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Original Paper

Risk of a Second Germ Cell Cancer After Treatment of a Primary Germ Cell Cancer in 2201 Norwegian Male Patients

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The aim of this study was to evaluate the risk of developing a second germ cell cancer (SGCC) among male patients with a primary germ cell cancer (PGCC). SGCCs, all metachronous, developed in 60 out of 2201 males treated for a PGCC at the Norwegian Radium Hospital in Oslo from 1953 to 1990. Further, 8 patients had synchronous germ cell cancers. The relative risk (RR) of developing an SGCC was 27.6 (95% confidence interval (CI) 21.1–35.6), and the cumulative risk at 15 years of follow-up 3.9% (95% CI 2.8–5.0%). In patients with primary non-seminoma, the cumulative risk of an SGCC at 15 years of follow-up was 5.0% and in patients with primary seminoma 3.4%. Patients less than 30 years of age had a higher cumulative risk of 7.8% compared to 2.1% in older patients at 15 years of follow-up. The RR of an SGCC, however, was equal in patients with primary seminoma and in patients with primary non-seminoma. If the interval between PGCC and SGCC was <5 years, the PGCC was most often followed by an SGCC of same histological type. Treatment applied for the PGCC did not seem to be of significant importance for the development of SGCC. In conclusion, patients with PGCC have high RR of developing an SGCC and age group <30 years display an especially high cumulative risk.

Key words: germ cell neoplasms, testicular neoplasms, seminoma, non-seminoma, second germ cell cancer, relative risk, cumulative risk

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INTRODUCTION

THE INCIDENCE of testicular cancer is increasing in many countries [1–3]. This trend, and the fact that the majority of these patients are cured, warrant research on subsequent malignancies observed in these patients. Analyses on risk of second germ cell cancer (SGCC) may also contribute to a better understanding of responsible aetiological factors and mechanisms of development of this type of cancer. Furthermore, several other studies have shown that the relative risk of an SGCC is particularly high compared to that of subsequent non-germ cell malignancies [4–7].

In another paper in this issue of the *European Journal of Cancer* (pages 253–262), we have analysed the risk of a subsequent non-germ cell cancer among patients with a primary germ cell cancer. In the present paper, we evaluate the risk of developing a second invasive germ cell malignancy on the same series of patients.

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PATIENTS AND METHODS

Patients

The present study originally comprised 2225 patients who were treated for primary germ cell cancer (PGCC) at the Norwegian Radium Hospital in Oslo during the period 1953–1990. 16 patients were subsequently excluded from the analysis due to death or emigration within one month from primary diagnosis. 8 patients with synchronous germ cell cancer, diagnosed within one month from PGCC, were analysed separately. The remaining 2201 patients represented the final study group (Table 1). Detailed information about diagnosis, stage, treatment and follow-up was obtained from the patients' hospital records, information on deaths from Statistics Norway, and information on SGCC was received from both the Norwegian Cancer Registry and the patients' hospital records. Pathology reports of all

Table 1. Characteristics of the patients in the study group

Characteristics	Patients	
	n	%
No. of patients	2201	100.0
Histology		
Seminoma	1135	51.6
Non-seminoma	1066	48.4
Location*		
Right	1161	52.7
Left	1020	46.3
Extragonadal	20	0.9
Stage		
Seminoma		
MI	0	0.0
I	864	39.3
II	204	9.3
III	37	1.7
IV	25	1.1
Extragonadal	5	0.2
Non-seminoma		
MI	4	0.2
I	490	22.3
II	267	12.1
III	47	2.1
IV	243	11.0
Extragonadal	15	0.7
Treatment group†		
RT	1248	56.7
CT	404	18.4
RT + CT	352	16.0
No RT nor CT	197	9.0

*8 patients with bilateral cancer are not included, but were analysed separately. †With or without surgery.
RT, radiotherapy; CT, chemotherapy.

patients with SGCC were examined to verify the histological subtypes (seminoma versus non-seminoma) of both the primary and the second germ cell cancer. Cases of carcinoma *in situ* without invasive cancer, were excluded from the study.

Clinical staging was based on the Royal Marsden classification system [9].

The mean age at primary diagnosis was 35.6 years for the whole study group and 40.1 and 30.8 years for patients with seminoma and non-seminoma, respectively. In 816 patients, the PGCC was diagnosed before the age of 30 years and in 1385 patients at or after the age of 30 years. Cancer interval was defined as the interval between diagnosis of a PGCC and diagnosis of an SGCC.

Treatment of unilateral testicular cancer

In patients with invasive tumours, complete removal of the tumorous testicle was performed as the principle initial treatment. Until 1978, irradiation was the principal post-orchiectomy treatment in patients with testicular cancer without distant metastases. Chemotherapy was only given in case of non-lymphatic spread or relapse after radiotherapy. The treatment policy for patients with non-seminoma was basically changed in 1979. Thereafter, radiotherapy was no longer given as the primary treatment to non-seminoma patients. These patients' principle postorchiectomy therapy consisted of retroperitoneal lymph node dissection or cisplatin-based chemotherapy or a combination of these treatment modalities. From 1987, patients with non-seminoma clinical stage I disease were included the "wait and see" policy or received two cycles of adjuvant chemotherapy.

The target irradiation field has most often included the lumbar and ipsilateral iliac lymph node regions. Seminoma patients received a total dose of 30–40 Gy and non-seminoma patients 50 Gy. Until 1980, the anterior field also included the inguinal region in patients with infiltration of the rete testis, epididymis or spermatic cord, in cases of infiltration through the tunica vaginalis, and if the patient had a history of previous scrotal or inguinal surgery [10].

The chemotherapy given before 1978 consisted, in most cases, of a cyclophosphamide and doxorubicin-based combination given as primary treatment or as relapse therapy after previous radiotherapy [11]. Modern cisplatin-based chemotherapy has been administered since 1978, initially in regimens combining courses of cyclophosphamide and doxorubicin-based chemotherapy and courses of cisplatin-based chemotherapy, but from 1979 as CVB regimens (cisplatin/vinblastine/bleomycin) [12]. From 1984 CVB was gradually replaced by the BEP-regimen (bleomycin/etoposide/cisplatin).

In 1248 patients, radiotherapy was the only treatment after orchiectomy (RT group), 404 patients were treated with chemotherapy only (CT group), 352 patients received both radiotherapy and chemotherapy (RT + CT group) and 197 patients received neither radiotherapy nor chemotherapy (No RT nor CT group), but underwent retroperitoneal surgery or were included in a surveillance policy. The combination of radiotherapy and chemotherapy was applied mainly in patients treated before 1978 when cyclophosphamide and doxorubicin-based chemotherapy was given. Cisplatin-based chemotherapy only without alkylating agents was given to 313 patients (77.5%) in the CT group. The mean age at primary diagnosis in the RT, CT, RT + CT and No RT nor CT groups was 38.0, 30.4, 34.4 and 33.7 years and the mean follow-up 15.2, 6.7, 5.6 and 7.7 years, respectively.

Statistical analyses

The patients were followed from one month after primary diagnosis to SGCC, emigration, death or 31 December 1992, whichever occurred first. The mean follow-up for the whole study group was 11.4 years (range 1 month–41.0 years) (primary seminoma: 13.5 years (range 1 month–41.0 years); primary non-seminoma: 9.2 years (range 1 month–40.9 years)). In analyses on second seminoma and second non-seminoma, the patients were followed until the date of diagnosis of an SGCC independently of the histology of the SGCC.

All analyses are based on a comparison between observed numbers of SGCC in the study group (O) and expected numbers of primary germ cell cancers in the general Norwegian population (E) during the observation period. Five-year age-specific incidence rates and 2-year diagnostic periods were used. A standardisation on age and period of diagnosis was performed and the standardised incidence rate ratio calculated (SIR, RR). A 95% confidence interval (95% CI) was calculated on the assumption of a Poisson distribution.

The cumulative risk of SGCC was estimated by the life table method of Kaplan and Meier [13] at 10 and 15 years after diagnosis of a PGCC.

RESULTS

Synchronous germ cell cancer

The median age of patients with synchronous bilateral testicular cancer was 35.4 years (range 31.8–53.3 years). In all 8 patients with synchronous germ cell cancer, the histological subtype was the same in both testicles. Seminomas occurred in 7 patients and non-seminomas in 1 patient. One patient with bilateral seminomatous cancer also had a Leydig cell tumour in one testicle.

Risk of SGCC for the study group

Among the 2201 patients in the study group, a total number of 60 invasive SGCCs were diagnosed after a mean cancer interval of 5.8 years (range 1 month–16.1 years), resulting in an RR of 27.6 (95% CI 21.1–35.6) (Table 2). All SGCCs were testicular cancers. 57 SGCCs occurred in 2181 patients with a primary testicular cancer and three SGCCs in 20 patients with extragonadal germ cell cancer. In 39 patients, the SGCC was a seminoma and in 21 patients a non-seminoma. The RR of developing an SGCC of seminomatous type (RR, 30.3) was slightly above the RR of developing an SGCC of non-seminomatous type (RR, 25.9). The cumulative risk of an SGCC for the whole group was 3.2% (95% CI 2.3–4.0%) at 10 years and 3.9% (95% CI 2.8–5.0%) at 15 years after diagnosis of a PGCC. No new cases were diagnosed after 16 years (Figure 1).

Risk of SGCC in relation to histology of PGCC

The mean cancer interval was 4.6 years for patients with a primary seminoma and 6.7 years for patients with a primary non-seminoma ($P = 0.06$).

No notable difference in the RR of SGCCs was observed comparing patients with primary seminoma (RR, 27.7) and those with a primary non-seminoma (RR, 27.6) (Table 2). The RR of developing an SGCC of the same histological type as the PGCC was higher than the RR of developing an SGCC of different histological type (Table 2).

The cumulative risk of an SGCC was 3.1% (95% CI 2.0–4.2) at 10 years and 3.4% (95% CI 2.1–4.6%) at 15 years after diagnosis of a primary seminoma. In patients with a primary non-seminoma, the respective figures were 3.7% (95% CI 2.2–5.2%) at 10 years and 5.0% (95% CI 3.1–6.9%) at 15 years (Figure 1).

Relationship between observation period and histology of SGCC

In 29 patients, the SGCC developed within the first 5 years after the diagnosis of a PGCC. In 26 of these patients (90%), the histological type was the same as that of the PGCC, whereas different histological type was only observed in 3 patients (10%) (Table 2). After 5 years, patients with a primary seminoma experienced an almost equally elevated RR of developing an SGCC of seminomatous type (RR, 20.9) and of non-seminomatous type (RR, 23.1). Corresponding observations were made for patients with a primary non-seminoma (RR = 34.3 for a second seminoma and RR = 31.8 for a second non-seminoma).

In the patients with PGCC of seminomatous type, only 5 cases of SGCC of non-seminomatous type occurred at a median cancer interval of 5.9 years (range 2.4–14.1 years) and a median age at primary diagnosis of 29.4 years (range 24.4–36.1 years).

Risk of SGCC in relation to age

The mean age at diagnosis of a PGCC of seminomatous type was 35.3 years for patients who developed an SGCC and 40.3 years for those who did not develop an SGCC ($P = 0.02$). Corresponding figures for patients with PGCC of non-seminomatous type were 26.4 years for those who developed an SGCC and 31.0 years for those who did not ($P = 0.03$). These findings corresponded with the observation that the RR of developing an SGCC was much higher when the PGCC was diagnosed before 30 years of age (RR, 35.6) than thereafter (RR, 20.5) (Table 3).

Also, the cumulative risk was higher in patients with the diagnosis of a PGCC before the age of 30 years than in those who had a PGCC after the age of 30 years. In the former age group, the cumulative risk continued to rise steeply after 10 years, whereas only one new case occurred in men ≥30 years (at 15.02 years). Figures for cumulative risk were at 10 years 5.7% (95% CI 3.7–7.7%) in the younger age group and 2.1% (95% CI 1.2–3.0%) in the older age group. Respective figures at 15 years were 7.8% (95% CI 5.2–10.4%) in the younger age group and 2.1% (95% CI 1.2–3.0%) in the older age group. Although a total of 372 patients were observed for more than 20 years, no SGCC occurred in these patients. (Figure 2).

Of 23 SGCCs which developed in patients aged ≥30 years at first orchiectomy, only 2 cases were of a non-seminomatous type (Table 3).

Risk of SGCC in relation to treatment

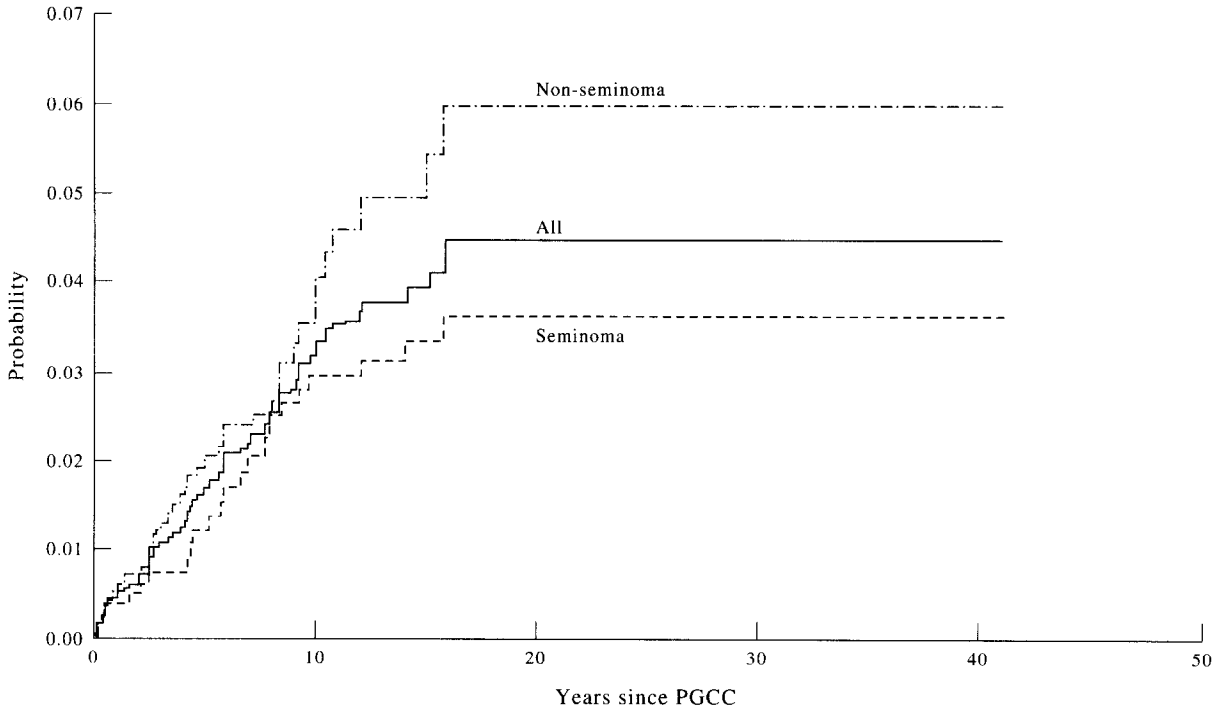
The RR was highly significantly increased in all treatment groups (Table 3). The mean cancer interval was 5.9 years (range 1 month–15.8 years) in the RT group, 3.3 years (range 5 months–6.6 years) in the CT group, 7.3 years (2 months–12.1 years) in the RT + CT group and 4.0 years (5 months–7.7 years) in the No RT nor CT group. Of 9 SGGCs in the CT group, 7 SGCCs occurred among patients treated with cisplatin-based chemotherapy without alkylating agents at a median cancer interval of 3.4 years (range 0.4–6.6 years). The cumulative risk of an SGCC increased up to 10 years of observation in all treatment groups (Figure 3). A slight increase also occurred after 10 years in the RT group, but reached a plateau after 16 years of follow-up. The number of cases was too small after 10 years in the other three treatment groups to draw any conclusions.

DISCUSSION

The present study takes advantage of a large number of patients and a long observation period. In addition, the registration routines of cancer to the Norwegian Cancer Registry have been regarded as very good throughout the period. All medical records have also been reviewed with emphasis on the occurrence of an SGCC.

When adding the 8 cases of synchronous germ cell cancer to the study group, the prevalence of bilateral germ cell cancer would have been 3.1%. This corresponds with the prevalence found by Fordham and associates [14] of 3.1%, Østerlind and associates [6] of 2.6%, Bokemeyer and associates [15] of 3.5%, Dieckmann and associates [16] of 4.0% and recently by Colls and associates [17] of 2.2%.

There are important differences regarding the RRs of developing an SGCC versus a subsequent non-germ cell cancer. The RR of developing an SGCC (RR, 27.6) is



Patients at risk at start of interval

Time from diagnosis (years)	Histological subtype of PGCC (*n*)		
	All PGCCs	Seminoma	Non-seminoma
0.1–9	2201	1135	1066
10–19	1061	659	402
20–29	372	253	119
30–39	95	60	35

PGCC, primary germ cell cancer.

Figure 1. Cumulative risk of an SGCC in all patients, in patients with a PGCC of seminomatous type and in patients with a PGCC of non-seminomatous type.

almost 17 times higher than the RR of developing a subsequent non-germ cell cancer (RR, 1.65) according to another report on the same material of patients (see pages 253–262). However, the cumulative risk of a subsequent non-germ cell cancer continues to increase after many years of follow-up [7, 8], whereas for SGCC the risk reaches a plateau after 15–20 years as shown in the present study and also by Østerlind and associates [6]. Significantly elevated figures of RR for subsequent non-germ cell cancer occur in irradiated patients [7, 8]. In the present study, however, the figures of RR for SGCC were significantly elevated in all treatment categories. These observations indicate that the mechanisms of development of SGCC and subsequent non-germ cell cancer are different. Furthermore, they support the hypothesis that germ cell cancer is initiated early in life, and that risk factors during adult life are of relatively minor significance.

The proportion between expected cases of seminomas and non-seminomas in our analyses is different from that in the general population. In the general population, seminomatous and non-seminomatous cancer occur with almost equal frequency, whereas the figures of expected cases in our material are 1.3 for seminomas and 0.8 for non-seminomas. In the study group, the mean age is 40.1 years for patients with PGCC of seminomatous type, constituting 61% of the person-years in the whole study group. Only 15% of non-seminomatous cancers, however, are diagnosed after the age of 40 years in the general population, from where the expected cases are registered (data from the Norwegian Cancer Registry).

The influence of age distribution in the study group on expected cases is even more clearly illustrated by the analyses on age at time of diagnosis of PGCC. When correcting for different numbers of person-years in the two age groups (age group <30 years: 7666.7 person-years and age group ≥30 years: 161 65.2 person-years), the expected cases of non-seminomas in the older age group would have been only one-third of that in the younger age group.

The analyses dividing the study group by age into younger than 30 years and 30 years or older show that young age at diagnosis of a PGCC is a risk factor for an SGCC. The 10 year lower mean age of patients with a primary non-seminoma compared to patients with a primary seminoma is probably also the main reason why a higher cumulative risk of an SGCC is found in the patients with a primary non-seminoma.

It is believed that all germ cell cancers develop from a state of carcinoma *in situ*. The prevalence of carcinoma *in situ* in the contralateral testis is somewhat higher than the incidence of SGCC and is reported to be 4–6% [18–20]. Approximately 50% of all cases of carcinoma *in situ* will develop into invasive cancer within 5 years, and it is stipu-

Table 2. RR of SGCC among men with a PGCC treated at the NRH in Norway during the period 1953–1990 by histological subtypes and cancer intervals

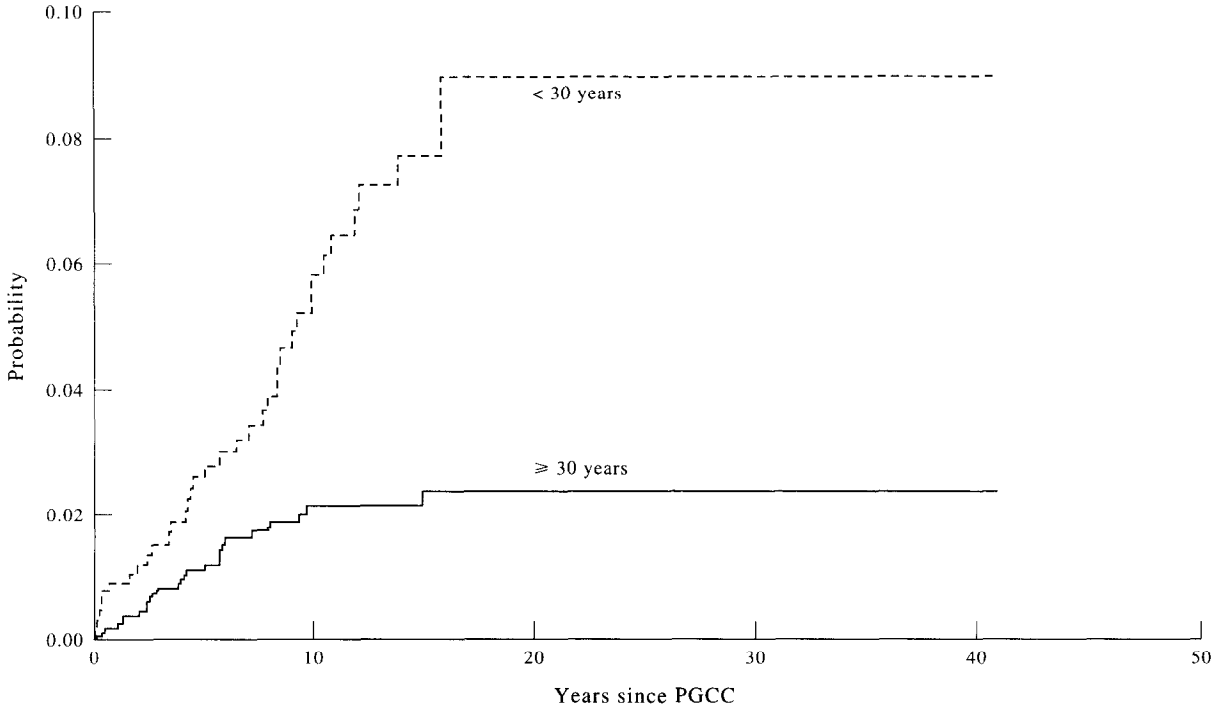
		PGCC*											
		All PGCCs				Seminoma				Non-seminoma			
SGCC		Observed	Expected	RR	(95% CI)	Observed	Expected	RR	(95% CI)	Observed	Expected	RR	(95% CI)
Total	All SGCCs	60	2.2	27.6	(21.1–35.6)	31	1.1	27.7	(18.9–39.3)	29	1.1	27.6	(18.5–39.6)
	Seminoma	39	1.3	30.3	(21.6–41.5)	26	0.7	36.1	(23.6–52.9)	13	0.6	22.8	(12.1–38.9)
	Non-seminoma	21	0.8	25.9	(16.0–39.6)	5	0.4	14.1	(4.6–33.0)	16	0.5	34.8	(19.8–56.5)
Observation period: 1 month–4.9 years†	All SGCCs	29	0.9	30.9	(20.6–44.3)	19	0.5	40.4	(24.3–63.2)	10	0.5	21.2	(10.2–39.1)
	Seminoma	18	0.5	35.3	(21.0–55.7)	17	0.3	58.6	(34.1–93.8)	1	0.2	4.5	(0.1–25.2)
	Non-seminoma	11	0.4	26.8	(13.4–48.0)	2	0.2	11.7	(1.4–42.3)	9	0.2	37.6	(17.2–71.5)
Observation period: ⩾5 years‡	All SGCCs	31	1.2	25.4	(17.3–36.1)	12	0.6	18.8	(9.7–32.8)	19	0.6	32.8	(19.7–51.2)
	Seminoma	21	0.8	26.9	(16.7–41.2)	9	0.4	20.9	(9.5–39.8)	12	0.4	34.3	(17.7–60.0)
	Non-seminoma	10	0.4	25.0	(12.0–46.0)	3	0.1	23.1	(4.6–67.7)	7	0.2	31.8	(12.7–65.5)

PGCC, primary germ cell cancer; SGCC, second germ cell cancer. *Total person-years in all PGCCs was 23 831.9, in the group with seminoma 14 590.2 and in the group with non-seminoma 9241.7. †Total person-years in first cancer interval for all PGCCs was 8843.8, in the group with seminoma 4981.2 and in the group with non-seminoma 3862.6. ‡Total person-years in second cancer interval for all PGCCs was 14 988.1, in the group with seminoma 9609.0 and in the group with non-seminoma 5379.1

Table 3. RR of SGCC, all types together and histological subgroups, among men with a PGCC diagnosed between 1953 and 1990, by age at diagnosis of PGCC and treatment groups

		SGCC											
		All SGCCs				Seminoma				Non-seminoma			
Category regarding PGCC		Observed	Expected	RR	(95% CI)	Observed	Expected	RR	(95% CI)	Observed	Expected	RR	(95% CI)
Age at diagnosis, years*													
	<30	37	1.0	35.6	(25.1–49.0)	18	0.5	34.8	(20.6–55.0)	19	0.5	38.0	(22.8–59.4)
	⩾30	23	1.1	20.5	(13.0–31.4)	21	0.8	27.3	(16.9–41.7)	2	0.3	6.3	(0.6–22.5)
Treatment group†													
	RT	38	1.4	27.0	(19.1–37.0)	30	0.9	33.7	(22.7–47.4)	8	0.5	17.4	(7.5–34.3)
	CT	9	0.4	24.0	(11.0–45.5)	1	0.2	5.4	(0.1–30.3)	8	0.2	44.3	(19.1–87.3)
	RT + CT	9	0.2	48.9	(22.4–93.0)	5	0.1	50.0	(16.0–117.0)	4	0.1	57.1	(15.7–145.7)
	No RT nor CT	4	0.2	19.4	(5.3–49.7)	3	0.1	28.5	(5.9–83.2)	1	0.1	10.6	(0.3–59.3)

PGCC, primary germ cell cancer; SGCC, second germ cell cancer; RT, radiotherapy, CT, chemotherapy. *Person-years in the age groups were for diagnosis <30 years 7666.7 and for diagnosis ⩾30 years 16 165.2. †Person-years in the treatment groups were RT, 17 968.7; CT, 2566.7; RT + CT, 1825.4 and in No RT nor CT, 1471.0.



Patients at risk at start of interval

Time from diagnosis (years)	Age at diagnosis (*n*)	
	< 30 years	≥ 30 years
0.1–9	816	1385
10–19	339	722
20–29	100	272
30–39	28	67

PGCC, primary germ cell cancer.

Figure 2. Cumulative risk of an SGCC in patients with diagnosis of a PGCC aged < 30 years and in patients aged ≥ 30 years.

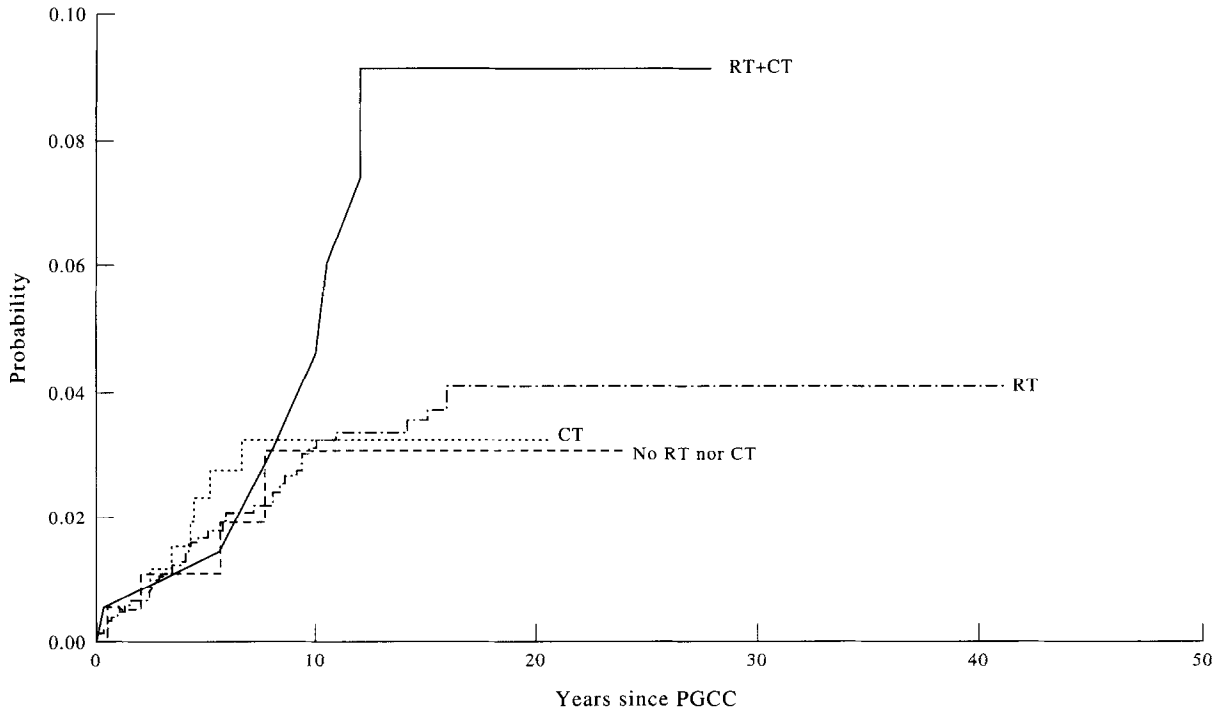
lated that most of the cases will become invasive within 10 years [19, 21]. However, the follow-up in these studies has not been long enough to determine the definite fraction of carcinoma *in situ* cases that will end up with invasive cancer. In our study, as many as 10 patients (17%) developed SGCC after 10 years of follow-up.

Development of a germ cell cancer in a biopsied testicle with benign histology occurs only occasionally. Skakkebaek and associates [21], von der Maase and associates [19], Giwercman and associates [22] and Dieckmann and associates [16] did not report any cases of invasive germ cell cancer among a total number of 1861 patients with a negative testicular biopsy. It is claimed that in those few cases which have been reported [23–25], the biopsies were not representative. Loy and associates [26] demonstrated that carcinoma *in situ* is not as widely distributed within the testicle as previously believed. Therefore, a tiny biopsy may miss focal changes of carcinoma *in situ*, which subsequently progress to invasion.

Assuming that germ cell cancers never or at least very seldom develop *de novo* in adults, these late occurring SGCCs prompt the question of whether an altered hormonal milieu after the first orchiectomy, i.e. low testosterone levels [27, 28], in some cases may delay development of the second cancer. The prevalence of carcinoma *in situ* in the contralateral testicle at the time of diagnosis of PGCC would have been of great interest in these patients, but all 10 patients had their PGCC before 1977 and before biopsy of the contralateral testicle had become a more common diagnostic procedure at our hospital.

Three second testicular cancers were diagnosed among 20 patients with extragonadal germ cell cancer. The follow-up for these patients in our material was short (median 2.3 years; range 1 month–18.0 years). Daugaard and associates [29] found a prevalence of 42% of carcinoma *in situ* of testis in 48 patients with extragonadal germ cell cancer. Anticipating that 50% of cases of testicular carcinoma *in situ* become invasive within 5 years of follow-up, that would result in four second testicular cancers within 5 years in our material, which is not far from the 3 cases we found.

The RR of an SGCC was the same for patients with PGCC of seminomatous and patients with PGCCs of non-seminomatous type in the present study, as also observed by Østerlind and associates [6]. This interesting observation may indicate that a common pathway exists for develop-



Patients at risk at start of interval

Time from diagnosis (years)	Treatment category (*n*) RT	CT	RT+CT	No RT nor CT
0.1–9	1248	404	352	197
10–19	816	105	82	58
20–29	360	1	6	5
30–39	95	0	0	0

RT, radiotherapy; CT, chemotherapy.

Figure 3. Cumulative risk of an SGCC by treatment categories.

ment of contralateral germ cell cancer for primary cancers of seminomatous and non-seminomatous type.

The difference in growth rate is probably an important determining factor for the order of presentation of seminoma and non-seminoma in patients with bilateral testicular cancer. The non-seminoma type usually have a much higher growth rate, the mean age of these patients at diagnosis is almost 10 years lower than that of patients with the seminomatous type. If a carcinoma *in situ* cell is programmed to be a seminoma in one testicle and a non-seminoma in the other testicle at the same time, the probability that the non-seminoma will manifest clinically first is very high. Actually, bilateral carcinoma *in situ* seldom becomes infiltrating concurrently, as illustrated by the fact that the prevalence of synchronous testicular cancers is much lower than the prevalence of carcinoma *in situ* in contralateral testicle. Nevertheless, most bilateral germ cell cancers are diagnosed within a few years. Further, seminomatous germ cell cancers are seldom succeeded by non-seminomatous germ cell cancers, whereas the opposite order is common, and SGCC of the same histological subtype as PGCC is more common within the first 5 years than after 5 years of follow-up.

In 12 of 13 cases in which a non-seminoma was followed by a seminoma, the second seminoma developed after 5 years. Chemotherapy, given to 6 of these patients, may have contributed to extend the cancer interval. In 5 patients, cyclophosphamide-based chemotherapy was given, which has a high propensity to produce germinal aplasia and permanent infertility [30]. If the effect on carcinoma *in situ* cells is similar to that on germinal epithelium, cyclophosphamide-based chemotherapy will extend the cancer interval more than cisplatin-based chemotherapy, which causes a more temporal damage on the germinal epithelium [27].

The RR according to treatment groups indicates that cytotoxic treatment is not an important factor in the carcinogenesis of an SGCC, although the highest RR was found in the RT + CT group among those patients who had received the most intensive cytotoxic treatment regimens. It further illustrates that chemotherapy does not eradicate SGCC as also demonstrated by von der Maase and associates [31], Fosså and associates [32], Gerl and associates [33] and recently by Colls and associates [17]. Based on findings of 417 patients treated with cisplatin-based chemotherapy for a PGCC and on experiences from other studies, Gerl and associates [33] suggested that cisplatin-based chemotherapy reduces the risk of an SGCC at least for the first 5 years of follow-up. Our data do not support this assumption since 7 of 9 SGCCs (77.8%) in the CT group

occurred in the subgroup of patients who only received cis-platin-based chemotherapy without alkylating agents (77.5%) after a median cancer interval of 3.4 years—this cancer interval, and also that of the whole CT study, group, being shorter than that of all the other treatment groups.

When comparing the RRs of the treatment groups, one should be aware that the groups differ as regards to age distribution, which again have influence on expected cases of germ cell cancer. The mean age at primary diagnosis was lower in the CT group and in the No RT nor CT group, mainly consisting of patients with PGCC of non-seminomatous type. Because young age appears to be a risk factor for development of SGCC, observed cases of SGCC are influenced by the age distribution. However, both observed cases (numerator) and expected cases (denominator) are influenced in the same direction, making minor changes to the resulting RR.

In conclusion, the cumulative risk of an SGCC is higher in patients with PGCC of non-seminomatous than in patients with PGCC of seminomatous type, the respective figures at 15 years being 5.0% (95% CI 3.1–6.9%) and 3.4% (95% CI 2.1–4.6%). Young patients have a higher cumulative risk than older patients, figures at 15 years being 7.8% (95% CI 5.2–10.4%) for patients <30 years and 2.1% (95% CI 1.2–3.0%) for patients ⩾30 years, respectively. The cumulative risk of an SGCC increases during the first 15 years of follow-up, but reaches a plateau thereafter. In contrast to the cumulative risk, the RR of an SGCC seems to be equal in patients with PGCC of seminomatous type and in patients with PGCC of non-seminomatous type. If the interval between PGCC and SGCC is short, a PGCC is most often followed by an SGCC of the same histological type. A seminomatous PGCC is seldom followed by a non-seminomatous SGCC. Treatment modalities of PGCC are without significant importance in the development of SGCC. Compared with risk of second non-germ cell cancer, our study supports the hypothesis that germ cell cancer is initiated early in life, and that risk factors acting in adult life are of minor significance for the development of SGCC.

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