Risk of secondary malignancies in testicular tumors

H. SIFFNEROVA[1], D. KRALOVA[2]

[1]*Department of Oncology, Hospital České Budějovice, B.Němcové 54, 370 87 České Budějovice, e-mail: siffnerova@nemcb.cz*
[1]*Department of Radiology and Toxicology, Faculty of Health and Social Studies, the University of South Bohemia, České Budějovice*
[2]*Centre of Biostatistics and Analyses, Medical Faculty, Masaryk University Brno*

Received January 30, 2007

The work is aimed at the occurrence of secondary malignancies after therapy for primary testicular tumors. The target of the work was determination of the number and type of secondary tumors, their effect on the survival and comparison of relative risk of the origination of secondary tumors depending on particular treatment modalities. Total of 313 patients with testicular tumors were assessed, who experienced orchiectomy in 1968 to 1998 with subsequent irradiation, chemotherapy or combination of the two modalities.

Total of 22 secondary tumors, i.e. 7%, were found in the group. The relative risk of the secondary malignancy development was of 1.04. The median time till the secondary tumor occurrence was of 143 months.

Total of 213 patients were subjected to radiotherapy, which was associated with enhanced risk of the secondary tumor development (RR = 8.38); the risk in 100 patients treated by chemotherapy was lower (RR = 0.38). The relative risk of the origination of the secondary malignancy located in the region of preceding irradiation is low (RR = 0.52).

In the case of the occurrence of secondary malignancies, the median symptomless survival and the total survival decreased from 271 months to 187.3 and 199.8 months, respectively.

Most patients with testicular tumors have favourable long-term prognosis and thus, it is desirable to know the risk of secondary malignancies and to include it into plan of long-term subsequent follow-up.

Key words: testicular tumors; radiotherapy; secondary malignancies

The number of patients is currently increasing, in which the development of late undesirable effects after the oncologic treatment can be expected. This fact is associated with a wider use of screening, early detection of tumors and use of effective therapeutic procedures, which improve the total survival [1].

Late complications of the treatment include e.g. infertility, premature menopause, numerous hormonal disorders, osteoporosis, pains, psychological problems and development of secondary tumors.

Secondary tumors most frequently occur after radiotherapy and they belong to severe complications, because of being causes of not only morbidity but often even mortality [2].

In accordance with worldwide statistics it is expected that 30% to 40% of population develop cancer disease in the course of the lifetime and up to 50% of them experience treatment including radiotherapy. This means that a considerable proportion of the population will be exposed to certain radiation doses with a possibility of the origination of radiation-induced tumors [3].

The relationship between the radiation dose and carcinogenesis is not yet clear in spite of the availability of a wide number of experimental and clinical data.

Irradiation with low doses, causing pre-malignant damage to DNA, was considered as more dangerous for the development of malignant tumors rather than irradiation with high doses, which cause the cellular death. It was, however, demonstrated that tumors can develop in the area of scattered radiation or at the margin of the field irradiated as well as at sites of high doses [3].

The work presented here was directed to primary testicular tumors, which most typically occur in young men, a majority of them being curable with a long-term favourable prognosis. The target of the work was the determination of effects and role of radiotherapy in the general occurrence of secondary malignancies in the group and also in the occurrence of these secondary malignancies in the region of preceding irradiation.

*Corresponding author

Patients and methods

The sample comprises 313 patients with testicular tumors, who were treated at the Department of Oncology, Hospital České Budějovice in 1968 to 1998.

Patient average age at the time of the diagnosis was of 35.2 years (SD 11.6 years), the median age was of 33 years (range 12–80 years). There were no differences between ages in particular treatment groups (Table 1).

In all patients, orchiectomy and histological examination of the tumor was implemented. Extra-gonadic testicular tumors and lymphomas of testes were eliminated from the group.

The analysis did not include patients with tumors of the second testis, since the occurrence of the contralateral tumor is rather associated with biology of the patients than with the treatment for the initial tumor. The secondary tumor of the second testis occurred in 6 men (1.9%).

After the surgery, the patients were treated by irradiation, chemotherapy or by combined treatment with the use of both approaches (Table 2).

Table 1. Classification of the group by age

Age	Treatment modalities			
	RT+CH	RT	CHT	Total of
Average age (years)	35	38	31	35.2
Median age (years)	33 (17 – 66)	35(12 – 80)	29(18 – 58)	33(12 – 80)
SD (years)	11	13	8	11.6

Table 2. Classification of the group by treatment modality

Total of	N	%
RT+CHT	60	19.2
RT	153	48.9
CHT	100	31.9

Table 3. Classification of the group by histology

Histology		Treatment	N	%
Seminomas	(N = 180)	RT+CHT	37	20.6
		RT	136	75.6
		CHT	7	3.8
Non-seminomas	(N = 133)	RT+CHT	23	17.0
		RT	17	13.0
		CHT	93	70.0

Squared Chi test of maximum reliability: $p < 0.001$

Table 4. Time till the secondary malignancy development

	Treatment modalities			
	RT+CHT	RT	CHT	Total of
Number of second tumors	4	17	1	22
Median time (months)	111.5 (46 – 409)	143 (41 – 418)	84	143 (41 – 418)

The tumors were defined by histology as seminomas and non-seminomas in 180 and 133 patients, respectively. Patients with seminoma were more frequently irradiated (Table 3).

A ^{60}Co radiation source was used for actinotherapy till 1993; thereafter, a linear accelerator was employed for this purpose. In patients with seminoma, the volume irradiated included paraaortal, paracaval and ipsilateral inguinopelvic nodes. Irradiation was typically carried out by large-volume technique, from two opposite fields situated within the shape of hockey stick. In indicated cases, contralateral pelvic nodes were also irradiated with the use of entrance fields situated within the shape of Y turned upside down. The total dose in subdiaphragmatic nodes was of 30 Gy, individual dose of 1.8-2 Gy, with the use of 5 fractions every week.

Patients with non-seminoma were, particularly in previous years, irradiated by a similar technique or by the BOX technique aimed at retroperitoneal nodes. The individual radiation dose was also 1.2–2 Gy till the total dose of 30–40 Gy was achieved with the use of 5 fractions every week.

In previous years, irradiation in supradiaphragmatic region – mediastinum was also indicated in our group, with or without irradiating the left supraclavicular region in a dose of 25 Gy, 5 fractions every week, individual dose of 2 Gy.

Chemotherapy comprised mostly combinations of cisplatin, vinblastine and bleomycin. Vinblastine was later replaced by etoposide. In the era before cisplatin, dactinomycin, cyclophosphamide, methotrexate, doxorubicin and bleomycine were administered in various combinations.

The average time of follow-up was of 119.4 months (SD 87.0 months); the median follow-up was of 111.5 months (range 1 – 444 months).

The relative risk (RR) of the secondary tumor development was evaluated, as a ratio of observed occurrence to expected occurrence of secondary tumors (O/E).

Effects of the occurrence of secondary tumors on the survival were furthermore followed. The survival analysis was carried out by the log-rank test. For the evaluation of the role of particular treatment modalities in the development of secondary malignancies, the Fisher test or the squared Chi test was used. The result was supplemented again by determining the relative risk of the secondary tumor development.

Effects of age at the time of the primary tumor diagnosis on the development of the second tumor were also considered. Differences in age between patients with and without secondary tumors were tested with the use of the non-parametric Mann-Whitney test.

Results

In 1968 to 1998, total of 21 608 patients were treated at the Department of Oncology, Hospital Č. Budějovice, in which 1459 secondary malignancies, i.e. 6.7%, were found. In the same period, in the sample of 313 patients with testicular malignancies, 22 secondary tumors, i.e. 7%, were observed.

The relative risk of the secondary malignancy development in testicular tumors was low in the followed period: 1.044 .

The median time till the secondary tumor development was of 143 months (41–418 months) and it was the same as in patients treated by irradiation alone. The median decreased to 111.5 months occured when combining irradiation with chemotherapy (Table 4).

Lung carcinoma was the most frequently occurring secondary tumor (5 patients); next to it, there were, in order of decreasing frequencies, carcinomas of the skin (4), pancreas (3), kidneys (2), malignant melanoma (2), tumor of rectosigmoid (2) and prostate (2). Single findings of secondary tumors were observed in the urinary bladder and mediastinum.

Total of 213 patients underwent radiotherapy and 21 secondary malignancies were observed in this group, i.e. 9.9%, which is a much larger occurrence than that in non-irradiated patients ($p = 0.002$).

The determined relative risk (RR) of the secondary tumor development in irradiated patients is of 8.38 (Table 5).

Chemotherapy was stepwise employed in a group of 160 patients with occurence of five secondary tumors, i.e. 3.1%. The relative risk of the secondary tumor development was of 0.38, which means that in chemotherapy, there is a reverse dependence. The patients, who were treated by chemotherapy, have a lower relative risk of the occurrence of the second tumor (Table 6).

Both treatment modalities (irradiation and chemotherapy) were used in 60 patients, and 4 secondary malignancies, i.e. 6.6%, were observed in them (Table 7).

The average age of patients with the diagnosis of secondary malignancy was of 58.1 years (SD 11.6 years), median 60 years (range 36–77 years).

There was a statistically significant difference in the age at the time of diagnosis between patients with and without secondary tumors. Patients, who developed secondary tumors, were older at the time of the diagnosis (Figure 1).

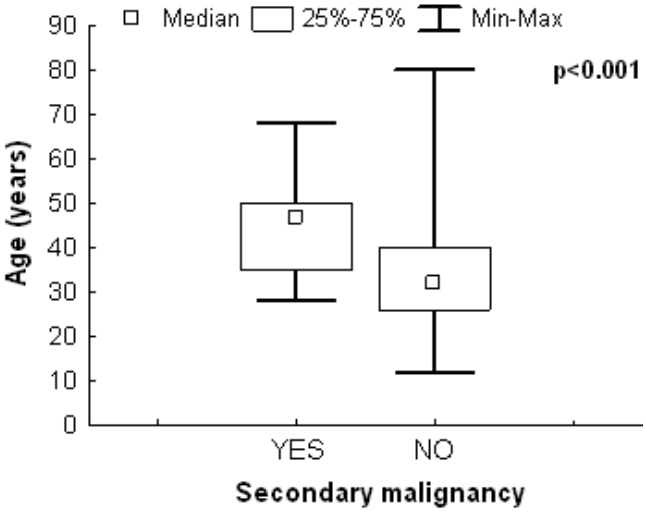

Figure 1. Relationship of age at diagnosis of primary tumor on secondary malignancy development

The origination of secondary malignancies as late complications of the therapy affected the asymptomatic as well as total survival of the patients.

The patients without the secondary malignancy had the median of disease free period as well as total survival of 271 months. As soon as the secondary malignancy occurred, the median disease free survival decreased to 187.3 months and the median total survival decreased to 199.8 months (Tables 8, 9).

Table 5. Occurrence of second tumors in radiotherapy group

		Secondary malignancy	
		Yes	No
Radiotherapy	yes	21 (9.9%)	192 (90.1%)
	no	1 (1.0%)	99 (99.0%)

Fisher test: p=0.002
O/E=8.38

Table 6. Occurrence of second tumors in chemotherapy group

		Secondary malignancy	
		Yes	No
Chemotherapy	yes	5 (3.1%)	155 (96.9%)
	no	17 (11.1%)	136 (88.9%)

Fisher test: p=0.005
O/E=0.38

Table 7. Occurrence of second tumors depending on treatment modality

		Secondary malignancy	
		Yes	No
Treatment modality	RT+CHT	4 (6.6%)	56 (93.4%)
	RT	17 (11.1%)	136 (88.8%)
	CHT	1 (1.0%)	99 (99.0%)

Squared Chi test: p=0.003

Table 8. Median disease free survival in the presence or absence of secondary malignancy

	Second tumors (N=22)	No second tumors (N=291)
Median survival	187.3 months	271.0 months

log-rank test: p = 0.770

Table 9. Median total survival in the presence or absence of secondary malignancy

	Second tumors (N=22)	No second tumors (N=291)
Median survival	199.8 months	271.0 months

log-rank test: p = 0.769

Table 10. Occurrence of secondary malignancies according to region irradiated

			Second tumors	
			Yes	No
Irradiation region	Below diaphragm only	N= 127	8 (6.3%)	119 (93.7%)
	Above and below diaphragm	N= 86	13 (15.1%)	73 (84.9%)
	Total of	N= 213	21 (9.9%)	192 (90.1%)

Fisher test: p=0.30

With respect to a high relative risk of the secondary tumor development after radiotherapy, a group of patients irradiated in the period considered was subjected to a more detailed analysis. Total of 213 patients were subjected to radiotherapy and the secondary malignancy occurred in 21 (i.e. 9.9%) of them.

When irradiation was restricted to the infradiaphragmatic region, the secondary malignancy was developed in 8 patients (i.e. 6.3%). If the infradiaphragmatic as well as supradiaphragmatic regions were irradiated, the occurrence of secondary malignancies increased to 13 (i.e. 15.1%). The occurrence of secondary malignancies is more frequent in patients with irradiated both supradiaphragmatic and infradiaphragmatic regions (Table 10).

For radiation doses in particular organs or locations see Table 11. These are average doses during standard large-volume irradiation from 2 opposite fields situated within the shape of a hockey stick by a total dose of 30 Gy, as obtained by interpolation from a work by Travis et al. [4]

Tumors of the lungs and pancreas were observed most frequently. The other tumors were less frequent. As expected, patients with primary seminoma type tumor (86%) were prevalent, who were irradiated more frequently (Table 12).

Table 11. Radiation doses in particular organs

Organ	Dose Gy
Stomach	15.8
Small intestine	15.0
Gut	1.7-14.9
Rectum	15.0
Liver	12.8
Gall bladder	8.0
Pancreas	20.0
Prostate	27.0
Kidneys	9.4
Urinary bladder	27.0
Thyroid	0.2
Bone marrow	9.6

Table 12. Location and histology of secondary malignancies depending on histology and treatment of primary tumor

No.	Second tumor location	Second tumor histology	Primary tumor histology	Irradiation region	Chemotherapy
1	Lungs	Epidermoid ca	S	Below d.	No
2	Lungs	Epidermoid ca	S	Above and below d.	Yes
3	Lungs	Epidermoid ca	S	Above and below d.	Yes
4	Lungs	Epidermoid ca	S	Above and below d.	No
5	Lungs	Small-cell ca	S	Above and below d.	No
6	Pancreas	Adenocarcinoma	S	Above and below d.	No
7	Pancreas	Adenocarcinoma	S	Above and below d.	No
8	Pancreas	Lymphoma	S	Above and below d.	No
9	Kidney	Adenocarcinoma	S	Below d.	No
10	Kidney	Adenocarcinoma	NS	Below d.	No
11	Rectosigmoid	Adenocarcinoma	S	Above and below d.	No
12	Rectosigmoid	Adenocarcinoma	S	Below d.	No
13	Prostate	Adenocarcinoma	S	Below d.	No
14	Prostate	Adenocarcinoma	NS	Above and below d.	No
15	Urinary bladder	Papillocarcinoma	NS	Below d.	Yes
16	Mediastinum	Mal. schwanoma	S	Above and below d.	No
17	Skin – back	Malig. melanoma	S	Above and below d.	No
18	Skin – shoulder	Melanoblastoma	S	Below d.	Yes
19	Skin – neck	Epidermoid ca	S	Below d.	No
20	Skin – hand	Epidermoid ca	S	Above and below d.	No
21	Skin – head	Epidermoid ca	S	Above and below d.	No

S= seminoma, NS= non-seminoma, d.= diafragma

For the assessment of the relative risk of the secondary malignancy development in irradiated patients, data from the Czech Republic database SVOD (System for Visualisation of Oncologic Data) were employed. For the estimation of the relative risk of the origination of radiation-induced secondary malignancies, ratios were considered between the observed number of new primary tumors and number expected in the population, and relative risks were established for the most frequent locations: lungs, pancreas, kidneys, rectosigmoid and prostate.

The highest relative risk after irradiation was determined for secondary tumors of the pancreas (RR = 109.2) and, next to them, for malignant melanoma (RR = 105.3). Tumor of the lungs was the most frequently observed secondary malignancy, but it did not have the highest relative risk (RR = 42.3) (Table 13).

A special group comprises secondary malignancies located in the region of preceding irradiation. Of 213 irradiated patients with testicular tumors, 17 secondary malignancies (i.e. 8%) occurred in the region of preceding irradiation.

All the secondary malignancies were checked by histology and their latency period was at least of 12 months, as published in the work by Travis et al. [4]

The secondary malignancies occurred most frequently in the lungs and pancreas and they were located at the centre of the field irradiated as well as at its margins.

For the evaluation of the secondary malignancy development relative risk in the region of preceding irradiation, it was first necessary to define an independent control group of patients, who shared as much similar characters as possible, and who could represent the expected number of secondary malignancies. Into the control group, men were included with diagnoses of carcinoma of the head and neck, larynx, pharynx, colorectum, prostate, urinary bladder and kidneys, curatively exposed to doses of 45 to 65 Gy. These were patients with rather long-term prognoses, who could survive up to the secondary malignancy development, similarly as patients with testicular tumors. Skin basaliomas were excluded from the secondary tumors and the secondary malignancy was always verified by histology. The latency period till the secondary malignancy development was at least of 12 months.

The control group comprised total of 951 men and 134 secondary malignancies (14%) were identified.

The relative risk of the secondary malignancy development in the region of preceding irradiation was low for patients with testicular tumors: 0.529 (Table 14).

Relative risks were furthermore calculated for all the secondary malignancies except for malignant schwammoma in the mediastinum, whose incidence is rare. The highest relative risk of the secondary malignancy induced inside of the field irradiated was found with the malignant skin melanoma (RR = 5.5) and, next to it, with tumors of the pancreas, rectosigmoid, kidney, lungs, urinary bladder and prostate (Table 15). The average latency period till the secondary tumor developed at the site of former irradiation was of 178.3 months, the median period being of 143 months (range 41-418 months, SD 112.3 months). The latency period longer than 60 months was found in 15 patients (88.2%). No difference was found in the latency period for the secondary malignancy location inside or outside of the field irradiated.

Discussion

The number of healed tumor patients is currently increasing and therefore, it is impossible to omit the question of late effects of the treatment and thus also the problem of secondary tumors.

It is to emphasize that not all the secondary tumors are induced by the oncologic treatment. The enhanced risk of secondary malignancies is also supported by a number of factors, such as life style (smoking, alcohol and diet), environment, genetic predisposition of individuals, their hormonal and immunity conditions and many others [5].

Table 13. Secondary malignancies developed after radiotherapy

Second tumor	N	%	RR
Lungs	5	23.8	42.4 (95% IS: 17.1-104.6)
Pancreas	3	14.2	109.3 (95% IS: 31.3-380.5)
Skin	3	14.2	17.8 (95% IS: 5.68-56.0)
Kidney	2	9.5	62.7 (95% IS: 14.4-272.5)
Rectosigmoid	2	9.5	95.5 (95% IS: 21.0-433.5)
Prostate	2	9.5	24.7 (95% IS: 5.9-101.6)
Malignant melanoma	2	9.5	105.4 (95% IS: 22.9-484.8)
Urinary bladder	1	4.9	34.2 (95% IS: 4.5-259.7)
Mediastinum	1	4.9	Not determined
Total of	21	100	

Table 14. Development of secondary malignancies in the region of former irradiation

		Second tumor	
		Yes	No
Group	Observation	17	196
	Expectation	134	817

O/E = 0.529 (95% IS: 0.326-0.857)

Table 15. Secondary malignancies developed in the region of irradiation

Second tumor	N	%	RR
Lungs	5	29.4	1.0 (95% IS: 0.37-2.80)
Pancreas	3	17.6	4.5 (95% IS: 0.91-22.2)
Kidney	2	11.7	1.3 (95% IS: 0.26-6.11)
Rectosigmoid	2	11.7	1.3 (95% IS: 0.26-6.11)
Prostate	2	11.7	0.7 (95% IS: 0.15-3.00)
Melanoma on back	1	5.9	5.6 (95% IS: 0.51-60.9)
Urinary bladder	1	5.9	0.9 (95% IS: 0.10-7.60)
Mediastinum	1	5.9	Not determined
Total of	17	100	

Regardless of the cause, secondary tumors are the sixth most frequent group of malignancies after carcinomas of the skin, prostate, breast, lungs and colorectum [5, 6, 7].

Secondary tumors occur most frequently after irradiation, but their number is increased also when using other treatment modalities.

Chemotherapy with alkylation cytostatics and etoposide increases the number of secondary acute non-lymphatic leukaemias, which are refractory to treatment, and which typically occur as late as 5 to 10 years after the primary chemotherapy.

In addition, the alkylation cytostatic cyclophosphamide is associated with the development of secondary urinary bladder carcinoma.

The hormonal treatment with tamoxifen results in increased number of tumors of the uterus, adenocarcinomas as well as sarcomas [1, 6].

Of course, ionising radiation can induce many types of tumors, but it seems that there is different susceptibility of various organs and tissues.

Based on epidemiology studies, the bone marrow, thyroid and women breast belong to the most radio-sensitive organs. Sarcomas of bones and soft tissues and furthermore tumors of the lungs, stomach, intestine, urinary bladder and pharynx can also occur after irradiation. A possible association with irradiation was also described for tumors of the kidney, ovaries and brain [7].

For the consideration and quantification of the occurrence, it is necessary to establish the relative risk (RR) of the development of secondary malignancies induced by the treatment. For the determination of the relative risk of their origination, the ratio is considered between the number of new primary tumors and the number of tumors expected in the population (RR = O/E – observed/expected). Depending on these values, it is considered whether the differences in the occurrence can be ascribed to a random deviation or to the former therapy [6, 8].

Patients after the treatment of haematological malignancies are followed most frequently and, next to them, there are patients with carcinomas of the cervix, mammary gland and testicular tumors, which are also considered in the work presented here.

We established a hypothesis that in testicular tumors, the relative risk of the secondary malignancy development will be low regardless of the treatment, but it will differ depending on the method of the treatment. We assumed that the RR will be higher in irradiated patients, particularly for the occurrence of secondary malignancies in the region of the preceding radiotherapy.

In our group of 313 patients with primary testicular tumors, the relative risk of the secondary malignancy development was low regardless of the treatment (RR = 1.04). The median follow-up period was not quite 10 years.

A number of authors were interested in the occurrence of secondary malignancies in patients with testicular tumors. For example, in 1997, Travis et al. [4] published the still largest cohort study, which was based on 16 national registers in North America and Europe. The average follow-up period was of 10.2 years.

The diagnosis of secondary malignancies was established in 1406 patients. The relative risk of the secondary malignancy was of 1.43 (95%, IS 1.36–1.51). The risk of solid tumors increased with extending the time after the testicular tumor diagnosis. Patients, who survived for periods longer than 20 years, had the RR of the secondary malignancy development of 1.54.

Bokemeyer and Schmoll [9] compiled a review of works dealing with secondary malignancies. They concluded that in patients with testicular tumors, the risk of the secondary malignancy occurrence is doubled (RR = 0.7x-3.4x) regardless of the treatment modality.

They also published a doubled to tripled risk of the secondary malignancy development if the patients were irradiated.

In a work by Moller et al. [10], also concerning primary testicular tumors, the relative risk of the secondary malignancy development (RR = 1.6) is reported with the median follow-up of 11.6 years for seminomas and 7.4 years for non-seminomas.

In 2005, F. E. Van Leeuwen et al. [11] published an enhanced risk of the secondary non-testicular tumor development (RR = 1.7) in patients with primary testicular tumors, who were followed for at least 12 months after the treatment.

In contrast to the works mentioned, in our group, the relative risk of the secondary tumor development was not increased. We consider the data as exact, since this is a homogeneous group of patients subjected to the treatment and long-term follow-up at one institution.

We also possess detailed data on radiotherapy, including doses and sizes of fields irradiated and on type and doses of chemotherapy.

In the work presented here, we intended to ascertain, whether the radiotherapy of testicular tumors is also associated with an increased risk of the secondary malignancy development in our group, as was the case in the scientific works published.

For example Zablotska et al. [7] describe a significant increase in the risk of the development of all the solid tumors after irradiation for primary testicular tumors (RR = 1.6). They report doubled risk for carcinomas of the stomach, urinary bladder and pancreas and tripled risk for the leukaemia development.

Fossa et al. [4] followed 876 patients with testicular tumors, treated in the Norwegian Radium Hospital in 1956 to 1977. All the patients were irradiated, and not quite a quarter of them were also administered with chemotherapy based on cyclophosphamide and adriamycin.

The secondary malignancy occurred in 65 patients, which resulted in a statistically significantly increased relative risk (RR = 1.58). The risk was even enhanced in the case of concomitant irradiation and chemotherapy (RR = 2.44) or in the

case of irradiation above as well as below the diaphragm (RR = 4.13).

The dependence on the extent of irradiation was particularly found for the secondary lung cancer. The patients irradiated below as well as above the diaphragm had the relative risk of the secondary lung cancer development of 7.69.

As far as a further type of secondary malignancies is concerned, the highest relative risk was found for malignant melanoma (RR = 3.89). Half of the melanomas were present inside of the field irradiated, second half being present outside.

Chao et al. [12] followed 128 patients with non-advanced testicular seminomas, which were irradiated only below the diaphragm without irradiation of supradiaphragmatic nodes. The median follow-up was of 11.7 years. Secondary malignancies occurred in nine patients and the relative risk of the radiation-induced tumor development was of 2.09. The secondary malignancies were located twice in the lungs, and once in each of the following regions – rectum, pancreas, kidney, ureter, adrenal gland and pelvis. In six patients, there were secondary malignancies inside of the irradiated field.

Van Leeuwen et al [13] report an increased relative risk of the gastrointestinal tumor development after irradiation (RR = 2.9); the RR increases to 5.5 if irradiation is combined with chemotherapy. They found a high relative risk of the secondary stomach tumor development (RR = 6.9) in the region of preceding irradiation with median time of the secondary malignancy development of 12.4 years. They also found a higher risk of the leukaemia development after irradiation alone (RR = 5.2), after a combination of irradiation and chemotherapy (RR = 66.7) and after chemotherapy alone (RR = 20).

In an assessment of 131 patients irradiated for stage I and II seminoma, Bachaud et al. [14] report the total relative risk of the secondary malignancy development of 2.81. The risk is low (0.62), if irradiation is performed below the diaphragm only, but considerably increases, when irradiating the supradiaphragmatic region, too (RR = 3.08).

Similarly as in former publications, in our group, radiotherapy was also associated with a significantly increased risk of the secondary malignancy development (RR = 8.38). The occurrence of the secondary malignancies was most frequent in patients with irradiated both infra- and supradiaphragmatic regions. Lung cancer was encountered most frequently, but it did not have the highest relative risk due to its considerable incidence in the population.

In agreement with the work of Fossa et al. [15], we found a high relative risk of the malignant melanoma development after irradiation. A high risk was also present in tumors of the pancreas and rectosigmoid, which is also reported in works by Ganz [1] and Zablotska et al. [7] Relative risks of the development of secondary malignancies in other organs were lower.

In contrast to Zablotska et al. [7], F. E. Van Leeuwen et al. [13] or Chao et al. [12], neither secondary leukaemia nor stomach tumor occurred in our group.

A special group of secondary tumors is formed by those occurring in the region of preceding irradiation.

General criteria for this type of radiation-induced tumors were first defined by Cahan et al. in 1948. These criteria include the tumor origination in the formerly irradiated tissue, histological verification of the secondary malignancy and latency period longer than 5 years [16].

Similar criteria were defined by Goolden in 1951 with the aim to differentiate malignancies occurring as a consequence of local irradiation.

It was necessary to adhere to the following conditions: history of preceding irradiation, determination of the malignancy inside of the formerly irradiated field, clear or microscopically defined radiation damage to surrounding tissues, and long interval between preceding radiotherapy and malignancy development.

Only the first two criteria are considered as principal ones [7, 17].

For example Travis [5] or van Leeuwen et al. [13] evaluated patients, in which the secondary malignancy was produced as soon as after 12 months.

In a work by Stein et al. [18], the development of radiation-induced tumors was followed in patients with clinical stage I testicular seminoma. The secondary tumors adhering to Cahan criteria occurred in three of 81 irradiated patients (4%). In one patient, there was sigmoid adenocarcinoma as the induced tumor, in the second patient there was a urinary bladder tumor from transient cells and the third patient had pancreas carcinoma. The median time till the secondary malignancy development was 92 months (12–168 months).

Hellbardt et al. [19] assessed 122 patients with testicular seminomas, who were solely irradiated after surgery. In 11 patients, the secondary malignancy occurred; in four of them, it was located in the region of preceding irradiation. This was secondary tumor of the urinary bladder in two patients, one rectal adenocarcinoma and one lung adenocarcinoma. The relative risk of the tumor development in the formerly irradiated region was not significantly increased (RR = 2.2, $p = 0.1$).

In a Scottish group, a doubled risk of the secondary malignancy development was observed after irradiation for testicular malignancy. The risk was significantly increased and it was the same for secondary malignancy inside of the irradiated region (RR = 1.94) or outside of it (RR = 1.99). Inside of the field irradiated, urothelial carcinomas occurred most frequently and, in contrast, secondary malignancies in the gastrointestinal tract were not more frequent [6].

In our group, we used the following criteria for the definition of the subgroup of secondary malignancies located in the region of preceding irradiation: development of the secondary malignancy in the field irradiated, histology different from that of the primary tumor and latency period of at least 12 months.

The second tumor occurred in the irradiated region in 17 of 213 patients (i.e. in 8% of patients). The relative risk of the

development of radiation-induced secondary malignancy in the region of preceding irradiation was low: 0.52. The median time till the secondary malignancy development in the region of preceding irradiation was of 143 months (41–418 months).

Most second tumors were found in the lungs: in 4 of 86 patients, who experienced irradiation in supradiaphragmatic region. In spite of this, the relative risk of the secondary malignancy development in the lungs was not increased, since in control group, the lung carcinoma occurred in 43 of 951 irradiated patients, which means RR = 1.03.

Similarly as Fossa et al. [15], we found the highest risk of the malignant melanoma development (RR = 5.58), which is easy to recognize and which can be removed at early stages.

Next to malignant melanoma, there was the highest relative risk of the pancreas carcinoma development. Secondary pancreas carcinoma occurred in 3 of 213 irradiated men with testicular tumor; in the control group it occurred in 3 of 951 patients, which means RR = 4.51.

In the other second tumors located in the formerly irradiated region, the risk was not statistically significantly increased.

Nearly none of studies considering the occurrence of secondary malignancies in testicular tumors includes the second tumor in the second testis into the evaluation.

It is well known that in about 3-5% of patients, second contralateral testicular tumor occurs in the course of the subsequent follow-up. This phenomenon is likely associated rather with the patient biology than with the treatment for the primary tumor [7].

Chemotherapy, which was administered for primary tumor, can even reduce the risk of the contralateral tumor development [9].

As a matter of fact, the second testis is also exposed to scattered radiation in the course of radiotherapy, the doses being of 50-90 cGy according to Hellbardt et al. Given the fact that there is no clear relationship between the radiation dose and the secondary malignancy development, the contribution of radiotherapy to the development of the contralateral testicular tumor cannot be excluded [19].

In a work by Patel et al. [20], the second tumor incidence in the contralateral testis ranges from 1.2% to 3.4%. Identical histological findings were obtained in 44% of patients with primary testicular seminoma and in 39% of patients with primary testicular non-seminoma. Almost a quarter of secondary testicular tumors occurred as late as ten years after the primary tumor diagnosis and thus, necessary follow-up of patients after the treatment should be emphasized.

In our group, the contralateral testicular tumor occurred in 1.9% of patients, the histology being identical.

Our results demonstrate a significantly increased risk of the secondary tumor development in irradiated patients compared to patients treated by chemotherapy. The location of the secondary malignancy inside of the formerly irradiated region does not furthermore enhance this risk.

The risk of the occurrence of second tumors should be included into plan of long-term and complex subsequent follow-up.

References

[1] GANZ PA. Late effects of cancer in adult survivors: What are they and what is the oncologist's role in follow-up and prevention? Am Soc Clin Oncol 2005; 724–730.

[2] VAN LEEUWEN FE,TRAVIS LB. Second cancers. In: De Vita VT, Hellman S, Rosenberg SA. Cancer. Principles and practice of oncology, 7.Edition, Lippincott, 2005: 2575–2598.

[3] HOSKIN P. Secondary malignancies after radiotherapy. Lancet 2002; 3: 577–578.

[4] TRAVIS LB, CURTIS RE, STORM H, et al. Risk of second malignant neoplasms among long-term survivors of testicular cancer. J Natl Cancer Inst 1997; 89: 1429–39.

[5] TRAVIS LB. Therapy-associated solid tumours. Acta oncologica 2002; 41: 323–333.

[6] HAY JH, DUNCAN W, KERR GR. Subsequent malignancies in patients irradiated for testicular tumours. Br J Radiol 1984; 57: 597–602.

[7] ZABLOTSKA LB, MATASAR MJ, NEUGUT AI. Second malignancies after radiation treatment and chemotherapy for primary cancers. In: Chang AE. Oncology, An Evidence-Based Approach, Springer Science+business Media, Inc., 2006: 1929–1940.

[8] MAKUCH R, SIMON R. Recommendations for the analysis of the effect of treatment on the development of second malignancies. Cancer 1979; 44: 250–253.

[9] BOKEMEYER C, SCHMOLL HJ. Treatment of testicular cancer and the development of secondary malignancies. J Clin Oncol 1995; 13: 283–292.

[10] MOLLER H, MELLEMGAARD A, JACOBSEN GK, et al. Incidence of second primary cancer following testicular cancer. Eur J Cancer 1993; 5: 672–676.

[11] VAN LEEUWEN FE, et al. Long-term risk of non-germ cell malignancies in 5-year survivors of testicular cancer. EJC Supplements 2005; 3: 152.

[12] CHAO CKS, LAI PP, MICHALSKI JM, et al. Secondary malignancy among seminoma patients treated with adjuvant radiation therapy. Int J Radiation Oncology Biol Phys 1995; 33: 831–835.

[13] VAN LEEUWEN FE, STIGGELBOUT AM, VAN DEN BELT-DUSEBOUT AW, et al. Second cancer risk following testicular cancer: a follow-up study of 1.909 patients. J Clin Oncol 1993; 11: 415–424.

[14] BACHAUD JM, BERTHIER F, SOULIE M, et al. Second non-germ cell malignancies in patients treated for stage I-II testicular seminoma. Radiotherapy and Oncology 1999; 50: 191–197.

[15] FOSSA SD, LANGMARK F, AASS N, et al. Second non-germ cell malignancies after radiotherapy of testicular cancer with or without chemotherapy. Br J Cancer 1990; 61: 639–643.

[16] CAHAN WG, WOODARD HQ, HIGINGOTHAM NL, et al. Sarcoma arising in irradiated bone. Cancer 1948; 1: 3–29.

[17] GOOLDEN WG. Radiation cancer of the pharynx. Br Med J 1951; 2: 1110–1117.

[18] STEIN ME, LEVIOV M, DRUMEA K, at al. Radiation-induced tumours in irradiated stage I testicular seminoma: Results of a 25-year follow-up (1968-1993). J Surg Oncol 1998; 67: 38–40.

[19] HELLBARDT A, MIRIMANOFF RO, OBRADOVIC M, et al. The risk of second cancer (SC) in patients treated for testicular seminoma. Int J Radiation Oncology Biol Phys 1990; 18: 1327–1331.

[20] PATEL MI, FRACS MM, MOTZER RJ, et al. Management of recurrence and follow-up strategies for patients with seminoma and selected high-risk groups. Urol Clin N Am 2003; 30: 803–817.