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Original Paper

Risk of Subsequent Non-germ Cell Cancer After Treatment of Germ Cell Cancer in 2006 Norwegian Male Patients

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The aim of this study was to evaluate the risk of subsequent non-germ cell cancer (SNGC) among men with germ cell cancer and the significance of radiotherapy and chemotherapy as risk factors. The study group consisted of 2006 male patients treated for germ cell cancer at the Norwegian Radium Hospital from 1952 to 1990 with a mean follow-up of 12.5 years. A group of 1194 patients had received radiotherapy only, 346 patients chemotherapy only (mainly cisplatin-based), 277 patients both radiotherapy and chemotherapy (mainly cyclophosphamide and doxorubicin-based), and 189 patients no cytotoxic treatment. A total number of 153 SNGCs were diagnosed after a mean interval of 15.9 years. The RR was 1.65 (95% confidence interval (CI), 1.4–1.9), and the mean cumulative risk after 15 years 7.8% (95% CI, 6.2–9.5%). Significantly elevated RRs were found for gastrointestinal cancer combined, cancer of stomach, liver and biliary system, lung, melanoma, bladder and sarcoma. Significantly elevated RRs were found in patients who had received radiotherapy (with or without chemotherapy), and the trend increased with very long follow-up. Patients given both radiotherapy and chemotherapy experienced the highest risk (RR = 3.54; 95% CI, 2.0–5.8), probably due to a high cumulative dose of cytotoxic treatment. Modern chemotherapy did not seem to increase the risk of SNGC, although this study's size and follow-up period did not allow definite conclusions as regards this risk factor. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: germ cell neoplasms, testicular neoplasms, subsequent cancer, second cancer, treatment induced risk, relative risk, radiotherapy, chemotherapy, second sarcoma

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INTRODUCTION

TESTICULAR CANCER is the most common cancer among Norwegian young men. Today most patients are cured, and their life expectancy is believed to be comparable to that of the age-adjusted normal population. The patients' overall survival may theoretically be decreased by life-threatening treatment-induced disorders. An increased risk of cardiovascular complications, including cardiac infarction, has been described by some authors [1]. Most importantly, however, the risk of subsequent malignancies has been discussed in series varying from some hundreds [2–6] to some thousands of patients [7–10].

At the Norwegian Radium Hospital (NRH), radiotherapy has been and remains the main treatment modality in patients with early seminomatous malignancies after orchiectomy. Before the introduction of cisplatin in the treatment of germ cell cancer, radiotherapy was also used in the management of testicular cancer of non-seminomatous type. Chemotherapy was introduced in treatment of advanced testicular cancer at NRH in 1961. However, it was not until 1978, with the introduction of cisplatin, that chemotherapy became a cornerstone in the routine management of non-seminomatous and advanced seminomatous testicular cancers in Norwegian patients.

In this study, we report the risk of a subsequent non-germ cell cancer (SNGC) related to treatment modalities in a large cohort of Norwegian male patients with testicular or extragonadal cancer. Observation times which exceed those of most previous studies enable the estimation of relative risk (RR) of SNGCs after long periods of follow-up. The

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present study expands the number of patients from a previous report from this hospital by a factor of two [3].

PATIENTS AND METHODS

Patients

During the period 1953–1990, a total number of 2225 male patients were treated for germ cell cancer at NRH in Oslo, representing 61.2% of all male patients treated for this malignancy in Norway during the same period. The analyses in the present study were based on an observation period starting one year after diagnosis of the primary cancer. Subsequently, 219 patients were excluded. Of these patients, 215 died and a further 4 patients were living abroad at the time of diagnosis or emigrated within one year after diagnosis.

Detailed information about diagnosis, treatment and follow-up was obtained from the patients' hospital records; information on subsequent cancers from the Norwegian Cancer Registry and information on deaths from Statistics Norway. The registration in the Norwegian Cancer Registry is based on the International Classification of Diseases, 7th Revision (ICD-7, 1955). The histological classification and coding are done according to the Manual of Tumor Nomenclature and Coding, 1968 (MOTNAC) and Systematised Nomenclature of Pathology, 1965 (SNOP). In cases of uncertainty of the histological coding in the Registry's database, the histological report in the medical record was reviewed.

Cancer reporting to the Norwegian Cancer Registry has been compulsory since the registry was established in 1952. All hospitals and histopathological laboratories are committed independently to report all newly diagnosed cases of cancer, also subsequent primary cancers. All death certificates are coded by Statistics Norway, which regularly transfers the information to the Norwegian Cancer Registry.

The routines of reporting and registration of basal cell carcinomas to the Cancer Registry have varied considerably during the period of investigation, and these cancers were not included in the analyses.

Seminomas constituted 54.8% and non-seminomas 45.2% of the study group (Table 1). In 1060 patients (52.8%), the tumour was in the right testicle, in 921 (45.9%) in the left, 8 patients (0.4%) had synchronous bilateral cancer and 17 patients (0.8%) had an extragonadal cancer. Clinical staging used in patients with unilateral testicular cancer only was based on the Royal Marsden classification system [11].

The mean age at initial diagnosis was 40.2 years (3 months–82 years) for patients with seminoma, and 30.8 years (15 months–81 years) for patients with non-seminoma. The mean follow-up from diagnosis was 12.5 years for all 2006 patients, and 14.0 and 10.7 years for patients with seminomas and non-seminomas, respectively. The mean follow-up in the RT, CT, RT + CT and No RT nor CT group was 15.9, 7.8, 6.9 and 8.0 years, respectively.

Of 17 cases with extragonadal cancer, 6 were of seminomatous and 11 of non-seminomatous type, the mean follow-up was 3.7 years (1.1–18.0 years). The cytotoxic treatment consisted of radiotherapy in 1 patient, chemotherapy in 8 patients and both radiotherapy and chemotherapy in 8 patients.

Table 1. Characteristics of the patients in the study group

Characteristics	Patients	
	n	%
No. of patients	2006	100
Histology		
Seminoma	1099	54.8
Non-seminoma	907	45.2
Location		
Right	1060	52.8
Left	921	45.9
Bilateral	8	0.4
Extragonadal	17	0.8
Clinical stage		
MI	3	0.1
I	1331	66.4
II	427	21.3
III	64	3.2
IV	156	7.8
Bilateral*	8	0.4
Extragonadal	17	0.8
Treatment category†		
Seminoma		
RT	949	86.4
CT	25	2.3
RT + CT	116	10.6
No RT nor CT	9	0.8
Non-seminoma		
RT	245	27.0
CT	321	35.4
RT + CT	161	17.8
No RT nor CT	180	19.8

*Diagnosed within one month from first cancer. †With or without surgery.
RT, radiotherapy; CT, chemotherapy.

Treatment

During the first few years, irradiation was given by X-ray machines, from 1955 to 1969 by Betatron 31 or 33 MV, and from 1970 by linear accelerator 5–8 MV.

Seminomas. The treatment for stage I and early II seminomas has been infradiaphragmatic irradiation throughout the period. The irradiation field has most often included the lumbar and ipsilateral iliac lymph node regions (L-field). Until 1980, the anterior field also included the inguinal region in patients with tumour infiltration of the rete testis, epididymis or spermatic cord, in cases of infiltration through the tunica vaginalis, and if the patient presented with a history of previous scrotal or inguinal surgery [12]. During the period of investigation, the abdominal irradiation dose has been reduced from 40 to 36 Gy and recently to 30 Gy. Patients with stage II and stage III tumours additionally received radiotherapy to mediastinal fields, including the left or both supraclavicular fossae. The use of supradiaphragmatic irradiation was stopped in 1981. Furthermore, since 1978, patients with advanced stage IIb and stage ≥IIc received cisplatin-based chemotherapy in some cases followed by irradiation (or surgery).

Non-seminomas. Until 1978, the treatment principles were the same for non-seminomas as for seminomas; radiotherapy being the main treatment modality. However, patients with non-seminoma received an abdominal dose of 50 Gy. Before 1978, chemotherapy was mainly given to

patients with stage IV disease or as secondary treatment in case of relapse. Until 1965, cyclophosphamide was given as a single drug. From 1966 to 1974, multidrug regimes including cyclophosphamide, vincristine, actinomycin-D, methotrexate and 5-fluorouracil were given. During the period 1970–1973, mithramycin was used as single drug treatment. From 1974 to 1977, the patients most often received the VACAM regimen (vincristine, doxorubicin, cyclophosphamide, actinomycin-D and medroxyprogesterone acetate) described by Klepp and associates [13].

The therapeutic principles for non-seminoma patients were basically changed in 1979. Since that time, patients with non-seminoma stage I and IIa underwent primary retroperitoneal lymph node dissection (RLND) followed by cisplatin-based chemotherapy if metastases were present. During the early 1980s, cisplatin was administered as regimens consisting of cisplatin, vinblastine and bleomycin (CVB). In most cases, four courses were given. Patients with non-seminoma stage IIb or worse were given four courses of this CVB regimen followed by surgery of residual masses and two to four further courses if vital cancer cells were still present. From 1984, CVB was gradually replaced by the BEP regimen containing etoposide, cisplatin and bleomycin. From 1984, patients with hyperadvanced non-seminomas were given a variant of the BEP regimen with high-dose cisplatin, or the BOP/VIP regimen [14], usually consisting of three courses of BOP (bleomycin, vincristine, cisplatin) and three courses of VIP (etoposide, ifosfamide, cisplatin). In most patients, surgery of residual masses was routinely performed. From 1987, patients with low-risk stage I were included in the "wait and see" policy. Patients with stage I and with histological high-risk criteria received two cycles of adjuvant BEP [15].

Surgical treatment in addition to orchiectomy, in most cases retroperitoneal lymph node dissection, was applied in 528 of 2006 patients.

The study group of 2006 patients was divided into four groups according to overall cytotoxic treatment given to the individual patient as primary treatment and, in patients with relapse, as salvage therapy: 1194 patients had only received radiotherapy (RT), 346 patients only chemotherapy (CT), 277 patients both radiotherapy and chemotherapy (RT + CT) and 189 patients neither radiotherapy nor chemotherapy (No RT nor CT).

Of the patients in the RT group, 1179 patients (99%) received irradiation to only one target volume. In 111 patients (9%) the irradiation dose was ⩾50 Gy, in 488 patients (41%) 40–49 Gy and in 595 patients (50%) <40 Gy.

In order to analyse the relative risk of a subsequent cancer according to the abdominal irradiation dose, the patients from the RT group without relapse and without supradiaphragmatic irradiation were divided into three subgroups: 531 patients with irradiation dose 1–36 Gy, 413 patients with irradiation dose higher than 36 Gy and less than or equal to 40 Gy and 117 patients with irradiation dose higher than 40 Gy.

The chemotherapeutic regimens given to patients in the CT group are listed in Table 2. As many as 330 of 346 patients (95%) in this group received cisplatin-based chemotherapy. In addition to the aforementioned regimens, HOP (ifosfamide, vincristine, cisplatin), VIP (etoposide, ifosfamide, cisplatin) and CEB (carboplatin, etoposide, bleomycin) were administered to a limited extent during the investigation period.

In the RT + CT group, irradiation was applied to only one target volume in 156 patients (56%), to two in 49 patients (18%) and to three or more target volumes in 72 patients (26%). The total irradiation dose was ⩾50 Gy in at least one region in 69 patients (25%), 40–49 Gy in 162 patients (58%) and <40 Gy in 46 patients (17%). The chemotherapeutic regimens in 180 patients (65%) of the RT + CT group consisted of cyclophosphamide given alone, cyclophosphamide/doxorubicin multidrug regimens or other cyclophosphamide combinations without doxorubicin. Cisplatin-containing regimens were administered to 67 patients (24%) and other chemotherapeutical regimens (mithramycin, ifosfamide or doxorubicin without cyclophosphamide) to 30 patients (11%).

Statistical analyses

The patients were followed from one year after diagnosis until death, emigration, third subsequent cancer (only one patient) or until 31 December 1992, whichever occurred first.

The analyses were based on a comparison between observed numbers of subsequent cancer (*O*) in the study group and expected numbers of cancer (*E*) in the general Norwegian population when a standardisation on age and period of follow-up was performed. Age was divided into 5-year age groups, and follow-up into 2-year observation periods. A standardised incidence rate ratio (SIR) was calculated, in the present study termed relative risk (RR). A 95% confidence interval (CI) for RR was calculated on the assumption of a Poisson distribution.

The analyses on expected and observed cases of cancer were based on organ location of tumour for all types of subsequent cancers except for sarcomas. For this latter cancer

Table 2. Chemotherapy in patients who did not receive radiotherapy (CT group). Primary and relapse treatment summarised

Type of chemotherapy	No. of patients	No. of cycles Mean (range)	Follow-up (years) Mean (range)
Cisplatin combinations only*	310	4.2(1–18)	7.5(1.1–15.5)
Cisplatin combinations + cyclo/dox†	20	14.8(6–58)	8.7(1.1–18.4)
Chemotherapy excluding cisplatin‡	16	8.7(2–18)	11.8(1.0–20.3)
Total	346	5.0(1–58)	7.8(1.0–20.3)

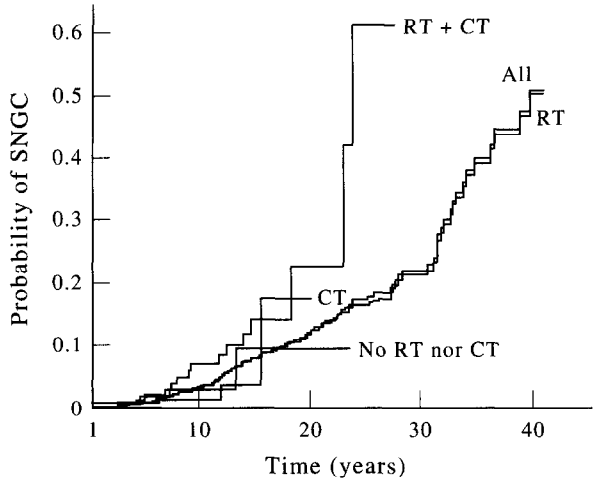
*CVB (163 pts), BEP (85 pts), BEP/CVB (30 pts), BOP/VIP (18 pts), HOP (6 pts), VIP (3 pts), CEB (6 pts), other cisplatin combinations (12 pts)—some pts received more than one regime. †CVB (18), other cisplatin combinations (2). Cyclo/dox combinations, in most cases VACAM. ‡Courses including cyclophosphamide and doxorubicin (9), mithramycin (2) and other types (5).
Cyclo/dox, cyclophosphamide/doxorubicin.

type, the histological coding of soft tissue sarcomas formed the base, independently of tumour site. One case of sarcoma in the urinary bladder was only included in the analyses on sarcomas. Cases of malignant mesothelioma were not included in the sarcoma analyses. Cases of malignant Schwannoma were included in the analyses of tumours in the central and peripheral nervous systems (CNS and PNS).

The cumulative risk of SNGC at a certain point of time after diagnosis was calculated by the life table method of Kaplan and Meier [16].

RESULTS

A total of 153 SNGCs were diagnosed after a mean interval of 15.9 years from diagnosis of a primary testicular cancer. In 144 cases (94%), the SNGCs were histologically verified. In those 9 cases which were not histologically verified, the diagnosis was based on explorative surgery, X-ray or ultrasound investigations. No SNGCs developed among patients with an extragonadal germ cell cancer. In 142 patients, the tumour represented the patients' second cancer, 10 tumours were the third cancer and one tumour the patient's fourth cancer. The cumulative risk of an SNGC for the whole group of patients was 7.8% (95% CI 6.2–9.5%) at 15 years of follow-up from primary diagnosis (Figure 1). Corresponding values at 15 years were in the RT group: 7.6% (95% CI 5.8–9.4%), in the CT group: 3.6% (95% CI 0–8.1%), in the RT + CT group: 14.0% (95% CI 5.9–22.1%) and in the No RT nor CT group: 9.3% (95% CI 0–21.9%). After 30 years of follow-up, the cumulative risk for the whole group of patients was 21.9% (95% CI 17.5–26.3%) and in the RT group 21.0% (95% CI 16.5–25.5%).



Patients at risk at start of interval

Time from diagnosis (years)	Treatment category (*n*) RT	CT	RT + CT	No RT nor CT	All
1–9	1194	346	277	189	2006
10–19	827	112	83	59	1081
20–29	365	2	7	5	379
30–39	92	–	–	–	92

RT, radiotherapy; CT, chemotherapy.

Figure 1. Cumulative risk of a SNGC by time from primary diagnosis for different treatment groups. Only first SNGC included.

Table 3. RR of SNGC (O/E numbers) diagnosed ⩾1 year after orchiectomy, irrespective of treatment‡

Site of SNGC	O/E	RR	95% CI for RR
All	153/92.8	1.65	1.4–1.9
Gastro-intestinal*	39/21.6	1.81	1.3–2.5
Stomach	13/5.8	2.24	1.2–3.8
Colon	10/7.1	1.41	0.7–2.6
Rectum	8/4.8	1.66	0.7–3.3
Pancreas	4/2.9	1.40	0.4–3.6
Liver/biliary†	4/1.0	4.04	1.1–10.3
Lung	28/12.1	2.31	1.5–3.3
Connective tissue	9/1.0	8.78	4.0–16.7
Melanoma of the skin	12/4.5	2.68	1.4–4.7
Urogenital	29/22.8	1.36	0.9–1.8
Prostate	9/12.9	0.70	0.3–1.3
Bladder	13/6.4	2.04	1.1–3.5
Kidney, renal pelvis, ureter	7/3.5	2.01	0.8–4.2
CNS and PNS	5/3.1	1.61	0.5–3.8
Lymphatic system	2/3.6	0.55	0.1–2.0
Leukaemia	6/3.2	1.89	0.7–4.1

*Oesophagus and small intestine not included. †Three of 4 SNGCs were located to the extrahepatic biliary system. ‡Person-years for the whole group of 2006 patients was 22904.5.
CNS, central nervous system; PNS, peripheral nervous system.

Table 3 lists site-specific RRs of SNGCs. Significantly elevated RRs were found for all cancers combined, for all gastro-intestinal cancers combined and for cancer of the stomach, liver and biliary system, lung, melanoma and urinary bladder. The RR of a subsequent sarcoma was considerably raised (RR, 8.78). The site specific RRs of 23 second cancers with rare incidence were not calculated. The organ location of these cancers were as follows: mouth (4), lower lip (1), tongue (1), larynx (1), epipharynx (1), cutis (4), pleura (1), maxillary sinus (1), oesophagus (3), parotid gland (1), peritoneum (1) and unknown origin (2), one myelofibrosis and one myelomatosis.

10 patients developed more than one subsequent cancer. Three primary malignant melanomas occurred in 1 patient, two primary angiosarcomas in a second, and two primary lung cancers in a third patient. In the other 7 patients, the first and second SNGCs were of different types. The mean interval between first and second SNGC was 3.4 years (range 0–9.3 years).

All types of SNGC listed in Table 3 were related to respective treatment groups, and the corresponding RRs calculated. Those malignancies which showed a significantly elevated RR in at least one of the treatment subgroups are listed in Table 4. For all SNGCs combined, a significantly elevated RR was only found in patients given radiotherapy (the RT and RT + CT groups), the highest RR being in the RT + CT group. In this latter group, significantly elevated RR was also demonstrated for lung cancer and malignant melanoma. In addition, in the RT group, which accounted for 59.5% of the patients, a significantly elevated RR of an SNGC was found for gastro-intestinal cancer combined and for cancer of the stomach, lung, connective tissue and urinary bladder. Among patients who had received chemotherapy only (CT), there was no significant elevation of the

Table 4. RR of SNGC by treatment category‡

Site of SNGC	Treatment	O/E	RR	(95% CI for RR)
All	RT	130/82.5	1.58	(1.3–1.9)
	CT	4/3.0	1.32	(0.4–3.4)
	RT + CT	15/4.2	3.54	(2.0–5.8)
	No RT nor CT	4/3.1	1.31	(0.4–3.4)
Gastro-intestinal*	RT	33/19.4	1.70	(1.2–2.4)
	CT	1/0.6	1.72	(0.0–9.7)
	RT + CT	3/1.8	1.70	(0.4–5.0)
	No RT nor CT	2/0.7	3.03	(0.3–10.9)
Stomach	RT	13/5.3	2.46	(1.3–4.2)
	CT	0/0.1	—	(0.0–29.3)
	RT + CT	0/0.2	—	(0.0–16.7)
	No RT nor CT	0/0.2	—	(0.0–22.6)
Lung	RT	24/10.2	2.19	(1.4–3.3)
	CT	0/0.3	—	(0.0–11.3)
	RT + CT	3/0.6	5.41	(1.1–15.8)
	No RT nor CT	1/0.3	3.22	(0.1–17.9)
Connective tissue	RT	8/0.9	9.22	(4.0–18.2)
	CT	0/0.1	—	(0.0–63.4)
	RT + CT	1/0.1	17.60	(0.5–98.1)
	No RT nor CT	0/0.0	—	(0.0–87.7)
Melanoma of the skin	RT	7/3.7	1.91	(0.8–3.9)
	CT	2/0.3	6.26	(0.8–22.6)
	RT + CT†	3/0.3	10.56	(2.2–30.9)
	No RT nor CT	0/0.2	—	(0.0–17.8)
Bladder	RT	12/5.7	2.10	(1.1–3.7)
	CT	0/0.2	—	(0.0–20.8)
	RT + CT	1/0.3	3.53	(0.1–19.7)
	No RT nor CT	0/0.2	—	(0.0–17.9)

*Oesophagus and small intestine not included. †All three cases of melanoma developed in the same patient. ‡Person-years in the four treatment categories were RT, 17674.6; CT, 2319.5; RT + CT, 1604.8; No RT nor CT, 1305.7.

RRs, the RR of all SNGCs combined being similar to that in patients who had not received any cytotoxic treatment (No RT nor CT). Of 4 SNGCs in the CT group, 2 cases occurred among 310 patients who were treated with modern cisplatin-based chemotherapy, and 2 cases among 29 patients after treatment with alkylating agents with or without cisplatin combinations.

The extended follow-up in the RT group of 40 years made it possible to divide the follow-up of this group into four decades (Table 5). The RR of all SNGCs combined was elevated in all decades, the highest RR being after 30 years of follow-up and the second highest between 10 and 19 years of follow-up. Between these two time intervals, during 20–29 years, there was a decrease in the RR to the same level as during the first 10 years of follow-up. For each specific type of SNGC, a somewhat varying picture was seen. The trend, however, seemed to be similar to that of all SNGCs combined. For leukaemia, the RR increased during the first three decades of follow-up.

There was no notable difference of the RR of an SNGC in general among patients with seminomatous and those with non-seminomatous cancer (data not shown). The RR of a gastro-intestinal cancer was higher in patients with non-seminomatous cancer than in those with seminoma, mainly caused by a much higher RR of stomach cancer in these patients. An opposite relationship was found in urogenital cancer, in which the RR was 5-fold higher among the patients with seminoma, mainly due to a high RR of subsequent cancer of the urinary bladder in these patients.

Five cases of acute and one case of chronic leukaemia were diagnosed more than one year after the primary diagnosis with a mean interval of 16.5 years (range 3.8–28.4 years). All events of leukaemia (4 acute myelogenous leukaemia, 1 acute lymphatic leukaemia, 1 acute myelomonocyte leukaemia and 1 chronic myelogenous leukaemia) developed among patients with a testicular seminoma who had received abdominal irradiation as their only treatment. A case of myelofibrosis that occurred in the RT + CT group after an interval of 12 years was not included in the analysis. This patient was one of 2 patients with a haematological disease that had received chemotherapy. The other was a patient in the CT group with a subsequent myelomatosis. In particular, no cases of leukaemia occurred in 213 patients during a mean observation period of 4.6 years from the start of treatment with etoposide-containing chemotherapy, the median cumulative dose being 1420 mg/m^2, 45 of these having received a dose of $\geq$2000 mg/m^2.

Nine cases (in 8 patients) of sarcoma occurred after a mean interval of 17.7 years (Table 6). Four were angiosarcomas located to skin (2), duodenum (1) and urinary bladder (1), three were malignant fibrous histiocytomas, one was leiomyosarcoma, and one sarcoma was not further specified. All patients had received radiotherapy. Five sarcomas were definitely located within an irradiation field, three at the border or close to an irradiation field, and only one

*Table 5. RR of SNGC in the RT group by follow-up intervals**

Site of SNGC	1–9 years No.	1–9 years RR	1–9 years 95% CI	10–19 years No.	10–19 years RR	10–19 years 95% CI	20–29 years No.	20–29 years RR	20–29 years 95% CI	30–39 years No.	30–39 years RR	30–39 years 95% CI
All	29	1.20	0.8–1.7	60	1.91	1.5–2.5	24	1.21	0.8–1.8	17	2.39	1.4–3.8
Gastro-intestinal	7	1.23	0.5–2.5	15	2.03	1.1–3.3	6	1.28	0.5–2.8	5	2.98	1.0–7.0
Stomach	4	2.26	0.6–5.8	6	3.05	1.1–6.6	1	0.87	0.0–4.8	2	5.06	0.6–18.3
Colon	1	0.58	0.0–3.2	3	1.25	0.3–3.6	2	1.26	0.2–4.5	3	5.00	1.0–14.6
Rectum/anus	1	0.85	0.0–4.8	5	3.00	1.0–7.0	0	—	0.0–3.4	0	—	0.0–9.5
Pancreas	0	—	0.0–5.0	0	—	0.0–3.7	2	3.40	0.4–11.5	0	—	0.0–16.6
Liver/biliary	1	3.80	0.0–21.5	1	2.94	0.0–16.5	1	4.76	0.0–26.7	0	—	0.0–46.3
Lung	6	1.99	0.7–4.3	12	2.82	1.5–4.9	2	0.73	0.1–2.6	4	4.35	1.2–11.1
Connective tissue	0	—	0.0–11.2	7	21.51	8.7–44.3	0	—	0.0–22.4	1	20.57	0.5–114.6
Melanoma of the skin	3	2.13	0.4–6.2	3	2.12	0.4–6.2	1	1.48	0.0–8.3	0	—	0.0–21.5
Urogenital	5	1.02	0.3–2.4	10	1.30	0.6–2.4	9	1.61	0.7–3.1	3	1.26	0.3–3.7
Prostage	4	1.60	0.4–4.1	2	0.47	0.1–1.7	3	0.89	0.2–2.6	0	—	0.0–2.3
Bladder	1	0.68	0.0–3.8	6	2.74	1.0–6.0	5	3.35	1.09–7.8	0	—	0.0–6.6
Kidney, renal pelvis, ureter	0	—	0.0–4.0	2	1.66	0.2–6.0	1	1.37	0.0–7.6	3	12.51	2.6–36.6
CNS and PNS	1	0.94	0.0–5.2	2	2.05	0.3–7.4	2	4.44	0.5–16.1	0	—	0.0–33.5
Lymphatic system	0	—	0.0–3.4	1	0.87	0.0–4.8	0	—	0.0–6.1	0	—	0.0–19.4
Leukaemia	1	1.02	0.0–5.7	3	2.70	0.6–7.9	2	3.03	0.4–11.0	0	—	0.0–17.0

No., number of SNGCs in specified observation periods. *Person-years in the first, second, third and fourth decade of follow-up: 9208.2, 5991.0, 2065.8 and 409.6.

Table 6. Characteristics of the patients with a subsequent sarcoma

	Primary germ cell cancer					Subsequent sarcoma		
		Radiation region*		Dose (Gy)				
Patient	Histology	Primary	Relapse	Primary	Relapse	Location	Histology	Interval from germ cell cancer (years)
1	Seminoma	Abdomen		40		Duodenum, bladder†	AS, AS	13.8, 15.0
2	Seminoma	Abdomen + med.	Head‡	40 + 36	28 + 23	Left renal region	MFH	18.4
3	Non-seminoma	Abdomen		40		Intraspinal, th 9–10	LMS	13.9
4	Seminoma	Abdomen + med.		40 + 36		Cutis, dorsal	AS	17.7
5	Seminoma	Abdomen		40		Abdomen, intest. infiltr.	MFH	10.6
6	Non-seminoma	Abdomen	Inguinal/scrotum	40	4	Cutis, lower limb	AS	18.4
7	Seminoma	Abdomen		40		Retroperitoneum	Sarcoma n.s.	19.3
8	Seminoma	Abdomen	Neck + med. + abdomen	35	44 + 48 + 18	Lumbar, dorsal	MFH	32.1

*Only patient no. 2 received chemotherapy: 11 VACAM + 6 courses containing cyclophosphamide, actinomycin-D, vincristine and bleomycin. †Two subsequent sarcomas in one patient. ‡Electrons on subcutaneous metastases.

med., mediastinum; intest. infiltr., intestinal infiltration; AS, angiosarcoma; MFH, malignant fibrous histiocytoma; LMS, leiomyosarcoma; Sarcoma n.s.; sarcoma not specified.

was located distant from the irradiation field, on the leg. All but the patient with the sarcoma on the leg died after a mean interval of one year from diagnosis of the SNGC.

There was only a slight tendency to increasing RR of an SNGC with increasing abdominal irradiation dose, the RRs being 1.78 (95% CI 1.4–2.3) (irradiation dose 1–36 Gy), 1.78 (95% CI 1.3–2.3) (irradiation dose >36 to ≤40 Gy) and 1.84 (95% CI 1.0–3.2) (irradiation dose >40 Gy) in the three irradiation subgroups, respectively. The RR of a subsequent lung cancer after infradiaphragmatic irradiation only was 1.73 (95% CI 1.1–2.8).

DISCUSSION

The present study takes advantage of a large number of patients and a long observation period, in addition to a high quality of registration routines of both primary and subsequent cancers in Norway.

Extragonadal germ cell cancers were not excluded from the present study, because these tumours are believed to develop from the same type of cells and consist of the same histological subtypes as testicular cancers. Since these patients contributed only 0.3% to the total number of person-years in the whole study group, exclusion of these patients would only lead to minimal change in the results.

The RR value for SNGC varies in the literature. In the present study, the RR of 1.65 for all SNGCs is superior to the median of previously reported figures. Van Leeuwen and associates [9], Kaldor and associates [17] and Hay and associates [2] reported an RR for all second cancers of 1.6, 1.3 and 1.87, respectively. Excluding contralateral testicular cancers from these figures, however, the RR of an SNGC was 1.2, 1.2 and 1.66, respectively. In the Danish report by Møller and associates [8], the RR of SNGC was 1.6, and Travis and associates [10] recently reported an RR of 1.56 in a cohort of almost 10 000 patients in the United States. Included in this large study were patients from the Connecticut Registry, for whom an RR of 2.0 for an SNGC was reported earlier [7]. The difference between figures of RRs from various reports have at least three explanations. (1) Different routines with regard to reporting new and, especially, subsequent cancers to the registries. These routines are considered to be good in Norway. (2) Variable length of the follow-up. The mean follow-up from diagnosis in the present study was 12.5 years. In the previously mentioned studies it was 15.4 years [2], 9.6 years [8], 8 years [7], 7.7 years (median) [9], 7.2 years [10] and 7.0 years [17]. As shown in the present and some aforementioned studies [7–10], the RR of an SNGC seems to be higher during the second compared to the first decade after treatment for most types of SNGCs. Thus, a long period of follow-up favours high RRs of SNGC. (3) Inclusion of up to three SNGCs. All but two of the aforementioned studies [2] calculated RRs for the first SNGCs only. If we had included the first SNGCs only, our figure for RR of an SNGC would have been 1.58 (95% CI 1.3–1.8).

The RR of an SNGC according to type of cytotoxic treatment administered, clearly demonstrates the significance of radiotherapy and the combination of radiotherapy and chemotherapy as carcinogenic factors. Significantly elevated RRs were only found in the RT and in the RT + CT groups, and 145 of the 153 subsequent malignancies occurred in these two subgroups. The RT group was by far the largest with 17 674.6 person-years, included the highest number of patients and covered the longest mean observation period, in contrast to the much smaller RT + CT group with only 1604.8 person-years. The highest RR was found in this latter group, which is in accordance with the findings of de-Vathaire and colleagues [18] and Abrahamsen and colleagues [19], who also analysed comparable treatment subgroups. In the present study, the high RR in the RT + CT group was probably caused initially by the high total cumulative dose of cytotoxic treatment given to these patients. Compared with the RT group, patients in the RT + CT group had generally received multiple irradiation fields and higher total irradiation doses. In addition, they had received chemotherapy with a similar number of courses on average as the patients in the CT group. Also, cyclophosphamide was given to 65% of the patients. The strong carcinogenic potential of cyclophosphamide has been demonstrated in both clinical [20, 22] and experimental studies [23, 24].

Patients in the CT group experienced the same RR for an SNGC in our study as patients in the No RT nor CT group. Since 90% of the patients in the CT group were given modern cisplatin-based chemotherapy (without alkylating agents), and only 2 of 4 SNGCs in the CT group occurred in these patients, this observation is encouraging. The observation period, however, is still short, and the number of patients small in the CT group. Our observations should, therefore, be regarded as preliminary and do not allow a more definite association between modern cisplatin-based chemotherapy of germ cell cancer and SNGC. Our results are in agreement with other clinical reports on a low risk of cisplatin-associated subsequent solid malignancies after cisplatin-based chemotherapy.

In the publication by Travis and associates [10], the RR was 1.40 (95% CI 0.99–1.63) among those American patients who had been treated with surgery alone and had survived more than 10 years. The elevated RR of an SNGC among patients who were not given any cytotoxic treatment in our study (RR, 1.31) is in accordance with this finding, although our figures do not reach the level of statistical significance. Nevertheless, when considered together with the corresponding RR from the United States, our observations support the hypotheses that patients with a primary testicular cancer display an increased risk of developing an SNGC independently of whether cytotoxic treatment is given or not.

The cumulative risk of 7.8% in the whole study group of developing an SNGC after 15 years of follow-up is slightly lower than the corresponding RR found by Van Leeuwen and associates [9]. The cumulative risk of 21.9% at 30 years of follow-up is very high, and a comparison with other studies has not been possible. However, it must be considered in connection with the high cancer risk generally observed among the elderly. The patients in the present study with a long period of follow-up were on average 64.0 years of age (30.3–87.7 years) when passing 30 years of follow-up.

With an observation period of approximately 30 years, Møller and associates [8] found in their study a decreasing tendency of RR for several cancer sites after 15–20 years of follow-up. The high RR found in irradiated patients after 30 years in the present study suggests that the preceding fall in

RR, present in all cancer sites combined, in gastro-intestinal cancers combined and in lung cancer in our study, is a temporary phenomenon. For urogenital cancers combined, we found a continuously elevated RR. For the other cancer sites, the limited number of patients did not allow any definitive statements.

The hypothesis that irradiation truly is involved even in very late clinical manifestation of cancer, and that this late development is not only due to a predisposition of cancer patients to develop malignancies, is supported by similar observations in cohorts of individuals who were exposed to irradiation due to non-malignant reasons. Cancer risk is well studied in large cohorts of atomic bomb survivors in Japan [25]. Exposed persons who were at the same age at the time of bombing as patients in the present study, 30–39 years of age, show an increasing trend of RR of all cancers combined excluding leukaemia during 40 years of follow-up. No temporary fall was seen for this age group. For individual cancer sites, somewhat different trends were seen. In Scottish women irradiated for metropathia haemorrhagica at a mean age of 45 years [26] and followed for more than 30 years, an increasing trend of RR was observed for several cancer sites preceded by a temporary fall in most cases. An opposite trend of a decreasing RR with time from irradiation was found among patients irradiated for ankylosing spondylitis [27].

The reasons for these differences in trends of RR are not clear. The study cohorts were different in terms of age at irradiation, sex and state of illness. Further, the irradiation differed in quality, dose, length of irradiation period and size of irradiation field. Even within one study, important variability may have occurred. Therefore, in the present study, we verified the irradiation dose to see if patients with a follow-up of more than 30 years had received high irradiation doses, which could contribute to the high RR found in these patients after 30 years. We found that this was not the case.

The location of SNGCs in relation to irradiation fields was not consistently registered. However, the high risk of cancers located in regions usually included in irradiation fields is conspicuous, such as cancer of the stomach, liver and biliary system, urinary bladder and kidney. The fact that malignancies may also develop outside irradiation fields is illustrated by the increased risk of subsequent lung cancer in patients given infradiaphragmatic irradiation only.

It is generally assumed that the majority of treatment-induced cases of leukaemia occur within 10–15 years from the primary treatment, irradiation-induced leukaemia occurring later than those induced by chemotherapy [8, 9, 28]. In our study, only one case (RR, 1.02) of leukaemia occurred within ten years, three (RR, 2.70) during 10–20 years and two (RR, 3.03) after 20 years, and all were in the RT group. In atomic bomb survivors in Japan [25] and in the patients irradiated for ankylosing spondylitis [27], the RR of a leukaemia was also highest during the first 10–15 years, but the risk remained increased several years later. Thus, in our testicular cancer patients, a combined effect of irradiation and other late acting factors may explain the late occurrence of leukaemia.

No cases of subsequent leukaemia occurred in the group of 213 patients who had received etoposide-containing chemotherapy, which is noteworthy. Since Pedersen-Bjergaard and associates [29] published a report of an extremely high risk of epipodophyllotoxin-related secondary leukaemia in patients treated with chemotherapy containing more than 2000 mg/m^2 of etoposide, much concern has been drawn to this problem. Fortunately, the same high risk has not been confirmed in later reports on patients given lower and ordinary doses of etoposide [30–33]. Our observation supports these later reports which diminish the perceived hazards when etoposide is given in ordinary doses in a BEP regimen.

A high risk of a subsequent sarcoma has been demonstrated by others [7, 10, 17, 34]. An even higher risk is reported in the present paper. The mode of registration of sarcomas is probably the most important contributor to the higher risk found in our study. Of 9 cases of sarcoma, 4 were angiosarcomas. These very rare tumours tend to develop in different organs and are subsequently spread in the classification system. They were included because we also verified the histological codes of the observed SNGCs and not only the localisation codes.

The fact that all sarcomas except one occurred within or close to an irradiation field indicates the significance of radiotherapy as an important aetiological factor in the development of subsequent sarcomas. A somewhat longer mean latent period of 17.7 years in this study as compared to some other studies [34, 35] may partly be due to the longer observation period in the present study. All cases of sarcoma developed ten or more years after the primary diagnosis, indicating that these tumours most probably are true primary subsequent sarcomas and not part of or developed from multipotent cells of the primary testicular cancer [36].

The number of four angiosarcomas among nine soft tissue sarcomas is high. This tumour type constituted only 2% of all soft tissue sarcomas diagnosed in Norway during the investigation period. Radiotherapy [35, 37], chronic lymphoedema [38] and thorotrast used in angiography [37, 39] are among the known causal agents in the development of angiosarcoma, although most cases are not associated with any known aetiological factors [37]. In the present study, chronic lymphoedema seemed to be the cause in one patient with an angiosarcoma of the leg. The other three angiosarcomas developed within or at the border of an irradiation field. Thorotrast has not been used in any of these patients.

The RR of a subsequent lung cancer of 2.31 is higher than in any other comparable studies [2, 7–10, 17]. The differences may be due to differences in irradiation routines, genetic factors, smoking habits or simply to different diagnostic or registration routines.

The RR of a malignant melanoma would be reduced from 2.68 to 2.00 if only the first SNGC were included in the analyses, since three malignant melanomas were either second or third SNGCs. The RR of 2.00 is within the range of previously reported figures [7–10, 17].

Cancer of the prostate is the only malignancy in addition to malignant lymphoma in which the RR tended to be lower than in the general Norwegian population. This is interesting because androgens are believed to be intimately involved in prostate cancer development [40], and patients with a germ cell cancer often display relatively low serum concentrations of testosterone [41].

In conclusion, patients with germ cell cancer have an increased risk of developing an SNGC after treatment (RR, 1.65). In the present study, significantly raised RRs were

observed for gastro-intestinal cancers combined and for cancer of the stomach, liver and biliary system, lung, melanoma and urinary bladder. The increased risk was significantly related to the application of radiotherapy without and in particular with chemotherapy. The RR of an SNGC remained elevated during the third and fourth decade of follow-up in irradiated patients and showed an even increasing trend with very long follow-up. Patients given both radiotherapy and chemotherapy experienced the highest RR, probably mainly due to a high cumulative dose of cytotoxic treatment. The same RR of an SNGC among patients given mostly modern cisplatin-based chemotherapy and no radiotherapy compared to those who did not receive any cytotoxic treatment was, thus far, encouraging, but the observation period was too short and the number of patients too small to make definite associations between modern cisplatin-based chemotherapy of germ cell cancer and risk of SNGC. Even for patients receiving no cytotoxic treatment, the RR of SNGC tended to be above that observed in the general population.

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