation for testicular cancer. Acta Radiol Oncol 1986;25:33–6.
(20) Hansen PV, Glavind K, Panduro J, Pedersen M. Paternity in patients with testicular germ cell cancer: pretreatment and post-treatment findings. Eur J Cancer 1991;27:1385–9.
(21) Arai Y, Kawakita M, Okada Y, Yoshida O. Sexuality and fertility in long-term survivors of testicular cancer. J Clin Oncol 1997;15:1444–8.
(22) Herr HW, Bar-Chama N, O'Sullivan M, Sogani PC. Paternity in men with stage I testis tumors on surveillance. J Clin Oncol 1998;16:733–4.
(23) Bohlen D, Burkhard FC, Mills R, Sonntag RW, Studer UE. Fertility and sexual function following orchiectomy and 2 cycles of chemotherapy for stage I high risk nonseminomatous germ cell cancer. J Urol 2001;165: 441–4.
(24) Huyghe E, Matsuda T, Daudin M, Chevreau C, Bachaud JM, Plante P, et al. Fertility after testicular cancer treatments: results of a large multicenter study. Cancer 2004;100:732–7.
(25) Fossa SD, Aas N, Kaalhus O. Long-term morbidity after infradiaphragmatic radiotherapy in young men with testicular cancer. Cancer 1989;64:404–8.
(26) Schmoll HJ, Souchon R, Krege S, Albers P, Beyer J, Kollmannsberger C, et al. European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG). Ann Oncol 2004;15:1377–99.
(27) Peckham MJ, Barrett A, McElwain TJ, Hendry WF. Combined management of malignant teratoma of the testis. Lancet 1979;ii:267–70.
(28) Klepp O, Dahl O, Flodgren P, Stierner U, Olsson AM, Oldbring J, et al. Risk-adapted treatment of clinical stage 1 non-seminoma testis cancer. Eur J Cancer 1997;33:1038–44.
(29) Klepp O, Olsson AM, Henrikson H, Aass N, Dahl O, Stenwig AE, 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;8:509–18.
(30) Aass N, Klepp O, Cavallin-Stahl E, Dahl O, Wicklund H, Unsgaard B, et al. Prognostic factors in unselected patients with nonseminomatous metastatic testicular cancer: a multicenter experience. J Clin Oncol 1991;9:818–26.
(31) Cullen MH, Stenning SP, Parkinson MC, Fossa SD, Kaye SB, Horwich AH, et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. J Clin Oncol 1996;14:1106–13.
(32) Kaye SB, Mead GM, Fossa S, Cullen M, deWit R, Bodrogi I, et al. Intensive induction-sequential chemotherapy with BOP/VIP-B compared with treatment with BEP/EP for poor-prognosis metastatic nonseminomatous germ cell tumor: a Randomized Medical Research Council/European Organization for Research and Treatment of Cancer study. J Clin Oncol 1998;16:692–701.
(33) Fossa SD, Droz JP, Stoter G, Kaye SB, Vermeylen K, Sylvester R. Cisplatin, vincristine and ifosphamide combination chemotherapy of metastatic seminoma: results of EORTC trial 30874. EORTC GU Group. Br J Cancer 1995;71:619–24.
(34) Horwich A, Oliver RT, Wilkinson PM, Mead GM, Harland SJ, Cullen MH, et al. A medical research council randomized trial of single agent carboplatin versus etoposide and cisplatin for advanced metastatic seminoma. MRC Testicular Tumour Working Party. Br J Cancer 2000;83:1623–9.
(35) Horwich A, Sleijfer DT, Fossa SD, Kaye SB, Oliver RT, Cullen MH, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic non-seminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. J Clin Oncol 1997;15:1844–52.
(36) Yao WQ, Fossa SD, Dearnaley DP, Horwich A. Combined single course carboplatin with radiotherapy in treatment of stage IIA,B seminoma—a preliminary report. Radiother Oncol 1994;33:88–90.
(37) Fossa SD, Aass N, Kaalhus O. Radiotherapy for testicular seminoma stage I: treatment results and long-term post-irradiation morbidity in 365 patients. Int J Radiat Oncol Biol Phys 1989;16:383–8.
(38) Sagstuen H, Aass N, Fossa SD, Dahl O, Klepp O, Wist EA, et al. Blood pressure and body mass index in long-term survivors of testicular cancer. J Clin Oncol 2005;23:4980–90.
(39) Nord C, Bjoro T, Ellingsen D, Mykletun A, Dahl O, Klepp O, et al. Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer. Eur Urol 2003;44:322–8.
(40) Therneau T, Grambsch P. Modelling survival data. Extending the Cox model. New York (NY): Springer; 2000.
(41) Fossa SD, Ous S, Åbyholm T, Loeb M. Post-treatment fertility in patients with testicular cancer. I. Influence of retroperitoneal lymph node dissection on ejaculatory potency. Br J Urol 1985;57:204–9.
(42) Nijman JM, Jager S, Boer PW, Kremer J, Oldhoff J, Koops HS. The treatment of ejaculation disorders after retroperitoneal lymph node dissection. Cancer 1982;50:2967–71.
(43) Chevreau C, Mazerolles C, Soulie M, Gaspard MH, Mourey L, Bujan L, et al. Long-term efficacy of two cycles of BEP regimen in high-risk stage I nonseminomatous testicular germ cell tumors with embryonal carcinoma and/or vascular invasion. Eur Urol 2004;46:209–14; discussion 214–5.
(44) Macintyre S, Sooman A. Non-paternity and prenatal genetic screening. Lancet 1991;338:869–71.
(45) Brock DJ, Shrimpton AE. Non-paternity and prenatal genetic screening. Lancet 1991;338:1151.
(46) Sasse G, Muller H, Chakraborty R, Ott J. Estimating the frequency of nonpaternity in Switzerland. Hum Hered 1994;44:337–43.
(47) Comhaire FH. Basic investigation of the infertile male and andrological aspects of erectile dysfunction. In: Comhaire FH. Male infertility. Clinical investigation, cause evaluation and treatment. 1st ed. London (UK): Chapman & Hall Medical; 1996. p. 133–42.
(48) Hansen PV, Trykker H, Svennekjaer IL, Hvolby J. Long-term recovery of spermatogenesis after radiotherapy in patients with testicular cancer. Radiother Oncol 1990;18:117–25.
(49) Aass N, Fossa SD, Theodorsen L, Norman N. Prediction of long-term gonadal toxicity after standard treatment for testicular cancer. Eur J Cancer 1991;27:1087–91.
(50) Rosenlund B, Sjoblom P, Tornblom M, Hultling C, Hillensjo T. In-vitro fertilization and intracytoplasmic sperm injection in the treatment of infertility after testicular cancer. Hum Reprod 1998;13:414–8.
(51) Damani MN, Master V, Meng MV, Burgess C, Turek P, Oates RD, et al. Postchemotherapy ejaculatory azoospermia: fatherhood with sperm from testis tissue with intracytoplasmic sperm injection. J Clin Oncol 2002;20:930–6.
(52) Jacobsen KD, Olsen DR, Fossa K, Fossa SD. External beam abdominal radiotherapy in patients with seminoma stage I: field type, testicular dose, and spermatogenesis. Int J Radiat Oncol Biol Phys 1997;38:95–102.
(53) Joos H, Sedlmayer F, Gomahr A, Rahim HB, Frick J, Kogelnik HD, et al. Endocrine profiles after radiotherapy in stage I seminoma: impact of two different radiation treatment modalities. Radiother Oncol 1997;43:159–62.
(54) Magelssen H, Haugen TB, von Düring V, Melve KK, Sandstad B, Fossa SD. Twenty years experience with semen cryopreservation in testicular cancer patients: who needs it? Eur Urol 2005, article in press, access online ahead of print.

Notes

The support of the Health Region West and the Norwegian Health and Rehabilitation Fund (grant no. 1998/207) is gratefully acknowledged. This study is a joint national clinical study as part of the Norwegian Urological Cancer Group III project. Clinics outside the Norwegian Radium Hospital are members of the Swenoteca Group.

Funding to pay the Open Access publication charges for this article was provided by the Institute of Medicine, Medical Faculty, University of Bergen.

Manuscript received March 9, 2005; revised August 26, 2005; accepted September 14, 2005.