

BARBARA IZMAJŁOWICZ^{1, A, C, D}, JAN KORNAFEL^{2, E, F}, JERZY BŁASZCZYK^{3, B}

Multiple Neoplasms Among Cervical Cancer Patients in the Material of the Lower Silesian Cancer Registry

¹ Department of Oncology, Gynecological Oncology Clinic, Wrocław Medical University, Lower Silesian Oncology Center in Wrocław, Department of Gynecological Radiotherapy I, Poland

² Department of Oncology, Gynecological Oncology Clinic, Wrocław Medical University, Poland

³ Lower Silesian Oncology Center in Wrocław, Lower Silesian Cancer Registry Wrocław, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article; G – other

Abstract

Background. According to the definition by the International Agency for Research on Cancer (IARC), primary multiple neoplasms are two or more neoplasms of different histopathological build in one organ, or two or more tumors occurring in one patient, regardless of the time of their occurrence (synchronic – up to 6 months, metachronous – after 6 months), coming from an organ or a tissue and not being an infiltration from another neoplasm, a relapse or a metastasis.

Objectives. It was the aim of the study to analyze the frequency of the occurrence of multiple neoplasms among patients suffering from uterine cervix cancer, with a special interest in coexistent neoplasms, the time of their occurrence and total 5-year survivals.

Material and Methods. The data from the Lower Silesian Cancer Registry concerning the years 1984–2009 formed the material of the present study.

Results. 5.3% of all cervix neoplasms occurred as multiple cancers. Cervix neoplasms were 13.4% of multiple neoplasms. On average, cervical cancer occurred as a subsequent cancer in 6 patients yearly (60.7% of the occurrences of cervical cancer were in the period of 5 years following treatment for the first neoplasm). 5-year survival in patients suffering from primarily multiple cervix neoplasms constituted 57% and was convergent with the results for all patients suffering from cervical cancer. Cervical cancer as the first neoplasm occurred in 287 patients, on average in 11 patients annually. In the period of the first 5 years after the treatment of cervical cancer, there were 42.8% occurrences of other cancers. Cervical neoplasms most frequently coexisted with cancers of the breast, lung and large intestine.

Conclusions. The frequency of the occurrence of multiple neoplasm among cervical cancer patients is increasing. Most frequently they coexist with other tobacco-related neoplasms, those related to HPV infections and with secondary post-radiation neoplasms. These facts should be taken into consideration during post-treatment observation and when directing diagnostic and prophylactic tests. Synchronic neoplasms require detailed diagnostics and planning of treatment by a team of specialists. The occurrence of primary multiple cervical neoplasms does not worsen the prognosis as compared to patients suffering exclusively from cervical cancer (*Adv Clin Exp Med* 2014, 23, 3, 433–440).

Key words: primary multiple neoplasms, synchronic neoplasms, metachronous neoplasms, cervical cancer.

According to the International Agency for Research on Cancer (IARC), primary multiple neoplasms are two or more neoplasms occurring in one patient regardless the time of their occurrence (synchronic – up to 6 months, metachronous – after 6 months), coming from an organ or a tissue and not being an infiltration from another neoplasm, a relapse or a metastasis, or there are two

or more neoplasms with different histopathological structure in one organ [1]. Common etiological factors of some cancers, genetic conditioning and the carcinogenic effects of oncological treatment – radiation and cytostatics – are reasons for the occurrence of multiple neoplasms [2, 3]. Taking into account the increasing number of cancer cases, improvement in the effects of their treatment and

the increasing number of people living with cancer, multiple cancers evoke growing interest [4]. According to the data from the National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER), the number of people living with a cancer disease is increasing by 2% annually and in 2001 in the United States there were 10 m such people, i.e. 3.5% of the population [2]. According to the Polish National Cancer Registry, in 2006 there were 320,000 people in Poland with cancer, which is approximately 1% of the population [5]. 5-year overall survival according to SEER data presently constitutes 66% for men and 64.7% for women [6]. The effects of treatment in Poland are worse but improving and are currently 32.9% for men and 51.2% for women [7]. The data from the Lower Silesian Cancer Registry indicates that from 1985 to 2005 5-year survival in men increased from 26.5% to 37.5% and from 42.5% to 52.3% in women [8].

According to the literature data, the frequency of the occurrence of primary multiple cancers varies from 0.73% to 11.7%, and the risk of their occurrence increases with age [4, 9–11]. The SEER register shows that 18% are multiple neoplasms [12]. Compared to the total population, the risk of suffering from neoplasm in patients treated previously for cancer is approximately 14–20% higher [12, 13]. The risk of occurrence of a subsequent neoplasm in women with cervical cancer is 1.3–2.6% for all neoplasms and for lung cancer it is as high as 7.8% [13–15].

The data from the Lower Silesian Cancer Registry indicates that in 1984–2009, in Lower Silesia, there were 249,157 new cases of malignant tumors including 114,220 in women [16]. In the period studied, primary multiple neoplasms were diagnosed in 6160 patients (2.47% of new cases), including 3204 women. In 5969 patients, 2 neoplasms were diagnosed, in 187 patients 3 neoplasms were diagnosed and in 4 patients 4 neoplasms were diagnosed. A permanent increase in the number and frequency of the occurrence of primary multiple neoplasms was observed in the analyzed period from 5 (0.1%) in 1984 to 598 (5.1%) in 2009. The data from the Lower Silesian Cancer Registry shows that the frequency of concurrencies of multiple neoplasms decreases with the time from the diagnosis of the first neoplasm. However, it is worth remembering that during the first 5 years from diagnosis of the first neoplasm, only half were multiple. Multiple neoplasms are slightly more frequent in women but the risk of suffering from multiple neoplasms is higher in men. The most frequent cancers which are followed by multiple neoplasms in women are breast, skin and endometrial cancers. Breast, lung and uterine neoplasms are the most

frequent subsequent cancers in women. The following are the most frequently occurring pairs of cancers in women: breast and uterine body, uterine body and breast, breast and ovary. It is important that the prognosis for patients with a second cancer is better than with the first. In 1984–2004, 5-year survival in women who suffered from a second cancer was 50.5% and was 3.6% better than in the case of the first one.

Material and Methods

Detailed analysis of multiple malignancies in cervical cancer patients with special consideration of coexisting neoplasms, the time of their occurrence and total 5-year survivals was the aim of the present study.

The data obtained from the Lower Silesian Cancer Registry concerning multiple cervical cancers were the material for the detailed analysis. The bases of comparisons were the size of groups and percentages of particular malignancies occurring among patients suffering from cervical cancer. 8119 cases of cervical cancer (7.1 % of all cancer among women) were recorded in the Register in the years 1984–2009. Cervical cancer appeared as the first one in 287 patients among 3204 women suffering from multiple cancers and it appeared in 150 patients as the subsequent one, i.e. 5.4% of all cervix cancers appeared as multiple ones. Cervical cancer constituted 13.6% of multiple neoplasms. Most frequently, cervix cancers appeared together with lung and breast cancers.

Results

Despite a permanent decrease of the number of new cervical cancer cases observed in the years 1984–2009, a distinct increase of multiple neoplasms among cervical cancer patients in this period was observed (Fig. 1, 2).

In the years 1984–2009, cervical cancer occurred as a subsequent cancer on average in 6 patients annually (from 0 to 14) and this frequency increased during the studied period (Fig. 2).

All the cases of cervical cancer appeared during the period of seventeen years after the treatment of the first cancer treatment (Table 1). In the period of 5 years after treatment for the first neoplasms, there were 97 cases (64.7%) of cervical cancer, the most in the first year (Table 1). In 22% of cases (33 patients) there were synchronic neoplasms.

Most cervical cancers occurred in patients suffering from breast, large intestine, skin, uterine

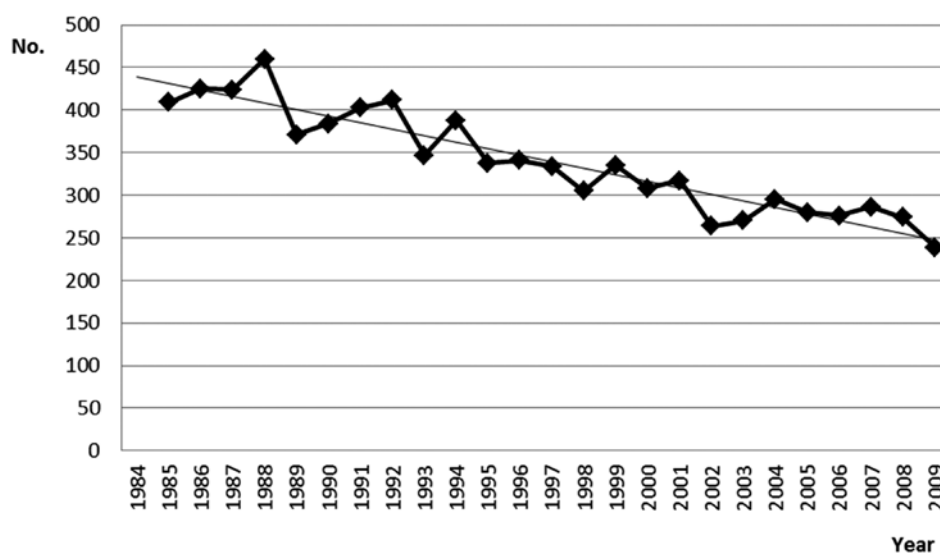


Fig. 1. Diminishing trend in cases of cervical neoplasm in the Lower Silesian Cancer Registry in the years 1984–2009

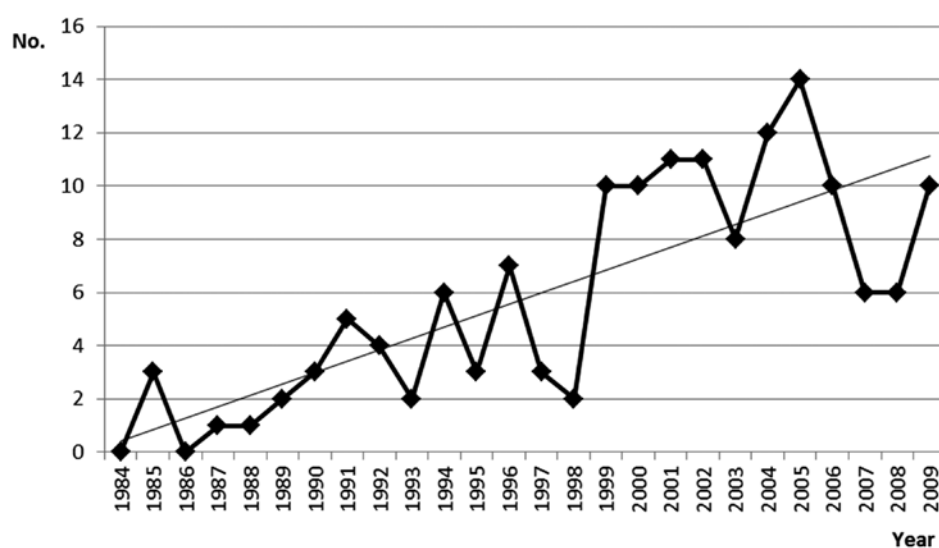


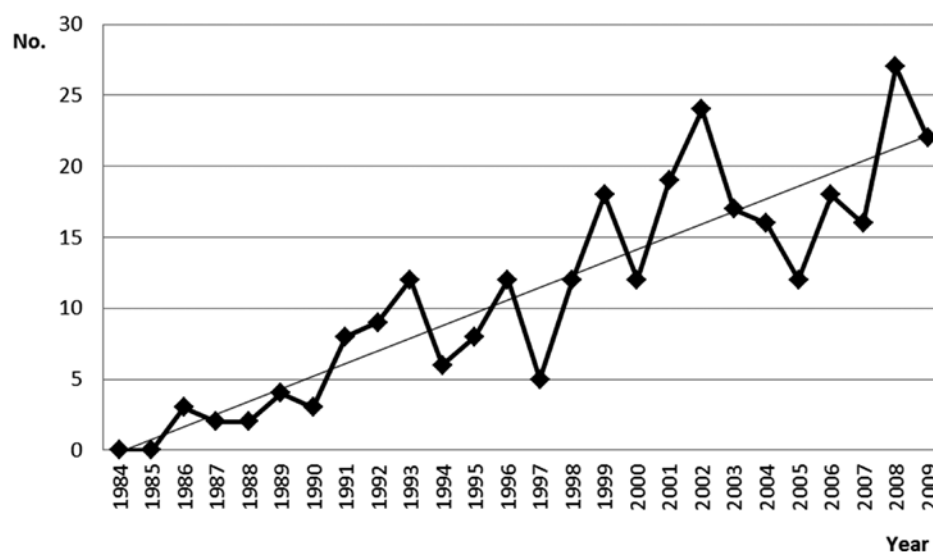
Fig. 2. Growing trend in cases of cervical neoplasm as a subsequent cancer in the Lower Silesian Cancer Registry in the years 1984–2009

Table 1. Cases of cervix neoplasms in patients suffering from multiple cancers in the Lower Silesian Cancer Registry in the years 1984–2009 in subsequent years after diagnosis of the first neoplasm

Year after the first neoplasm	Number of cases	% of cases	Year after the first neoplasm	Number of cases	% of cases
0	38	25.3	9	9	6
1	19	12.7	10	8	5.3
2	8	5.3	11	3	2
3	11	7.3	12	4	2.7
4	15	10.0	13	2	1.3
5	6	4	14	1	0.7
6	8	5.3	15	2	1.3
7	6	4	16	1	0.7
8	6	4	17	3	2

Table 2. Neoplasms after which cervix neoplasm occurred as a subsequent cancer

First location of the neoplasm	Number of cervix neoplasms	%	First location of the neoplasm	Number of cervix neoplasms	%
Breast	38	25.1	Thyroid	3	2.0
Large intestine	21	13.9	Malignant melanoma	2	1.3
Skin	13	8.6	Lymphoma	2	1.3
Corpus uteri	9	5.9	Lip	1	0.7
Ovary	9	5.9	Gallbladder	1	0.7
Bladder	7	4.6	Pancreas	1	0.7
Stomach	7	4.6	Bone	1	0.7
Vulva	6	4.0	Vagina	1	0.7
Lung	5	3.3	Fallopian tube	1	0.7
Leukemia	5	3.3	Multiple myeloma	1	0.7
Larynx	4	2.6	Skin <i>in situ</i>	2	1.3
Rectum	4	2.6	Breast <i>in situ</i>	1	0.7
Kidney	4	2.6	<i>Corpus uteri in situ</i>	1	0.7

**Fig. 3.** Growing trend in cases of the occurrence of subsequent cancers in patients suffering from cervical neoplasm in the Lower Silesian Cancer Registry in the years 1984–2009

body, bladder, stomach and vulva cancers (Table 2). However, taking into account the frequency of occurrence of the first neoplasms, cervical cancer occurred the most frequently in patients suffering from vulva, rectum, lip, bone, lung and bladder cancers.

In 101/150 patients suffering from primary multiple cervix neoplasms having 5 years of observation, the 5-year total survivals were 57% and were convergent with the results in Lower Silesia for all patients suffering from cervical cancer during the studied period.

From 1984 till 2009 cervical cancer as the first malignancy occurred in 287 patients, on average in 11 patients annually and the frequency of the occurrence of subsequent cancers in patients suffering from cervical neoplasms grew in the studied period (Fig. 3).

In the period of the first 5 years after treatment for cervical cancer, there were 123 cases (42.8%) of other malignancies, the majority during the first year (Table 3). In 38 patients (13.2% of cases), they were synchronous neoplasms.

Table 3. Cases of subsequent neoplasms in patients treated primarily due to cervical cancer in the Lower Silesian Cancer Registry in the years 1984–2009 in subsequent years after the diagnosis of the first cancer

Year after contracting cervix neoplasm	Number of cases	% of cases	Year after contracting cervical cancer	Number of cases	% of cases
0	43	15	13	8	2.8
1	27	9.4	14	13	4.5
2	26	9	15	2	0.7
3	17	5.9	16	3	1
4	10	3.5	17	11	3.8
5	14	4.9	18	7	2.4
6	12	4.2	19	9	3.1
7	14	4.9	20	1	0.3
8	13	4.5	21	4	1.4
9	10	3.5	22	3	1
10	13	4.5	23	1	0.3
11	12	4.2	24	1	0.3
12	12	4.2	25	1	0.3

Table 4. Neoplasms which occurred after the treatment of cervical cancer

Subsequent location of the neoplasms	Number of neoplasms	%	Subsequent location of the neoplasm	Number of neoplasms	%
Breast	64	20.9	<i>Corpus uteri</i>	11	3.8
Lung	48	16.7	Stomach	11	3.8
Large intestine	34	11.5	Leukemia	9	2.8
Bladder	27	9	Larynx	6	2.1
Ovary	12	4.2	Kidney	6	2.1
Skin	12	4.2	Other	55	18.8

Cancer of the breast, lung, large intestine, bladder, ovary, uterine body, stomach, leukemia and larynx were the most frequent in patients treated primarily because of cervical neoplasm (Table 4). In total, in patients suffering from cervical neoplasm, the subsequent neoplasms were found in 30 organ locations, and systemic cancers were also observed. In 279 of 287 patients, two multiple neoplasms were diagnosed, in 8 of the 287, three types of cancer were observed (Table 4).

Discussion

In the studied material, cervical cancer appeared most commonly as a subsequent neoplasm, together with vulvae, larynx, rectum, lung,

bladder, breast, large intestine, skin, uterine body, ovary and stomach malignancies. The cancers of breast, lung, large intestine, bladder, ovary, uterine body and leukemia were observed the most frequently in patients treated primarily because of cervical cancer.

These results are convergent with the data from the literature. The following are the most commonly occurring pairs of malignancies, synchronous with cervix neoplasm: cervix-ovary, cervix-uterine body and cervix-kidney. And of metachronous malignancies: cervix-lung, cervix-stomach and cervix-large intestine [17]. Almost 50% of neoplasms occurring together with gastrointestinal tumors are gynecological, among which 77.5% are cervical cancers [18]. Subsequent gynecological cancer occurs in 1.6% of patients with cervical cancer, 4.3%

of patients with vulvar cancer and 9.6% with vaginal cancer [19]. There is no unanimity in the literature concerning the coexistence of uterine cervix and breast cancers. Some of the authors pointed out the diminished risk of suffering from breast cancer after treatment for cervical cancer, which is explained by different etiological factors, different socio-economic status and loss of ovarian function after cervical cancer treatment [20, 21]. However, other series of patients often indicate the coexistence of these cancers.

The common aetiology in patients of cervical cancer is the reason for the increased risk of suffering from lung, esophagus, bladder and kidney cancers – tobacco related cancers and vulvar and rectal cancer – HPV related [14, 20–22]. Stopping smoking by the cancer patient can decrease the risk of suffering from a subsequent cancer of this aetiology. On the other hand, the recently introduced vaccinations against HPV virus should diminish the risk of getting not only cervical cancer but also vulvar cancer as well.

Furthermore, frequent occurrence of bladder, large intestine and ovary cancers and leukemia in patients treated primarily because of cervical cancer has been observed. Taking into consideration the fact that about 60% of cervical cancer patients are treated by pelvic area radiation, these cancers may be induced. The highest risk of leukemia is observed after 5–9 years following radiotherapy [2]. Also, cisplatin used in the combination treatment of cervical cancer increases the risk of leukemia [2]. The large volume of radiated bone marrow applied in patients with cervical cancer increases the risk of leukemia by 11 times compared to patients in whom a small amount of bone marrow is radiated with a high dose [2]. Solid neoplasms occur in the radiated area later than leukemia, most frequently after 10 years [2]. The relative risk (relative risk, RR) of neoplasm occurrence for radiated organs in the pelvis area is 1.2–5.4 for leukemia, 1–1.7 for colon, 1.1–1.8 for bladder 1.0–2.3 for ovaries, 1–1.2 for rectum, 1–1.01 for uterine body, 1–1.1 for bone and 1.2 for soft tissues, however an increased risk for uterine cervix has not been observed [2]. The risk of a subsequent cancer in the radiated area is higher in organs receiving a dose higher than 5Gy, and it falls together with the age of the radiated patients and with time after radiation [12]. The risk of secondary neoplasms after radiotherapy is higher for tobacco-related cancers, which in the case of radiation due to cervical carcinoma refers to the increased risk of bladder cancer developing [12]. It is generally estimated that about 8% of multiple secondary carcinomas are related to former radiotherapy and about 5% of multiple gynecological cancer cases [12, 19]. The risk

of developing a subsequent cancer after radiation oscillates from 1.03 after thyroid neoplasm treatment to 1.78 due to cervical cancer treatment [12]. In patients radiated in the pelvic area, 70% of secondary neoplasms occur in the radiated area [23]. The risk of the development of secondary cancers should be taken into consideration during observation of the patients after treatment, especially that their symptoms can frequently be the same as the side effects of radiotherapy and large intestine and bladder neoplasms after radiation due to cervical cancer. Taking into account the length of time of secondary neoplasm occurrence after radiation, the available data concerns conventional techniques. Observation and risk assessment of secondary neoplasm occurrence is recommended in modern radiotherapy techniques.

In the studied material, in the period of the first 5 years following first cancer treatment, there were 60.7% cases of cervical neoplasms, and in patients treated primarily because of cervical neoplasm, in 42.8% other subsequent cancers occurred. According to data from the literature, metachronous cancers occur after 1–32 years, on average after 3–9 years, and about 50% in the first 5 years after the first neoplasm treatment [15, 18, 23–25]. In the studied group in the situation when the cervical neoplasm was a subsequent cancer, synchronic neoplasms constituted 22% and in the situation when the cervical neoplasm was the first, the synchronic cancers constituted 13.2%. According to the data from the literature, synchronic cancers are 21.4–33.3% of multiple neoplasms, and synchronic gynecological cancers occurring after cervical cancer account for 9% of multiple cancers, with 70% of those as vulvar cancers and 30% vaginal cancers [18, 23, 25].

The high frequency of synchronic cancer occurrence implies the necessity for good diagnostics of the neoplasm before commencing treatment and, in the case of confirmation of synchronic cancer occurrence, treatment planning for both by a team of specialists. Optimal planning of treatment, even of advanced synchronic cancers, can bring good results (e.g. combination treatment with chemotherapy, radiotherapy and surgery in the case of breast cancer in stage IIIb of advancement and cervical carcinoma in stage Ib2) [26].

The occurrence of multiple cancers, especially metachronous ones, stresses the role of observation after treatment in their detection not only after the first 5 years. Attention should be paid to the occurrence of multiple neoplasms of common aetiology being the result of earlier oncological treatment, to directing the interviews and to running additional and prophylactic tests properly during the post-treatment observation period [3].

In the studied group of patients in whom cervical carcinoma was a subsequent cancer, 5 year survivals constituted 57%. In Lower Silesia, the total 5-year overall survival rate in patients with cervical carcinoma also constituted 57% [8]. Thus, in the case of cervical carcinoma, the occurrence of multiple cancers does not worsen the prognosis. Generally the prognosis for all cancers is even better [8, 23]. It may be the result of keeping patients under medical observation and detection of subsequent cancers in the earlier stages of advancement than in the average population [18]. The fact that the occurrence of a subsequent neoplasm does not worsen the prognosis is a reason to qualify patients with multiple cancers to radical treatment if the stage of advancement and general state of the patient allow it. Cases of efficient radical treatment of even more than two synchronic and metachronous neoplasms are known in literature [27–29]. These cases indicate the necessity for histopathological verification of subsequently appearing changes in order to run differential diagnostics of possible metastasis or an independent cancer, which

fundamentally changes the treatment method and as a result influences prognosis.

The frequency of multiple cervical neoplasms increases in relation to the increasing number of cancer cases, improvement of their treatment results and increasing number of people living with cancer. Cervical cancers most frequently coexist with other tobacco-related neoplasms, ones related to HPV infection and neoplasms being the upshot of pelvic minor area radiation. These facts should be taken into consideration during the observation of patients after cancer treatment and should direct the diagnostic and prophylactic tests. Frequent occurrence of multiple neoplasms, and especially induced ones, in the period longer than 5 years after the treatment may suggest that an extension of the follow-up period should be considered. The frequent occurrence of synchronic multiple cervical neoplasms makes detailed diagnostics and treatment planning run by a team of specialists necessary. The fact that the occurrence of primary multiple cervical neoplasms does not worsen the prognosis compared to the patients suffering solely from cervical cancer is worth emphasizing.

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Address for correspondence:

Barbara Izmajłowicz
Department of Oncology, Gynecological Oncology Clinic, Wrocław Medical University
Lower Silesian Oncology Center in Wrocław
Department of Gynecological Radiotherapy I
Hirszfelda 12
53-413 Wrocław
Poland
Tel.: +48 71 36 19 111
E-mail: izmajlow@wp.pl

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