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Second malignancies in patients with early stage (I, IIa, IIb) seminoma treated with post-orchidectomy radiotherapy

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Purpose. The evaluation of the risk of second non-germ cell malignancies after radiotherapy for early stage seminoma (I, IIa, IIb – according to Royal Marsden Hospital classification).
Materials and methods. A retrospective analysis of 164 patients with stage I, IIa, IIb seminoma who were treated between 1974 and 1990 with post-orchidectomy irradiation, was performed. 48% of patients had been treated with infradiaphragmatic radiotherapy only (IDRT), while in the remaining 52% prophylactic mediastinal and left supraclavicular irradiation (supradiaphragmatic radiotherapy SDRT) was performed additionally. Median follow-up was 12 years. The risk (O/E) of a second non-germ cell malignancies was estimated by the ratio of the observed number of second malignancies in the analysed group to the expected number of malignancies in the age-adjusted male population.
Results. Overall 5-year and 10-year survival was 92% and 86%, respectively. Twelve patients (7%) developed 13 subsequent non-germ cell malignancies, with a mean interval of 10 years after radiotherapy. The relative risk of second malignancies was 3.55 (95%CI – 1.89-6.07) and was significantly increased. The risk of lung cancer (O/E – 5.55; 95%CI – 2.03-12.04), and rectal cancer (O/E – 11.76; 95%CI – 1.39-41,62) was significantly increased, as compared to the age-adjusted male population.
Conclusions. The risk of second malignancies is significantly increased in patients with early stage seminoma treated with post-orchidectomy radiotherapy.

Wtórne nowotwory u chorych we wczesnym stopniu zaawansowania nasieniaka jądra (I, IIa, IIb), u których zastosowano pooperacyjną radioterapię

Cel. Ocena ryzyka wtórnych niezarodkowych nowotworów u chorych na nasieniaka jądra we wczesnym stopniu zaawansowania (I, IIa, i IIb – wg klasyfikacji Royal Marsden Hospital), u których przeprowadzono uzupełniającą radioterapię.
Materiał i metody. Retrospektywną analizą objęto grupę kolejnych 164 chorych na nasieniaka jądra w stopniu zaawansowania I, IIa i IIb, u których w latach 1974-1990 przeprowadzono radioterapię po uprzednio wykonanej orchidektomii. U 48% chorych obszar napromieniany obejmował wyłącznie układ chłonny podprzeponowy, a u pozostałych 52% chorych dodatkowo napromieniano śródpiersie wraz z lewym nadobojczem. Mediana obserwacji wyniosła 12 lat. Ryzyko wtórnych nowotworów określano w porównaniu do dopasowanej pod względem wieku generalnej populacji mężczyzn, obliczając stosunek liczby nowotworów obserwowanych do oczekiwanych (O/E).
Wyniki. Całkowite przeżycie 5-letnie i 10-letnie wyniosło, odpowiednio: 92% i 86%. W badanej grupie, u 12 chorych (7%) ujawniło się 13 wtórnych nowotworów, a średni czas do ich wystąpienia wyniósł 10 lat. Względne ryzyko (O/E) wystąpienia wtórnych nowotworów w badanej grupie wyniosło 3,55 (95%CI – 1,89-6,07), i było znamiennie podwyższone. Obserwowano znamienny statystycznie wzrost ryzyka wystąpienia raka płuca (O/E – 5,55; 95%CI – 2,03-12,04), i raka odbytnicy (O/E – 11,76; 95%CI – 1,39-41,62) w porównaniu do populacji generalnej mężczyzn.
Wniosek. Ryzyko wtórnych nowotworów jest znamiennie podwyższone u chorych na nasieniaka jądra we wczesnym stopniu zaawansowania, leczonych z zastosowaniem uzupełniającego napromieniania.

Key words: seminoma, radiotherapy, late morbidity, second malignancies
Słowa kluczowe: nasieniak jądra, radioterapia, późne powikłania, wtórne nowotwory

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Introduction

Seminoma accounts for about 40% of testicular germ-cell tumours and it is usually detected in the early stage [1]. Seminoma is a very radiosensitive neoplasm – the standard treatment of stage I-IIa,b seminoma has been orchidectomy followed by radiotherapy to the paraaortic and iliac lymph nodes. The results of this approach are excellent, with 5-year overall survival of 94% to 100% for stage I and 85% to 100% for stage IIa and IIb [1-5].

However, the large number of long-term survivors after succesful treatment of seminoma is at risk for late occurring radiation effects. The most serious late effects observed in patients treated for seminoma are second malignancies. Several studies revealed an increased risk of second malignancies in patients cured from testicular tumours [2, 6-9]. Controversies remain on the increase of the risk of second malignancies, which is attributable to radiotherapy. Some authors did not observe a significant increase in the risk of second malignancies in patients with testicular tumours [10-11], whereas other authors noted an increased risk even in non-irradiated patients [8, 13]. There are suggestions, that the increase in the risk of second malignancies after radiotherapy for testicular tumours may be, to a certain extent, associated with genetic predisposition [14].

Because seminoma is highly curable, the choice of the treatment modality should also be considered in view of its long-term deleterious effects.

The purpose of this study was the evaluation of the risk of second non-germ cell malignancies in a relatively large group of patients from a single institution who survived more than 10 years after the treatment of early stage seminoma.

Material and methods

Material

A total of 201 patients with histologically confirmed stage I and II seminoma were treated with post-orchidectomy radiotherapy at the Cancer Center and Institute of Oncology in Gliwice, between 1974 and 1990. A group of 170 patients was diagnosed with early stage seminoma (I, IIa, IIb), according to the Royal Marsden Hospital classification [15]. Six patients were excluded from the analysis: 4 due to emigration and, thus, loss from follow-up, 1 due to previous chemotherapy and 1 patient due to another cancer existing previously. The final analysis is thus based on long-term follow-up of 164 patients with stage I, IIa and IIb seminoma.

Stage I seminoma was diagnosed in 103 patients (63%), stage IIa and IIb – in 25 patients (15%) and 36 patients (22%), respectively.

Mean patient age was 36 years (21 to 57 years). The diagnostic proceures and clinical evaluation before treatment consisted of: medical history, physical examination, chest radiographs, intravenous pyelogram (IVP), bipedal lymphography (57% of patients) abdominal ultrasonography or CT (45% of patients) and laboratory investigations – blood count with evaluation of hepatic and renal function and urine analysis.

The routine treatment modality was orchidectomy and subsequent irradiation of the regional lymph nodes (after a median of 9 weeks), with or without prophylactic mediastinal and left supraclavicular irradiation. Orchidectomy was performed from a scrotal approach in 84 patients (51%) and from an inguinal approach in 80 patients (49%).

Radiation treatment

Between 1974 and 1985 radiotherapy was delivered using ^{60}Co photons and afterwards with 9-23 MV X photons beams. The PTV in all 164 patients enclosed the paraaortic and iliac lymph nodes bilaterally (infradiaphragmatic radiotherapy-IDRT). After a mean delay of 3 weeks prophylactic mediastinal and left supraclavicular irradiation (supradiaphragmatic radiotherapy-SDRT) was performed in 85 patients (52%). In a group of 103 patients with stage I seminoma, 40 patients (39%) were treated with prophylactic SDRT. In the group of 61 patients with stage IIa and IIb seminoma, 45 patients (74%) were treated with prophylactic SDRT.

IDRT was preformed with ^{60}Co photons in 96 patients (59%) and with high energy X beams in 68 patients (41%), using the two opposed fields (AP+PA) technique. The total radiation dose within the target volume was specified at the midplane and it was, generally, 40 Gy. The dose per fraction was 1.25-1.5 Gy when one field was treated alternately each day or 1.5-2.0 Gy per fraction when both fields were irradiated each day (in 7 patients different dose per fraction was used).

SDRT was performed with ^{60}Co photons in 60 patients (71%) and with high energy X beams in 25 patients (29%). Irradiation was delivered using a three field technique (i.e., mediastinum with AP+PA fields and supraclvicular fossa with one AP field) or with two field technique (i.e., mediastinum and supraclavicular fossa with AP+PA fields). The total radiation dose within the target volume was, on majority, either 35 or 40 Gy, specified at mid-plane. The dose per fraction was 1.0-1.25 Gy when one field was treated alternately each day or 2.0-2.2 Gy per fraction when both fields were irradiated each day.

Endpoints and Statistics

Median follow-up was 12 years (varied from 8 to 315 months), and 96% of living patients were followed-up for a minimum of 5 years. Patients were routinely examined monthly for the first year of observation, at 3 month intervals for the next two years and, thereafter, at 4-6 months intervals. At the long-term observation phase they were examined at 6-month or 12-month intervals.

The overall survival was estimated from the date of surgery using actuarial methods. The incidence of second malignancies was estimated either as a crude rate or using actuarial method. The latency to the occurrence of second malignancies was estimated from the date of completion of radiotherapy. The analysis of second malignancies was based on patient records and, in case of death, also on death certificates. All second malignancies were histologically confirmed.

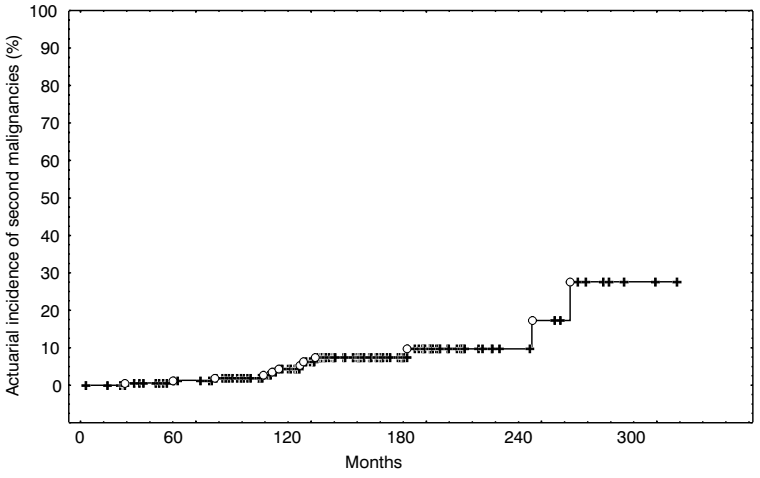
Cancers of the remaining testis were excluded from the analysis because of the probable host predisposition. Non-melanoma skin cancers were also excluded. The risk of second malignancies was estimated by the ratio of the observed number of second malignancies in the study group to the expected number of cancers (O/E) in the age-adjusted male population of Silesia. Cancer incidence rates to calculations were taken from the registry of the Cancer Center and Institute of Oncology in Gliwice (unpublished), which covers the same population as the seminoma patients. The expected number of cancers was calculated on the basis of the person-years at risk and the incidence rates in 1978-1989 for the age adjusted male population [16] by the Epidemiology Department. A Poisson distribution was assumed for the observed cases. Results were considered statistically significant if the 95% confidence intervals for O/E did not include 1.00. The actuarial incidence of second

malignancies was estimated using the Kaplan-Meier method, and the comparison in relation to the treatment volume (IDRT vs. SDRT) was performed with the log-rank test [17].

Results

The actuarial 5-year and 10-year overall survival of the whole group was 92% and 86%.

There were 13 subsequent cancers diagnosed in 12 patients – 6 cases of lung cancer, 2 cases of rectal cancer, 1 case of renal cancer, 1 case of tonsillar cancer, 1 case of stomach cancer, 1 case of melanoma on the arm and 1 case of malignant lymphoma. The mean interval to the occurrence of the second malignancies was 10 years, and varied from 2 to 21 years. The actuarial incidence of second malignancies was 6% at 10 years (Figure 1). Second malignancies occurred in 7 patients treated with IDRT alone and in 5 patients treated with IDRT+SDRT (Table I).



* For patient with two subsequent malignancies time to the first cancer was the basis for calculations

Figure 1. The actuarial incidence of second malignancies

Table I. Second malignancies in the study group

No	PTV*	Radiation dose**	Beam energy (^{60}Co vs XMV)	Second malignancies	Latency (months)	Location with regard to PTV
1	IDRT	40 Gy / 1.25 Gy [–]	^{60}Co	Lung cancer	23	Outside
2	IDRT	40 Gy / 1.25 Gy [–]	^{60}Co	Lung cancer	48	Oudside
3	IDRT	40 Gy / 1.6 Gy [–]	XMV	Lung cancer	122	Outside
4	IDRT	40 Gy / 1.25 Gy [–]	^{60}Co	Tonsillar cancer	70	Oudside
5	IDRT	40 Gy / 1.25 Gy [–]	^{60}Co	Stomach cancer	235	Inside
6	IDRT	40 Gy / 2.0 Gy [–]	XMV	Malignant lymphoma (mesenteric)	170	Close to
7	IDRT	40 Gy/ 1.7 Gy [–]	XMV	Melanoma mal. Rectal cancer	116 140	Outside Inside
8	IDRT+SDRT	40 Gy / 1.5 Gy [30 Gy / 1.25 Gy]	^{60}Co	Lung cancer	100	Close to
9	IDRT+SDRT	40 Gy / 1.6 Gy [14 Gy / 2.0 Gy]	XMV	Lung cancer	114	Close to
10	IDRT+SDRT	40 Gy / 1.25 Gy 35 Gy / 1.25Gy	^{60}Co	Lung cancer	255	Close to
11	IDRT+SDRT	40 Gy / 1.6 Gy [35 Gy / 1.0 Gy]	XMV	Renal cancer	103	Close to
12	IDRT+SDRT	40 Gy / 1.25 Gy [40 Gy / 2.0 Gy]	^{60}Co	Rectal cancer	95	Inside

* IDRT- infradiaphragmatic radiotherapy, SDRT- supradiaphragmatic radiotherapy
** total dose / dose per fraction – IDRT; [total dose/dose per fraction] – SDRT

With regard to treatment portals, 3 cancers developed inside, 5 cases in close proximity to the PTV and in 5 cases, second cancers were located outside the PTV. Second malignancies which were localized in-field developed after mean latency of 13 years, those which were localized in close proximity to the PTV developed after a mean latency of 12 years, but malignancies which were localized out-field occurred after a mean interval of 6 years. In 3 patients from the group treated with IDRT alone, lung cancer developed, however, those patients were habitual smokers and two of those cancers occured shortly after radiotherapy. The patient with tonsillar cancer was a smoker too. The patient who had two subsequent malignancies (skin melanoma on the arm followed by rectal cancer) had a distinct history of familial malignancies.

No significant differences were observed in the freedom from second malignancies between patients treated with IDRT alone or those treated with IDRT+SDRT, actuarial 10-year freedom from second malignancies was 94% and 93%, respectively (log-rank 1.19; p=0.23).

The relative risk of second malignancies was more than thrice that of the age-adjusted male population of Silesia (O/E=3.55), which was statistically significant. Among all second malignancies, the risk of secondary lung and rectal cancer compared to the age adjusted male population of Silesia was significant (Table II).

Table II. The risk of second malignancies

Malignancies	Observed (O)	Expected (E)	Risk (O/E)	95% CI intervals
All	13	3.66	3.55	1.89-6.07
Lung cancer	6	1.08	5.55	2.03-12.04
Rectal cancer	2	0.17	11.76	1.39-41.62

The risk of second malignancies increased over the first 10 years of observation after radiotherapy but decreased thereafter (Table III).

Table III. The risk of second malignancies by follow-up period

Years from radiotherapy	1-4	5-9	≥10
Observed (O)	2	6	5
Expected (E)	0.54	1.09	2.03
Risk (O/E)	3.70	5.50	2.46
95% CI	0.45-13.29	2.03-12.02	0.80-5.74

When separately analysed, the relative risk of second malignancies was significantly increased in the group treated with IDRT only (O/E=5.76; 95% CI=2.48-11.34), but not in patients treated with IDRT+SDRT (O/E=2.22; 95% CI=0.72-5.17).

Discussion

In response to the very favourable prognosis of patients with early stage seminoma and due to the risk of late complications after radiation treatment, a trend towards the reduction of the target dose and treatment volume is observed [3, 18, 19]. Furthermore, for patients with stage I seminoma some authors advocate replacing radiation by mono-chmotherapy [20] or even close surveillence [21]. It is assumed that late morbidity will decrease with the reduction of total radiation dose and PTV. In our study relatively high total doses and extensive treatment volume were used, as compared to the present standards of radiotherapy of seminoma patients [3, 5, 18, 19]. However, even if the PTV is reduced, the risk of radiation-induced carcinogenesis still exists and therefore, it is one of the main arguments against using radiotherapy in the management of early stage seminoma in this group of young patients, as it may considerably compromise survival. The risk of second malignancies may be influenced by many factors such as: duration of follow-up, combination of radiation with chemotherapy, inclusion of malignancies of the remaining testis, homogeneity of the material, sample size and others. In this study we decided to evaluate patients with early stage seminoma only, because of the relatively long expected survival and homogenous treatment (only RT post orchidectomy).

We recorded 13 cases (actuarial risk 6% at 10 years) of second malignancies, the mean interval to their development was 10 years and the risk (O/E) was 3.55. Although, in many studies, the latency to second malignancies increases with longer observation, our results (highest incidence in 5-10 years post-radiotherapy) are probably related to the duration of follow-up, but they are consistent with results of the study of Hanks et al. [2], in which the actuarial incidence of second malignancies was very similar to our results. Table 4 compares the results of the present study and other published articles; it reveals that an increased risk of second malignancies in patients with testicular cancer wasobserved by a majority of authors, with the exception of Coleman et al. [11]. However, in some studies, the increase in the risk of second malignancies did not reach the statistical significance. In the group analysed by Chao et al. [10], the risk of second malignancies was not statistically significant, however, that group was relatively small. Similarly, Horwich and Bell [12], analyzing a relatively large and homogeneous material and excluding cancers of second testis, revealed only a small, statistically insignificant increase in the relative risk.

It is not clear to what extent the incidence of second malignancies relates to radiotherapy and to what extent to ther factors. For instance Kleinerman et al. [8] and Travis et al. [13] report an increased risk of second malignancies even in non-irradiated patients. Dieckmann et al. [14] documented multiple neoplasms in patients with testicular

Table IV. The risk of second malignancies – a comparison of literature data

First author	No. patients	Tumour type*	Treatment	Second malignancies included	Mean follow-up (years)	Risk (O/E)	95% CI intervals	p-value
Horwich [12]	859	S	RT	Non-germ cell**	10	1.27	0.92-1.75	NS
Fossa [7]	876	S + non S	RT +/- CT	Non-germ cell	-	1.58	1.2-2.0	< 0.01
Kleinerman [8]	1,446	S + non S	+/- RT	All / (non-germ cell)	8	2.1 (2.0)	1.0-2.52 (-)	<0.05 (<0.05)
Chao [10]	128	S	RT	Non-germ cell	11.7	2.09	0.39-3.35	NS
Bachaud [6]	131	S	RT +/- CT	Non-germ cell**	11	2.81	1.54-4.72	<0.001
Travis [9]	28,843	S + non S	RT +/- CT	Non-germ cell	10.2	1.43	1.36-1.51	<0.05
Hanks [2]	387	S	RT	All	15	3.4	-	<0.001
Coleman [11]	2080	S + non S	RT +/- CT	All	6.8	0.7	0.5-1.0	NS
Majewski (present study)	164	S	RT	Non-germ cell**	12	3.55	1.89-6.07	<0.05

* S – seminoma, non-S – non-seminoma
** Non-melanoma skin cancer excluded

germ-cell tumours some 30% of which preceded or occurred synchronously to testicular cancer. Such results may reflect the contribution of genetic and enviromental predisposition as additional to radiotherapy.

Although the techniques of irradiation used in our study are historical (SDRT irradiation), the risk of second malignancies was still significantly increased even in patients treated with IDRT only. However, the technique of "inverted Y" has been abandonned in IDRT in early stage seminoma and maybe further reduction of the PTV [3, 18, 19] will lead to the decrease in the risk of second malignancies.

Among all second malignancies reported in our patient group, the most common was lung cancer, which remains in accordance with the observations of Zagars et a. [22]. We have observed that secondary lung cancer incidence was similar in patients treated with IDRT or IDRT+SDRT, and the risk of lung cancer was significantly increased in the whole group of patients treated with post-orchidectomy radiotherapy. That latter fact remains in accordance with the observations of other authors [7, 8]. This may reflect a certain pulmonary sensitivity to the oncogenic effects of irradiation. Tobacco smoking certainly plays an important part in the development of second malignancies. In the present study, all patients who were treated with SDRT and developed lung cancer were habitual smokers. Tobacco smoking habits were probably even more important in patients who were treated with IDRT alone and developed secondary lung cancer. All those patients were habitual smokers, and the interval to the development of cancer in two of these patients was very short, thus not characteristic for radiation-induced cancers [23]. The increased risk of lung cancer in patients who were not irradiated above the diaphragm, observed both in our study and reported by other authors [7], (though insignificant in the latter case) may indicate the additional influence of patient predisposition or enviromental factors.

The rectum, which is in close proximity to the PTV, may be another location of radiation-induced cancers, but the risk of second rectal malignancies reported in the literature is increased slightly and non-significantly [2, 8]. However, some authors observed a significantly higher risk of rectal cancer, as compared to the general population [9, 13]. Also, the time pattern for the developement of rectal cancer reported by Travis et al. [9] in irradiated patients was similar to our results. In our study the risk of second rectal malignancies is increased, however, one patient who developed rectal cancer may have had a genetic susceptibility to malignancies.

Conclusion

The risk of second malignancies is significantly increased in patients with early stage seminoma treated with post-orchidectomy radiotherapy.

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