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Testis Cancer

Paternity and Testicular Function Among Testicular Cancer Survivors Treated With Two to Four Cycles of Cisplatin-Based Chemotherapy

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Abstract

Background: Preserved fertility is an important issue for testicular cancer (TC) survivors.
Objective: Our aim was to examine any difference regarding paternity and testicular function following two, three, or four cycles of cisplatin-based chemotherapy for TC.
Design, setting, and participants: A national multicentre follow-up survey assessing morbidity among survivors of unilateral TC diagnosed from 1980 to 1994 was conducted during the period 1998 to 2002. Of the 1814 men invited, 1462 (80.6%) participated by responding to a mailed questionnaire and/or undergoing a clinical examination including laboratory assessments. The present study includes the 316 participants up to 65 yr of age treated with two to four cycles of standard cisplatin-based chemotherapy without additional treatment beyond surgery.
Measurements: Self-reported paternity following treatment for TC according to number of cycles was assessed among men who reported antegrade ejaculation and attempts at posttreatment conception ($n = 106$). Kaplan-Meier analysis, log-rank test, and Cox regression were applied. Gonadal hormones ($n = 305–314$) and sperm counts ($n = 71$) by number of cycles were assessed by linear by linear association or Mann-Whitney tests.
Results and limitations: At median 12-yr follow-up, 80% (85 of 106) had succeeded in their attempts of achieving posttreatment paternity (two cycles: 100%; three: 83%; four: 76%; $p = 0.022$). For all patients the 15-yr actuarial paternity rate was 85%. The association between posttreatment paternity and number of cycles remained significant in the multivariate analysis ($p = 0.032$). High serum follicle-stimulating hormone values were more common with increasing number of cycles ($p = 0.037$), but there were no differences in serum luteinising hormone, serum testosterone, or sperm counts. Few men treated with two cycles and a limited number of sperm samples are the main limitations of this study.
Conclusions: The prospects of future paternity after two to four cycles of cisplatin-based chemotherapy are good, and our data suggest that the prospects improve with decreasing number of cycles.

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1. Introduction

Testicular cancer (TC) typically occurs at the peak of reproductive age, and the ability to father children in the future is an important issue. However, impaired fertility and TC may share aetiological factors, and reduced spermatogenesis is often evident when TC is diagnosed [1]. Although cancer treatment commonly further impairs fertility, spermatogenesis often improves with time, depending on the extent of treatment [2–4].

Conception rates of about 71–85% (actual and cumulative, respectively) have been reported in two large studies among TC survivors who had attempted conception following chemotherapy [5,6]. We have previously reported 15-yr actuarial posttreatment paternity rates of 92% following orchiectomy only, compared with 63% and 48% following chemotherapy with cumulative cisplatin doses ≤850 mg and >850 mg, respectively (including combinations with retroperitoneal lymph node dissection [RPLND] and/or radiotherapy) [7].

During the last two decades, risk-adapted toxicity-sparing treatment strategies have increasingly been followed [8,9], and paternity rates were improved following fertility-sparing treatment modifications in the late 1980 s [7]. Whether the paternity chances are different following two, three, or four cycles of cisplatin-based combination chemotherapy remains an open question [10]. The aim of this study was to address this issue. We also report on gonadal hormones and sperm counts.

2. Materials and methods

2.1. Population and study design

From 1998 to 2002, a Norwegian national multicentre follow-up survey was conducted to assess long-term morbidity in TC survivors who were diagnosed with unilateral germ cell TC in 1980–1994 (the Norwegian Urologic Cancer Group [NUCG] III study). Exclusion criteria were bilateral orchiectomy for any reason, extragonadal germ cell cancer, other malignancies except skin cancer, and mental retardation. The Committee for Medical Research Ethics of the Southern Health Region of Norway approved the study. A total of 1814 men were invited, and after giving their written consent, 1462 (80.6%) participated by answering a 219-item questionnaire and/or undergoing an outpatient examination including laboratory assessments (Fig. 1) [7]. The questionnaire included 14 items assessing pre- and posttreatment fertility. Data including primary and relapse treatment were retrieved from the medical records. Initially, total cumulative cisplatin doses were collected [7]; details regarding type of combination regimen and number of cycles subsequently were retrieved for the present study.

The current report includes the 316 of the 1462 participants who fulfilled the following selection criteria (Fig. 1): Men up to 65 yr of age at the time of the survey who had been treated with two to four cycles of standard cisplatin-based chemotherapy, with cisplatin administered at 20 mg/m^2 per day for 5 consecutive days (BEP [cisplatin, etoposide, and bleomycin], n = 183; EP [cisplatin and etoposide], n = 4; or CVB [cisplatin, vinblastine, and bleomycin], n = 116), without additional treatment beyond surgery (orchiectomy with or without RPLND). Thirteen men received both CVB and BEP/EP. The total number of cycles were two (n = 20), three (n = 79), and four (n = 217) (Table 1). Men receiving androgen substitution therapy (n = 11) were categorised as having low

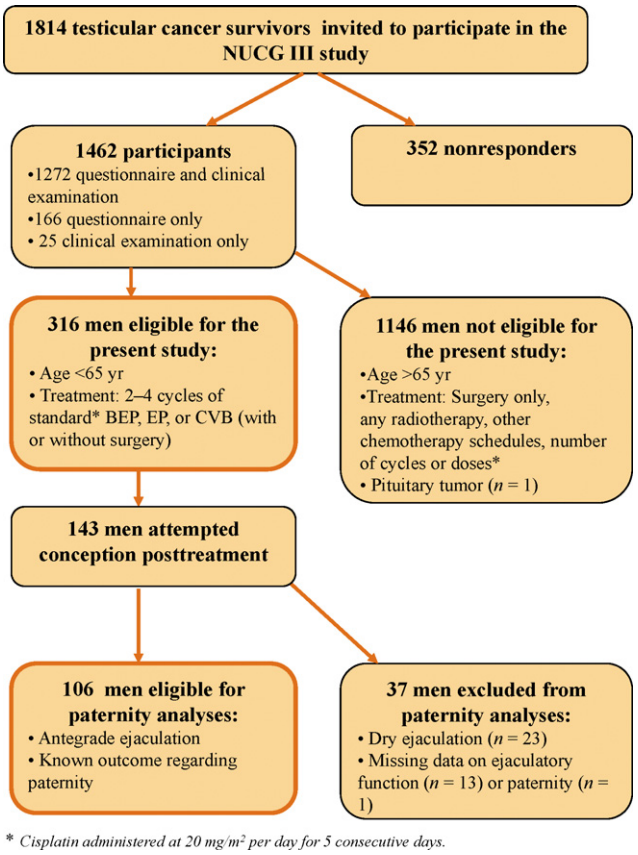

Fig. 1 – An overview of the selection criteria and number of men in the study samples presented (outline in orange), in relation to the whole Norwegian Urology Cancer Group (NUCG) III cohort.

testosterone, and they were excluded from the analyses of sperm counts, serum follicle-stimulating hormone (s-FSH), and serum luteinising hormone (s-LH).

The paternity analyses were confined to men who reported antegrade ejaculation, attempts at posttreatment conception, and whether or not they had fathered a child. Of 143 men reporting attempts at posttreatment conception, 106 were eligible for the paternity analyses (Fig. 1). For comparison, the actuarial paternity rate of 46 men with orchiectomy only who otherwise fulfilled the same selection criteria were included in Fig. 2 only.

2.2. Laboratory assessments

All 316 participants were eligible for hormone analyses. The blood samples were drawn by venipuncture, usually between 8 AM and 12 AM. Hormone assessments were based on commercial immunoassay technology at each of the five collaborating laboratories, with similar methods and reference ranges. The cut-off limits considered normal in this study were s-LH < 12 IU/l, s-FSH < 12 IU/l, and serum total testosterone (s-testosterone) ≥10 nmol/l. Optional semen specimens were collected from those participating at two of the collaborating hospitals, and sperm counts (million per millilitre) were assessed in accordance with the World Health Organisation guidelines [11].

2.3. Statistical analysis

The Kruskal-Wallis test (exact using Monte Carlo method) was used for group comparisons of continuous data, and the exact chi-square, linear

Table 1 – Characteristics according to total number of chemotherapy cycles in all 316 eligible cases and the subgroup of men ($n = 106$) included in the paternity analyses

	All cases*					Cases included in paternity analyses†				
	No. of cycles			Total	p value‡	No. of cycles			Total	p value‡
	Two ($n = 20$)	Three ($n = 79$)	Four ($n = 217$)	($n = 316$)		Two ($n = 8$)	Three ($n = 30$)	Four ($n = 68$)	($n = 106$)	
Age, yr, median (range)										
At treatment	31 (20–43)	29 (15–52)	28 (15–54)	29 (15–54)	0.30§	27 (20–32)	26 (19–34)	26 (15–37)	26 (15–37)	0.91§
At survey	40 (26–56)	41 (28–60)	41 (23–64)	41 (23–64)	0.98§	37 (26–30)	39 (28–49)	37 (25–53)	38 (25–53)	0.38§
Marital status, no. (%)‖					0.59					0.75
Married	13 (65)	43 (56)	121 (58)	177 (58)		4 (50)	20 (67)	43 (63)	67 (63)	
Cohabiting	4 (20)	14 (18)	43 (21)	61 (20)		3 (38)	7 (23)	18 (26)	28 (26)	
Separated/divorced	2 (10)	10 (13)	12 (6)	24 (8)		1 (12)	2 (7)	2 (3)	5 (5)	
Never been married	1 (5)	10 (13)	29 (14)	40 (13)		0	1 (3)	5 (7)	6 (6)	
Widowed	0	0	2 (1)	2 (1)		0	0	0	0	
Histology, no. (%)					0.065					1.0
Seminoma	0	4 (5)	26 (12)	30 (9)		0	1 (3)	3 (4)	4 (4)	
Nonseminoma	20 (100)	75 (95)	191 (88)	286 (91)		8 (100)	29 (97)	65 (96)	102 (96)	
Initial RMH stage¶, no. (%)					<0.001					0.002
I	18 (90)	47 (59)	54 (25)	119 (37)		8 (100)	18 (60)	16 (24)	42 (40)	
IM	0	2 (3)	3 (1)	5 (2)		0	2 (7)	2 (3)	4 (4)	
II	2 (10)	26 (33)	111 (51)	139 (44)		0	8 (27)	34 (50)	42 (40)	
III	0	1 (1)	9 (4)	10 (3)		0	0	5 (7)	5 (5)	
IV	0	3 (4)	40 (19)	43 (14)		0	2 (7)	11 (16)	13 (12)	
Paternity before diagnosis, no. (%)#	13 (65)	46 (58)	105 (50)	164 (53)	0.22	5 (63)	13 (43)	23 (34)	41 (39)	0.23

RMH = Royal Marsden Hospital.

* All 316 men were eligible for the current study.

† The 106 men fulfilling the criteria for inclusion in the paternity analyses: Men with antegrade ejaculation reporting attempts at posttreatment conception where outcome regarding paternity was known.

‡ Two-sided exact χ^2 test except where indicated.

§ Two-sided Kruskal-Wallis test (exact using Monte Carlo method).

‖ Missing data regarding marital status in 12.

¶ RMH stage according to Peckham et al. [30]. Only initial stage is given; number of cycles may include treatment at relapse.

Missing data regarding paternity before diagnosis in eight.

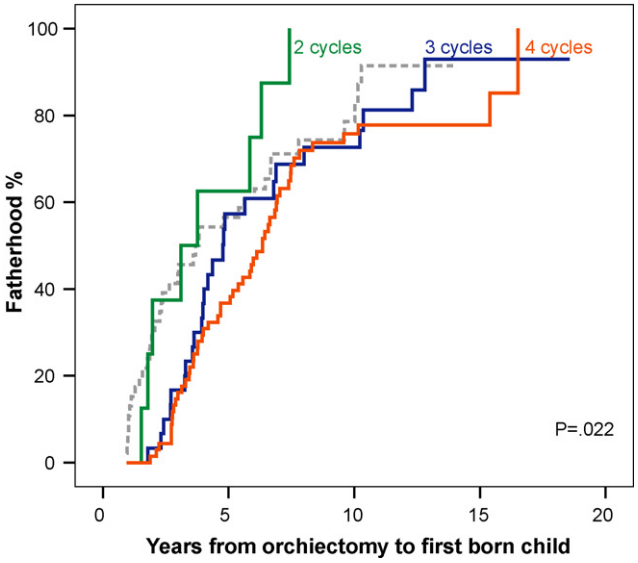

Fig. 2 – Actuarial posttreatment paternity rates according to number (two to four) of cisplatin-based chemotherapy cycles for the men who attempted conception without the use of cryopreserved semen ($p = 0.022$, two-sided log-rank test). For comparison, the dotted grey line illustrates the paternity rate of 46 men treated by orchiectomy only.

by linear association, or Mann-Whitney tests were used for categorical data. Kaplan-Meier analysis and the log-rank test were used to evaluate posttreatment paternity according to number of cycles. A Cox regression model was applied to adjust for age at diagnosis, marital status (single vs married or cohabiting), and paternity prior to diagnosis (yes/no). All tests were two sided. The data were analysed with the SPSS v.16.0 package (SPSS Inc, Chicago, IL, USA).

3. Results

The median follow-up was 12 yr (range: 5–20 yr). Overall, 79% (251 of 316) were either fathers prior to the TC diagnosis ($n = 164$) and/or had attempted to conceive a child following treatment for TC ($n = 143$). Table 1 shows the characteristics of the 106 men included in the paternity analyses.

At follow-up, 85 (80%; 95% confidence interval [CI], 72–87) had succeeded fathering a child following treatment without using cryopreserved semen, resulting in a 15-yr actuarial paternity rate of 85% (95% CI, 76–92) (Fig. 2). However, six (7%) reported that they had needed some form of assistance with reproduction (two after three cycles and four after four cycles). Fertility problems in the female partner were not specifically addressed, and type of assistance was mostly not specified.

According to number of cycles, all of the eight men (100%; 95% CI, 65–100) with two cycles succeeded, compared with 25 of 30 (83%; 95% CI, 66–93) after three, and 52 of 68 (76%; 95% CI, 65–86) after four cycles. The corresponding actuarial paternity rates are illustrated in Fig. 2 ($p = 0.022$; log-rank test). The only significant pairwise difference was between two and four cycles ($p = 0.005$; significant also after Bonferroni correction in a group of three post hoc tests). The difference between two and three cycles reached $p = 0.057$ and three versus four cycles reached $p = 0.43$. The median actuarial time from orchiectomy to the birth of the first child following two cycles was comparable with that following orchiectomy only (3.1 and 3.7 yr, respectively), whereas this interval was longer following three cycles (4.8 yr) and four cycles (6.4 yr)

Table 2 – Number of cycles as predictor of posttreatment fatherhood in 106 testicular cancer survivors reporting antegrade ejaculation and attempts at conception posttreatment*

	Unadjusted			Adjusted		
	HR	95% CI	*p* value	HR	95% CI	*p* value
No. of cycles			0.028			0.032
2	1			1		
3	0.44	0.19–0.98		0.44	0.19–.1.01	
4	0.36	0.17–0.76		0.36	0.17–0.78	

CI = confidence interval; HR = hazard ratio.
* Unadjusted and adjusted for age at diagnosis, marital status, and pretreatment fatherhood (zero vs one child or more) from a Cox model.

Table 3 – Sperm count (million per millilitre) according to number of cycles*

	No. of cycles			Total ($n = 71$)	*p* value†
	Two ($n = 8$)	Three ($n = 10$)	Four ($n = 53$)		
Sperm count, *n* (%)†					0.51
Overall cases, *n*	8	10	53	71	
Azoospermia	0	3 (30)	11 (21)	14 (20)	
Oligospermia (<20 million/ml)	3 (37)	1 (10)	13 (24)	17 (24)	
Normospermia (≥20 million/ml)	5 (63)	6 (60)	29 (55)	40 (56)	

* Men using testosterone substitution therapy were excluded.
† Exact linear by linear association test.

Table 4 – Gonadal hormones according to number of cycles

	No. of cycles			Total (n = 316)	p value*
	Two (n = 20)	Three (n = 79)	Four (n = 217)		
s-FSH, IU/L, n (%)†					0.037
<12 (normal)	12 (63)	47 (61)	112 (53)	171 (56)	
12–23.9	6 (32)	28 (36)	69 (33)	103 (34)	
24–35.9	0	2 (3)	14 (7)	16 (5)	
≥36	1 (5)	0	14 (7)	15 (5)	
s-LH, IU/L, n (%)†‡					0.76
<12 (normal)	18 (95)	73 (95)	191 (92)	282 (93)	
12–23.9	0	4 (5)	14 (7)	18 (6)	
≥24	1 (5)	0	2 (1)	3 (1)	
s-Testosterone, n (%)‡					0.16§
Low‖	4 (20)	9 (11)	44 (21)	57 (18)	
Normal	16 (80)	70 (89)	171 (79)	257 (82)	

s-FSH = serum follicle-stimulating hormone; s-LH = serum luteinising hormone.
* Exact linear by linear association test except where indicated.
† 11 men using testosterone substitution therapy excluded.
‡ Missing data in two cases.
§ Exact Mann-Whitney test.
‖ Low s-testosterone value (<10 nmol/l) or using androgen-replacement therapy.

(Fig. 2). The number of cycles remained an independent predictor for posttreatment fatherhood when adjusted for age at diagnosis, marital status, and paternity prior to diagnosis (Table 2).

Sperm counts (million per millilitre) in 71 men who delivered a semen specimen were not significantly related to number of cycles, although none had azoospermia following two cycles compared with 21% and 30% following four and three cycles, respectively (Table 3).

Overall, 44% had elevated (≥12 IU/l) s-FSH values, and there was a modest but statistically significant difference with number of cycles (p = 0.037; Table 4). There were no statistically significant differences with number of cycles for serum testosterone or s-LH.

4. Discussion

To our knowledge, this is the first report evaluating long-term effects on paternity and testicular function according to two, three, or four cycles of standard cisplatin-based chemotherapy (BEP/EP or CVB) administered to TC patients. The chances of achieving paternity were good, with an overall 85% actuarial paternity rate 15 yr after orchiectomy. We found a statistically significant association between number of cycles and paternity, and the time from orchiectomy to the birth of the first child born after treatment was 1.5 to 2 times longer following three and four cycles compared with two cycles. High s-FSH values were statistically significantly more frequently observed with increasing number of cycles.

The long-term follow-up and known intentions regarding conception are strengths of this study. The main limitation is the number of cases, particularly those with two cycles, which may explain why only the outcomes between two and four cycles were statistically significantly different in post hoc tests. Moreover, sperm samples were available in only 22% of the men, and only one semen sample was delivered, harbouring the risk of considerable day-to-day variations [12]. The low percentage and lack of pretreatment sperm analyses data allowed only descriptive assessment of posttreatment spermatogenesis according to the number of cycles. Other limitations were deficient information regarding subfertility in the female partner and when they started their attempts at conception.

The overall actuarial 15-yr posttreatment paternity rate of 85% is similar to the cumulative pregnancy rate following two to four cycles reported by Huyghe et al. [6], and higher than the 63% actuarial paternity rate we previously reported for men who received up to 850 mg total dose of cisplatin with or without RPLND and radiotherapy [7]. This difference is explained by the selection criteria. In particular, men who reported dry ejaculation were not included in the present study. The paternity rates presently reported, however, are probably more relevant for most TC patients currently treated with limited chemotherapy because most patients now retain antegrade ejaculation after RPLND if nerve sparing or modified template resections can be used [13,14]. However, the selection of men with retained antegrade ejaculation for paternity analyses may have introduced a bias towards less advanced cases in our sample, as men with large-volume disease may be less likely to have nerve-sparing surgery.

Number of cycles remained an independent predictor of posttreatment paternity after adjustment for having children prior to diagnosis and marital status, previously shown to be associated with posttreatment paternity [7].

Variations in time to recovery of spermatogenesis related to the number of cycles are likely to reflect corresponding differences in time to paternity. Thus our results may indicate a more prolonged suppressive effect on spermatogenesis with increasing number of cycles. However, we can only speculate on this because we lack information on when the couples started their attempts and for how long they attempted to conceive. Moreover, it is possible that psychosocial causes such as delayed personal decision due to worse prognosis or other factors related to

the extent of the disease and thus number of cycles may have had an influence on time to the first child born following treatment.

S-FSH is commonly used as a serum marker of spermatogenesis, and the extent of FSH elevation is, within wide margins, correlated with the number of seminiferous tubules lacking germ cells [15,16]. A correlation between s-FSH and sperm counts has also been shown in TC patients [17]. We found that high s-FSH values were statistically significantly more frequently observed with increasing number of cycles, probably mirroring a persisting negative effect on spermatogenesis. However, the differences were rather modest. With a median follow-up of 12 yr, it is likely that most of the possible recovery of spermatogenesis has taken place [3], and the elevated s-FSH values most probably thus reflect an inherent decreased function of the remaining testicle together with persisting long-lasting effects of treatment [18].

Although the overall paternity rate in this study is comparable with the pregnancy rate found by Huyghe et al. [6], and the overall frequency of azoospermia similar to that Stephenson et al reported among men treated with two to four cycles of standard cisplatin-based chemotherapy [19], relevant published data for comparison according to number of cycles in the range two to four are sparse. Following two cycles, all eight men achieved posttreatment paternity in our study, compared with 69% (11 of 16) and 80% (4 of 5) previously reported [20,21]. However, in the first study, Böhlen et al reported that four of five involuntarily childless survivors were so prior to treatment [20].

We found normal sperm counts in 63% (5 of 8) following two cycles, compared with 85% (23 of 27) reported by Böhlen et al. [20]. Other studies with a limited number of men ($n \leq 32$) assessed following two cycles found no significant differences in sperm parameters and/or gonadotrophins compared with pretreatment values [21,22] or compared with men on surveillance [23]. Among men treated with three to four cycles with 24- to 48-mo follow-up, Aass et al ($n = 51$, in multivariable analyses) and Palmieri et al ($n = 28$) found no significant differences in sperm counts or gonadal hormones compared with men treated with surgery only [24,25]. The frequency of normal sperm counts in the study by Palmieri et al (57%) was similar to what we found following three to four cycles. Despite promising results regarding preserved spermatogenesis following two cycles, sperm banking should still be an option for all men with TC, preferentially performed prior to orchiectomy because spermatogenesis may be marginal in some individuals, and we cannot guarantee sperm quality at possible relapse.

The current results imply an association between fertility and the amount of cisplatin-based chemotherapy for TC, even at the level of two to four cycles, questioning the concept that irreversible impairment of fertility is unlikely to occur at doses up to 400 mg/m^2 of cisplatin (four cycles) [26]. At higher doses, irreversible impairment is more likely [7,26], although not all reported data support an association between parenthood and total cisplatin dose [27].

We found no significant differences in the frequency of hypogonadism. This is in accordance with the knowledge that Leydig cells generally are more resistant to cytotoxic therapy than the germ cell line [28], although a larger sample is needed to clarify whether there are subtle differences at the level of two to four cycles. Nord et al previously addressed hypogonadism in the whole NUCG III cohort [29].

5. Conclusions

The prospects of future paternity after two to four cycles of BEP/CVB are good. Our data suggest that the prospects improve with decreasing number of cycles, but confirmation of these data by large studies is warranted.

Author contributions: Marianne Brydøy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Brydøy, Fosså, Klepp, Bremnes, Wist, Dahl.
Analysis and interpretation of data: Brydøy, Fosså, Dahl, Wentzel-Larsen.
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Editorial Comment on: Paternity and Testicular Function Among Testicular Cancer Survivors Treated with Two to Four Cycles of Cisplatin-Based Chemotherapy

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It was only yesterday that a couple came to my office to discuss reproductive medicine. The wife spoke first: "Doctor, we desperately want a child. This would complete us as a family. Unfortunately we are not able to... my husband survived testicular cancer five years ago and cannot give me a child."

Now it was my turn: "Did you bank sperm prior to either surgery or chemo?"

"No," she replied. "Nobody suggested that we bank sperm. We were so scared by his tumour that fertility issues were the last thing on our minds. Now what shall we do?"

Why, in 2010, are urologists and uro-oncologists not making their testicular cancer (TC) patients aware of the significant risks of subsequent infertility before any surgical or nonsurgical therapy that potentially endangers subsequent fertility?

Brydøy et al's study [1] addresses the eventual capacity of achieving paternity following intensive chemotherapy for TC in light of both public health and reproductive medicine. The authors discuss two key issues.

1. *Male cancer patients may be at high risk of infertility. Be aware of that when dealing with your reproductive-age patients.* Subfertility or infertility has been associated

with an elevated risk of several male cancers, mainly germ-cell TCs [2]. Specifically, a significant correlation has been found between male infertility and a higher risk of subsequently developing testicular germ cell tumors [2]. Therefore, TC patients might have decreased fertility even prior to the diagnosis of cancer, although it is not clear whether the subfertility is the result of an emerging tumor or whether subfertility and TC share causes. Likewise, because antineoplastic treatment with chemotherapy or radiation therapy has the potential to impair spermatogenesis through damage of the germinal epithelium, many male cancer survivors experience difficulties in fathering after treatment. The impairment can be temporary or permanent; many cancer survivors regain spermatogenesis months or years after treatment, while others become infertile, experiencing either oligozoospermia or azoospermia [3]. Risk-adapted toxicity-sparing treatment strategies have increasingly been used in the past decades, and Brydøy et al's study [1] highlights the fact that when the most widely used chemotherapy approach (ie, cisplatin-based treatment) is applied, future fatherhood may be considered possible for numerous men, especially with the decreasing number of cycles [1]. This strongly implies that antegrade ejaculation must be retained if at all possible in those cases in which nerve damage did not occur at all. Therefore, a cornerstone step when dealing with male patients with TC must be to comprehensively discuss aspects of future infertility, offering patients any procedure aimed at preserving their own fertility *well before* any potentially fertility-damaging treatment occurs.

2. *Cancer survivors desire, deserve, and need the chance to father children.* Multiple surveys have demonstrated that parenthood is important to survivors of cancer [4]. In this context, the American Society of Clinical Oncology (ASCO) has stated that because fertility preservation has become possible in men undergoing treatment for cancer, any fertility preservation approach should be considered as early as possible during treatment planning [5]. Therefore, ASCO has stressed that any oncologist seeing reproductive-age men for consideration of cancer therapy should address potential treatment-related infertility with them [5]. Doing so is certainly of major importance for men with TC, as TC usually occurs at the peak of reproductive age [1]; however, having the potential to father children could also be of interest to older men with other types of tumors [6], since men are more and more frequently experiencing fatherhood in late adulthood, at least in western countries [7]. Therefore, a cornerstone step when dealing with male patients with *any* cancer must be to comprehensively discuss aspects of future infertility, *offering them any procedure aimed at preserving their own fertility*. Hopefully, research in reproductive medicine will even more proactively join oncologic research in the near future.

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