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Multiple primary cancers: a case of successful treatment

Eduardas Aleknavičius,

Nadežda Lachej-Mikerovienė,

Laura Steponavičienė,

Teresė Pipirienė Želvienė

Clinic of Conservative Tumour Therapy,
Institute of Oncology,
Vilnius, Lithuania

Background. Due to advances in early detection and treatment, oncology patients live far longer; therefore, the diagnosis of multiple primary cancers is made more often.

Materials and methods. In this report, we present a case of a female who developed primary ovarian carcinoma and colorectal cancer, breast carcinoma and cancer of ureter and who was treated successfully with a combined modality treatment during an eighteen-year period.

Results. Long-term treatment results of multiple primary cancers are still unknown. Such cancers can occur because of the late sequence of treatment, the influence of lifestyle factors, environmental exposures, host factors, and combinations of these influences. The diagnosis of multiple cancers means that a patient will be treated with an aggressive combined anticancer treatment. Our patient received a combined anticancer treatment four times. Combined treatment allowed to cure ovarian, breast and rectal cancers in this patient. However, there is an open question whether such an aggressive treatment may be related to the occurrence of multiple cancers. It would be difficult to separate the long-term risk of multiple cancers associated with anticancer therapy from undefined genetic predisposition or co-carcinogenesis.

Conclusions. 1. Combined treatment is the most efficacious treatment of malignant tumors. It did not cause severe long-term complications in this case. 2. No resistance to cytostatics developed due to administration of long-term chemotherapy. 3. The increasing rate of multiple primary cancers among successfully treated patients allows to maintain that a constant observation of patients treated for cancer is needed.

Key words: multiple primary cancers, successful anticancer treatment

INTRODUCTION

Because of advances in early detection, supportive care and treatment, the number of cancer survivors has tripled since 1971 and is growing by 2% each year (1). The 5-year relative survival rate after a diagnosis of cancer has increased steadily over the last few decades to reach almost 64% in the mid-1990s (2). According to recent SEER (Surveillance, Epidemiology, and End Results) data, 5-year relative survival rates based on the follow-up of patients through 2004 are 66% (3).

With all these achievements, a new problem of multiple primary cancers arose. The phenomenon of multiple primary malignant neoplasms in the same individual was first described by Billroth at the end of the 19th century (4). Since then, several cases of double or even triple primary malignant neoplasms have been reported.

In earlier published articles, we found cases of multiple primary tumours in children or in very young people treated for Hodgkin's lymphoma or other childhood tumours. Later on, we discovered more cases of second cancer in older patients and in patients treated for various types of cancer.

Commonly, primary multiple cancers are described as two or more tumors of abnormal tissue. They vary in histological structure and may be found in the same or different sites (5). They are not due to recurrence, progression or metastases of the first cancer (6, 7).

Multiple primary cancers generally fall into two categories: synchronous, occuring at the same time (the SEER definition is within 2 months) and metachronous, when cancers follow in sequence (more than 2 months apart) (8).

According to recent SEER data, 14% of newly diagnosed cancers occur in patients with a previously diagnosed malignancy. This percentage is likely to rise as progress is made in the early detection of cancer. Boice et al. reported that, compared with the general population, patients with cancer had a 31% increased risk of developing a second primary tumour at the same site and a 23% increased risk of developing a second tumour at a different site (7).

Second cancers can reflect the late sequelae of treatment; the influence of lifestyle factors (e. g., chronic smoking, drinking, sun exposures), environmental exposures,

Correspondence to: Eduardas Aleknavičius, Institute of Oncology, Vilnius University, Santariškių 1, LT-08660 Vilnius, Lithuania.
E-mail: eduardas.aleknavicius@vuoi.lt

and host factors; and combinations of influences, including gene–environment and gene–gene interactions (9, 10).

Tumors induced by anticancer treatment can develop from radiotherapy and chemotherapy side effects. Radiotherapy and anticancer drugs can affect DNA, modify gene expression, thus leading to unstable genome and to abnormal cell growth and differentiation (11).

MATERIALS AND METHODS

The goal of our paper is to represent a woman, born in 1948, with several primary cancers. Till her first diagnosis of cancer she felt quite well. Her father had a history of gastric cancer, her sister was ill with colorectal cancer, grandmother had a gynecological malignancy, and a niece had a history of uterine and ovarian cancer.

For the first time the diagnosis of cancer was made in March 1986 when she, at the age of 40 years, underwent surgery for ovarian cysts diagnosed by ultrasound. Extirpation of the uterus with adnexes and omentectomy were performed. Histologically, cystcarcinoma from mucous cyst was confirmed. The patient was diagnosed with stage I (T1, N0, M0) carcinoma of the right ovary. From April till May she was treated with external beam radiotherapy by Co60. The lower pelvis was irradiated with two opposite 22–16 cm anterior and posterior gynecological fields (1.5 Gy/d, 5 times per week) up to the total dose of 39 Gy.

In June of the same year, adjuvant chemotherapy was started with the anticancer drug Lofenal (Lophenalum, N-((4-(bis(2-chloroethyl)amino)phenyl)acetyl)-dl-phenylalanine), which was produced at the Institute of Oncology, Vilnius University. The total dose of Lofenal was 15 g.

In accordance with protocols practiced at that time at the Institute of Oncology, the maintenance polychemotherapy was allocated. From September 1986 until April 1989, maintenance chemotherapy with Cyclophosphamide (total dose 3.2 g) and 6 cycles of LTFV regimen with intervals every 2, then 6 months was prescribed. One cycle consisted of Thiotepa 20 mg i/v, 5-Fluoruracil 2 g i/v, Vincristine 2 g i/v, Lofenal 0.3 g 1 tab. orally once a day.

In 1989, after the treatment a complete remission was stated. She was observed carefully in the outpatient department during the next years. There is no evidence of recurrence or metastases of ovarian cancer at the time of reporting.

Seven years later (January, 1995) the patient arrived to the Institute of Oncology with the complaint of bloody and mucous stools and abdominal pain. During the examinations, rectoromanoscopy was performed and a bleeding outgrowth involving 2 / 3 of the colon space diameter was found. On 2 February 1995, resection of the rectosigmoid part with end-to-end anostomosis was carried out. Histological examination showed adenocarcinoma mucoides. The diagnosis of rectal carcinoma stage III (T3, N1, M0) was made. Regarding to comorbidities, no radiotherapy was given.

After surgery, six cycles of Mayo adjuvant chemotherapy and maintenance chemotherapy with Ftorafur was administered. She received total doses of 5-FU 24 g, Leucovorin 2.25 g, and Ftorafur 150 g. Till now, follow-up examinations have not shown any progression of the disease.

In November 1999, bilateral mammograms were made and revealed a polycyclic 3×2.5 cm high density mass in the lower-inner quadrant of the left breast. A fine-needle aspiration of the lump was performed, and the cytological material was interpreted as a carcinoma. In December 1999, the patient underwent left modified radical mastectomy. The histopathological report was an infiltrating ductal adenocarcinoma without lymph node involvement. No hormone receptors or HER2 status were detected. The diagnosis was carcinoma of the left breast, stage II (T2N0M0). Since a 3-cm tumor was localized in the medial lower quadrant, the adjuvant treatment included distant beam radiotherapy (40 Gy to the left parasternal area; 40 Gy to the left neck and supraclavicular area; 38 Gy to the left axillary area and 40 Gy to the postoperative scar), and oral Tamoxifen (20 mg / day) was provided. Hormonal therapy was suspended in September 2003 because of a venous thrombosis. Chemotherapy was postponed due to persistent thrombocytopenia and leucopenia. In July 2000, chemotherapy according to the CMF (Cyclophosphamide, Methotrexate, 5-FU intravenously) regimen was begun, but after the first CMF cycle the patient refused the further chemotherapy.

The patient remained asymptomatic till January 2004 when she arrived to the Hospital of Vilnius University, Nephrology Division with a complaint of pain in the left waist region. After examining, the left enlarged ureter and left hydronephrosis were found. She subsequently underwent a resection and plastic of the left ureter (with neoimplantation) m.Boari. The pathological features revealed moderately differentiated (G2) transitional cell carcinoma. So, a diagnosis of ureteral carcinoma, stage II (pT2N0M0) was made. Later, in October 2004, excretory urography showed the non-functional left kidney, and left nephrectomy was performed.

Since then, the patient was kept at a close watch at the Institute of Oncology. She was well without signs of disease till 2008.

In September 2008, after a CT scan was done, a metastasis in the liver was suspected. In October 2008, liver mass biopsy was performed under the ultrasound control. The pathology report answer was a metastasis of the ureteral carcinoma in the liver. After the abdominal CT scan had been repeated (2008 12 01), a solitary hypervasculated metastasis in the 5th–6th segment of the liver was described (Fig. 1). On 2 December, 2008, percutaneous radiofrequency ablation of the liver metastasis in the 5th–6th segment was performed. No complications were observed.

Control CT scan demonstrated a sufficient ablation with no local or distant progression (Fig. 2). The patient was sent to the medical oncologist to decide about chemotherapy.

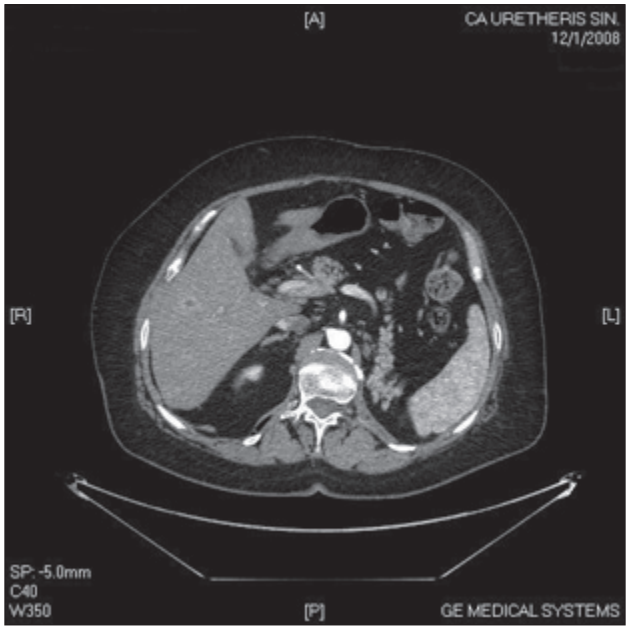

Fig. 1. CT scan shows metastasis in the liver

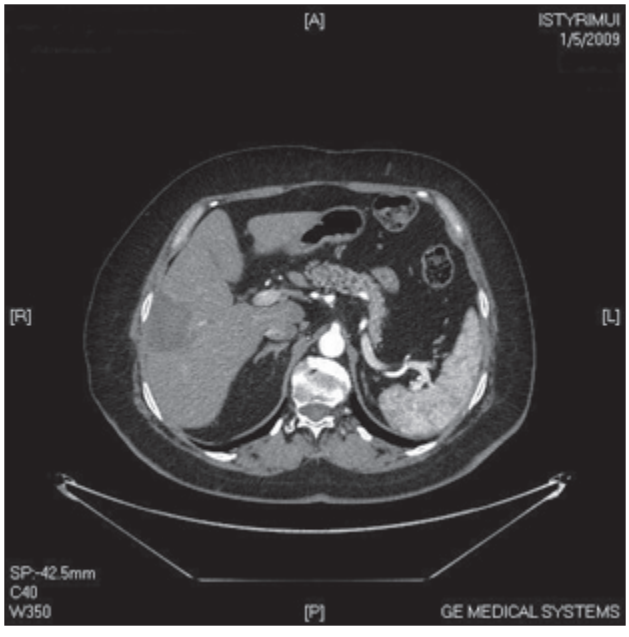

Fig. 2. CT scan shows sufficient ablation of the metastasis in the liver

DISCUSSION

In this report, we present a female who developed primary ovarian carcinoma and metachronous colorectal cancer, breast carcinoma and carcinoma of the ureter within an eighteen-year period. The interval between the first two primary neoplasms was 9 years, the subsequent intervals were 4 and 5 years (Table 1).

What was the cause of developing multiple primary cancers in this case? The patient received various types of anticancer treatment: she was treated with radiotherapy two times, underwent several chemotherapy regimens with different drugs including Lofenal, Thiotepa, 5-FU, Vincristine, Ftorafur, Cyclophosphamide, Methotrexate, and hormonal therapy with Tamoxifen. Aggressive combined treatment was efficacious in this case. No resistance to chemotherapy or severe long-term complications developed. The only possible complication that can be mentioned is development of several primary cancers, but such risk always exists when an aggressive anticancer treatment is administered.

Looking for data on similar cases, we have found that second cancers occure in 5% of ovarian cancer survivors (12). Travis et al. performed a study (13) with the aim to quantify the risk of second malignancies among 32,251 women with ovarian cancer, including 4,402 10-year survivors, reported to selected population-based registries within the United States. Significantly increased risks were observed for all solid combined tumours and for cancers of the colon, rectum, breast, bladder, and eye. Significantly elevated risks of solid tumours developed one year after the diagnosis of ovarian cancer and persisted throughout the follow-up period. Based on the results of this study, about one in five women with ovarian cancer would be expected to develop a new malignancy within two decades. In Travis' study, radiotherapy was associated with cancers of the connective tissue, bladder, and possibly pancreas.

Another study revealed very similar findings (14). In this study, the Stockholm-Gotland Cancer Register was used to evaluate the risk of developing second primary malignancies (SPM) in women diagnosed with cancer of the uterine cervix, uterine corpus and ovaries during the period 1958–1992. Among 5060 patients with ovarian cancer, 379 SPM were found (SIR 1.49; 95% CI 1.34–1.64). Increased risks of cancer of the colon, rectum, breast, uterine corpus, bladder and leukemia were observed.

Genetic and reproductive factors predisposing to ovarian cancer may have contributed to an elevated risk of breast and colorectal neoplasms and possibly ocular melanoma. Thus, excess malignancies following ovarian cancer represent complications of curative therapies and / or underlying susceptibility states that have etiological and clinical ramifications (13).

Table 1. **Short summary of all cancers in this case**

Cancer site	Date of diagnosis	Stage of cancer	Methods of treatment	Time to subsequent cancer
1. Ovarian cancer	1986	Stage I	Surgery + radiotherapy + chemotherapy	9 years
2. Colorectal cancer	1995	Stage III	Surgery + chemotherapy	4 years
3. Breast cancer	1999	Stage II	Surgery + radiotherapy + chemotherapy	5 years
4. Ureteral cancer	2004	Stage II	Surgery	?

Cancer of the rectum could be caused by radiotherapy, since there are data about radiation-induced rectal cancer (15). Radiotherapy increases the risk of cancer occurrence in another site than primary cancer. The risk grows with the time after treatment. The probability of second cancer development depends on the histology of irradiated tissues, total irradiance dose and other unfavourable factors, such as patient's age, additional chemotherapy and others (16). However, cancer of the rectum can be associated with hormonal factors or diet habits.

We can suggest that breast cancer has developed due to similar ethiological factors. Breast and ovarian cancer are reported to share several associations, such as genetic and hormonal factors, which may contribute to an increased risk of a second primary breast or ovarian cancer. Women with a history of breast cancer have a twofold higher risk of developing a subsequent ovarian cancer and those with a history of ovarian cancer have a 1.5 times higher risk of developing a subsequent breast cancer (17).

The occurrence of the other cancers found in this patient may also be linked to her predisposition to malignancy. The family history of this patient can be important because it is the strongest risk factor for ovarian cancer. Three clinical manifestations of hereditary ovarian cancer have been recognized: (1) "site-specific" ovarian cancer, (2) the breast and ovarian cancer syndrome, and (3) the hereditary nonpolyposis colorectal cancer (HNPCC; Lynch II) syndrome. The first two groups are associated with germ line mutations in the BRCA1 and BRCA2 tumor suppressor genes. BRCA1 gene mutation carriers have a 60–85% (tenfold) increased lifetime risk of breast and 40–60% (30–40-fold) increased risk of ovarian cancer. Individuals with mutations in the BRCA2 gene are at slightly lower risks of ovarian and breast cancer as compared with the previously mentioned population. Lynch II syndrome is associated with germ line mutations in the DNA mismatch repair (MMR) genes, primarily hMLH1 and hMSH2. Families with this syndrome are characterized by a high risk for developing ovarian, breast, colorectal, endometrial, stomach, small bowel, renal and ureteral cancers. It has been noticed that hereditary ovarian cancers have a distinctly better clinical outcome with a longer overall survival and recurrence-free interval after chemotherapy than sporadic cancers. Other important clinical genetic predispositions include Cowden, Li–Fraumeni and Peutz–Jeghers symdromes (18, 19). Unfortunately, the genotype of this patient is unknown.

Among other cancer risk factors, in this patient obesity should be mentioned. Besides, she denied alcoholism, smoking.

It is difficult to make a final conclusion about the reason for developing multiple primary cancers in this case. It would be difficult to separate from the long-term risk associated with anticancer therapy, undefined genetic predisposition or co-carcinogenesis (20).

However, further studies concerning the role of common etiology, for instance hereditary and hormonal factors, also studies for clarifying the carcinogenic risks associated with modern therapies for cancer, are needed to increase the knowledge on the etiology of second primary malignancies (14, 20).

An increased awareness is necessary in patients treated for cancer, as the risk of developing a second primary malignancy may exist for many years. Patients should be followed clinically, with appropriate investigations initiated promptly and based on reported symptoms (20).

Our patient was followed carefully by various specialists for many years. The instrumental tests were performed constantly. Also, from 1997 tumor markers (CA 19–9, CEA, CA 125, CA 15–3) were repeated. It should be mentioned that they always remained within normal limits. Thus, new cancers were diagnosed at early stages and treated appropriately.

Our case corresponds to malignancies which usually develop after ovarian cancer treatment. But this case is unique in the sense that even three second primary cancers developed after ovarian cancer. The first three cancers were of benign course, with no metastases or recurrence. Only the last one, cancer of the ureter, had solitary liver metastases. After the successful treatment of the first malignancy (ovarian cancer) the patient has survived 18, after rectal cancer 14 and after breast cancer 10 years. Moreover, the patient, despite the aggressive treatment (chemotherapy, radiotherapy, multiple surgery), is still in good general condition and free of any symptoms.

The future of this patient is unknown. Will there be a recurrence of any tumours or maybe another primary cancer will occur?

CONCLUSIONS

1. Aggressive combined treatment is the most efficacious treatment of malignant tumours.

2. A combination of aggressive treatment modalities did not cause severe long-term complications in this case.

3. No resistance to cytostatics developed due to administration of long-term chemotherapy.

4. The increasing rate of multiple primary cancers among successfully treated patients allows to maintain that a constant observation of patients treated for cancer is needed in order not only to detect metastases or recurrence as early as possible, but also to notice second cancer in time.

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References

1. Cancer survivors: living longer, and now, better. Lancet 2004; 364: 2153–4.
2. Ries LA, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L et al. SEER cancer statistics review. 1975–2000.

Bethesda (MD): National Cancer Institute; 2003. Available from: http://seer.cancer.gov/csr/1975_2000.
3. Surveillance, Epidemiology, and End Results Program, 1975–2004. National Cancer Institute. Available from: http://seer.cancer.gov/statfacts/html/all.html.
4. Billroth T. General surgical pathology and therapy. Guidance for students and physicians. Khirurgiia 1991; 10: 136–43.
5. Multiple Primary Neoplasms: term definition. Available from: http://www.medicalglossary.org/neoplasms_neoplasms_multiple_primary_definitions.html.
6. International Agency for Research on Cancer (IARC). 2004. International rules for multiple primary cancers (ICD-O). 3rd ed., Lyon, World Health Organization. Internal Report No. 2004/02. Available from http://www.iarc.com.fr/MPrules_July2004.pdf.
7. Howe HL, Weinstein R, Hotes J, Kohler B, Roffers SD, Goodman MT. Multiple Primary Cancers of the Ovary in the United States, 1992–1997. North American Association of Central Cancer Registries 2003; 10: 2660–75.
8. Howe HL. A review of the definition for multiple primary cancers in the United States. Workshop proceedings from December 4–6, 2002, in Princeton, New Jersey, North American Association of Central Cancer Registries, Springfield, IL (May 2003).
9. Travis LB, Rabkin CS, Brown ML et al. Cancer survivorship – genetic susceptibility and second primary cancers: Research strategies and recomendations. J Natl Cancer Inst 2006; 1: 15–25.
10. Mayne ST, Cartmel B. Chemoprevention of second cancers. Cancer Epidemiol Biomarkers Prev 2006; 15: 2033–7.
11. Uleckienė S, Didžiapetrienė J, Griciūtė L. Vėžio profilaktika. Lietuvos mokslas, kn. 66. Vilnius: Mokslotyros institutas; 2008; 118–21.
12. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. The Oncologist 2007; 12: 20–37.
13. Travis LB, Curtis RE, Boice JD et al. Second malignant neoplasms among long-term survivors of ovarian cancer. Cancer Res 1996; 56: 1564–70.
14. Bergfeldt K, Einhorn S, Rosendahl I, Hall P. Increased risk of second primary malignancies in patients with gynecological cancer: A Swedish record-linkage study. Acta Oncologica 1995; 6: 771–7.
15. Kazutaka N, Hideyuki I, Shoichi F et al. A case of radiation-induced rectal cancer. Japan J Gastroenterol 2006; 103: 551–7.
16. Atkočius V, Valuckas KP. Įvadas į radiobiologiją. Lietuvos mokslas, kn. 71. Vilnius: Mokslotyros institutas; 2008; 60–83.
17. Liou WS, Hamilton CA, Cheung MK et al. Outcomes of women with metachronous breast and ovarian cancer. Gynecol Oncol 2006; 103: 190–4.
18. Prat J, Ribé A, Gallardo A. Hereditary ovarian cancer. Hum Pathol 2005; 36(8): 861–70.
19. Janavičius R, Kasnauskienė J, Rudaitis V et al. Paveldimas kiaušidžių vėžys. Praktinės gairės gydytojams. Lietuvos akušerija ir ginekologija 2007; 10(3): 230–6.
20. Dent SF, Klaassen D, Pater JL, Zee B, Whitehead M. Second primary malignancies following the treatment of early stage ovarian cancer: Update of a study by the National Cancer Institute of Canada – Clinical Trials Group (NCIC–CTG). Annals of Oncology 2000; 11: 65–8.

Eduardas Aleknavičius, Nadežda Lachej-Mikerovienė, Laura Steponavičienė, Teresė Pipirienė Želvienė

SĖKMINGO DAUGYBINIŲ PIKTYBINIŲ NAVIKŲ GYDYMO KLINIKINIS ATVEJIS

Santrauka

Labai pagerėjus piktybinių navikų ankstyvai diagnostikai, daugybiniai piktybiniai navikai nustatomi vis dažniau, o specifinis gydymas gerokai pailgina onkologinių ligonių gyvenimą.

Medžiaga ir metodai. Šiame straipsnyje pristatome ligos istoriją moters, kuriai per 18 metų išsivystė keturi pirminiai navikai – kiaušidžių, storosios žarnos, krūties ir šlapimtakio, sėkmingai gydyti taikant kombinuotus gydymo metodus.

Rezultatai. Daugybinių pirminių piktybinių navikų ilgalaikiai gydymo rezultatai vis dar nežinomi. Šie navikai gali atsirasti kaip taikyto priešvėžinio gydymo pasekmė, taip pat gali būti nulemti gyvenimo būdo, išorės veiksnių ar individualių paciento savybių. Diagnozavus daugybinius navikus, ligoniui skiriamas agresyvus kombinuotas priešvėžinis gydymas. Minėtai pacientei 4 kartus taikytas agresyvus kombinuotas gydymas padėjo išgydyti ligonę nuo kiaušidžių, krūties ir storosios žarnos vėžio, tačiau lieka neaišku, ar toks agresyvus gydymas nėra susijęs su daugybinių navikų atsiradimu. Labai sudėtinga yra atskirti ilgalaikę riziką atsirasti daugybiniams navikams, susijusią su priešvėžiniu gydymu, nuo genetinio polinkio ir kokancerogenezės veiksnių.

Išvados. 1. Kombinuotas gydymas yra efektyviausias navikinių ligų gydymo būdas. Šiuo atveju jis nesukėlė ilgalaikių gydymo komplikacijų. 2. Pakartotinė ilgalaikė chemoterapija nesukėlė rezistentiškumo citostatikams. 3. Daugybinių navikų skaičiaus augimas tarp sėkmingai išgydytų ligonių leidžia teigti, kad vėžiu sirgusius pacientus būtina nuolat stebėti.

Raktažodžiai: daugybiniai pirminiai navikai, sėkmingas priešvėžinis gydymas