

Multiple Malignant Tumors

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Rezumat

Tumorile maligne multiple

Introducere: datorită îmbunătățirilor diagnosticului și tratamentului pentru numeroase tumori maligne, ne confruntăm în prezent cu pacienți care dezvoltă în timp mai multe tumori maligne.

Metode: am condus o analiză retrospectivă a pacienților diagnosticați cu cel puțin două cancere primitive, internați și tratați în Spitalul Clinic Municipal din Cluj-Napoca. Studiul a urmărit pacienții pe o perioadă de 7,5 ani.

Rezultate: am inclus în studiul de față 217 pacienți (4,33%) cu două sau mai multe tumori maligne primitive din 5003 cazuri diagnosticate cu un cancer primitiv. Cele mai frecvente localizări pentru tumorile multiple au fost sânul, colonul și rectul, vezica urinară, prostata și rinichii.

Concluzii: trebuie întotdeauna să luăm în considerare posibilitatea apariției tumorilor sincrone posibile și trebuie să reținem faptul că un succes terapeutic al bolii canceroase la un pacient nu îl va apăra pe acesta de o nouă tumoră primitivă.

Cuvinte cheie: cancer, tumori multiple primitive, tumori sincrone, tumori metacrone

Abstract

Background: due to the improvement in diagnosis and therapy for certain malignant tumors, we are now faced with patients who develop in time multiple malignancies.

Methods: we conducted a retrospective analysis of the patients diagnosed with at least two primary cancers that were admitted and treated in Cluj-Napoca Municipal Hospital. The study followed patients for a period of 7.5 years.

Results: we included in the present study 217 patients (4.33%) with two or more malignant primary tumors from 5003 cases diagnosed with a primary cancer. The most common sites for multiple malignant tumors were related to the breast, colorectum, urinary bladder, prostate and kidneys.

Conclusions: we should always take into consideration the possibility of synchronous tumors and we have to keep in mind that a successful treatment of cancer might not prevent the onset of another primary mass.

Key words: cancer, multiple primaries, synchronous tumors, metachronous tumors

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Introduction

It is a well-known fact that all over the world cancer disease represents an important cause of death, being exceeded only by cardiovascular diseases. Along with the increase in life expectancy a growing possibility to develop a malignant tumor

was observed, and, in some cured cases, another primary cancer can appear. Life expectancy is increased by several factors, among which are early diagnosis of many diseases, including cancer, through superior imagistic methods and modern therapies. Nowadays, many people with cancer can be cured, and may develop another primary malignancy.

Objectives

Our aim was to evaluate the patients diagnosed with cancer, admitted in Cluj-Napoca Municipal Hospital throughout a period of 7.5 years, which developed multiple malignant tumors in time. We investigated the associations between different types of cancers, the frequency of synchronous and metachronous malignant lesions, the most common types of multiple malignant tumors and their diagnosis and treatment.

Materials and Methods

Our study is a retrospective one, conducted in Cluj-Napoca Municipal Hospital. Between January 2005 and June 2012 5003 patients were admitted and diagnosed with at least a malignant primary tumor at the time of admission or before it. The use of clinical and paraclinical data was approved by the Medical Ethic Committee of Cluj-Napoca Municipal Hospital. The patients signed an informed consent concerning the use of their clinical data for scientific and research issues at the time of admission in the hospital. There were patients with cancer located on the: prostate - 923, urinary bladder - 868, breast - 521, kidneys - 454, colorectum - 420, skin - 147, cervix - 143, stomach - 143, testicles - 112, lymph nodes - 137, endometrium - 90, liver - 70, ovarian - 60, pancreas - 56, thyroid - 32, esophagus - 28, and with history of digestive cancer - 246, history of urological cancer - 195, history of breast cancer - 176, history of genital cancer - 160, history of lung cancer - 9 and history of unknown cancer - 6.

From these 5003 subjects, 217 patients (4.33%) were diagnosed with multiple malignant primary tumors. We included the patients that had at least two malignant primary tumors in our study (but there were patients with 6 cancers). The patients included had malignant primary tumors diagnosed at the same time, before or after a period of time after the first tumor, at different sites but also in the same organ (new cancers developed after 28-35 years after the first cancer). We excluded multiple bladder tumors, knowing that usually they are multifocal and bilateral ovarian cancer, knowing that this type of cancer frequently develops metastases in the contralateral ovary. Some patients presented synchronous tumors (the diagnosis of the second primary no more than 6 months after the index tumor). The patients' age was between 17 to 95 years old, and 154 patients lived in urban places and 63 in the country side. We had a high number of cases with bilateral breast cancers; multiple synchronous colorectal cancers and synchronous association of colorectal cancer with another type of cancer; also cases with multiple urologic cancers. The great majority of cases were metachronous.

Results

Breast cancer was found to be one of the most frequent malignant tumors associated with other primary cancers. Sixty-nine patients (31.79% of 217 patients with multiple cancers, or 13.47% of the 521 patients admitted in our hospital with a breast cancer) were found with at least one breast cancer. Twenty-one patients developed the first breast cancer at an early age under 50 years, before menopause. The median period of time between the two primary cancers was 10.69 years, with limits between 1 and 34 years. Forty patients (7.68% of 521 patients with a breast cancer) were diagnosed with multiple breast cancers: 28 with bilateral breast cancer (developed in a mean period of 11.32 years, with limits between 3 to 28 years), 12 of these having the index tumor in the right breast and the other 16 in the left breast; 9 with synchronous bilateral breast cancer, 2 of these being diagnosed and treated for multifocal tumors (one breast containing 3 tumors and the other 2 tumors). Two patients developed breast cancers in the same breast after a very long period of time (28 years) and in another patient the second malignant tumor appeared 6 years after the first one. The patients were between 34 and 83 years old. A third malignant primary tumor among the patients with a breast cancer was diagnosed in 10 patients (1.92%): ovary, endometrial, gastric, thyroid, retroorbital, kidney, lymphoma and contra-lateral breast. 13 patients (2.49%) with breast cancer were diagnosed also with another type of malignant tumor (cervical, endometrial, ovarian, basocellular carcinoma of the skin, rectal, gastric, melanoma and lymphoma), most of the cases being metachronous (except 3 cases). Breast cancer was the second malignant tumor diagnosed in 7 patients, 5 to 34 years after the index tumor (the average period of time was 13.42 years). The index malignant tumor was breast cancer in 3 patients and it was followed by the second primary cancer after a median period of 8 years (range between 7 to 10 years). 16 patients (4.99%) from the other departments of our hospital had an association of breast cancer with another malignant tumor: bladder, kidney, ovarian, large bowel, thyroid, cervical, vaginal, gastric and endometrial.

Twenty patients (4.76%), 13 men and 7 women, had synchronous colorectal cancers. The average age was 65.87 years (range between 39 to 81 years old). One patient had a familial adenomatous polyposis, and 2 patients had malignant rectocolic polyposis. Most of them had two synchronous cancers, and the maximum was six synchronous malignant colorectal tumors. The diagnosis was established by colonoscopy with biopsy, irigography, computed tomography, abdominal ultrasound. Some of the malignant tumors were diagnosed only intraoperatively and a small part of the multiple tumors were diagnosed after the surgical interventions, in cases other operations being necessary too. We have to mention that it was not possible to perform an entire and complete colonoscopy preoperatively in all our patients because of distal intestinal obstruction. Colorectal tumors were discovered in 35 men and 14 women. There were also

metachronous colorectal cancers developed in these patients: in the sigmoid (either before or after the synchronous lesions), ascending colon, pancreas and prostate. Including all malignant tumors, synchronous and metachronous, there were 53 malignant colorectal primary tumors (1), the most frequent site being the sigmoid colon. The surgical treatment was: segmentary resections with restoration of the bowel continuity usually end-to-end, most of them performed manually and in one patient mechanically (4 cases); hemicolectomies (9 cases); total colectomy with ileo-rectal anastomosis in one patient, with ileal J-pouch (2) in 2 patients; internal by-pass in one patient; Hartmann resections (2 patients); external palliative derivation (2 patients) and one sigmoidostomy. Some of the patients had metastases: liver (6 patients), pulmonary (2 patients), and peritoneal carcinomatosis was described in 2 patients. We had no immediate postoperative deaths, but nowadays only 14 patients are still alive. Associated diseases were described in many patients: ischaemic heart disease and hypertension, diabetes mellitus, alteration of the glucose metabolism, liver cirrhosis, renal chronic failure, bronchial asthma. The histopathological examination revealed tubular, tubulovillous adenocarcinoma, most of them with mild differentiation and some of them poorly differentiated. We also treated 9 patients (4.14% of all multiple cancers) with synchronous malignant tumors, one of them being at colorectal level and the other in some other places: 6 men and 3 women. The most frequent association with a colorectal cancer was a synchronous cancer of the kidney (5 patients); in the other cases there were a gastric, prostatic, breast and pancreatic cancer. Rectum was involved in 6, descending colon in 2 and the transverse colon in one case. One patient had previously had a basocellular carcinoma of the skin one year before. The average age was 67.66 years. At present 8 patients are alive. The surgical interventions for colorectal cancers consisted in: one left hemicolectomy, one segmentary transverse colon resection, one Hartmann procedure, two Miles procedure, two recto-sigmoidal resections, one transversostomy and no operation (because of refuse) in one. The other malignant tumors were treated by radical nephrectomy, total gastrectomy, radical mastectomy, internal biliary-digestive derivative anastomosis for jaundice (pancreatic cancer) and orchidectomy.

In the same period 2440 patients with an urologic cancer (bladder, kidney, prostate) and with a personal history of such malignant tumors were evaluated. 36 patients (4.1%) had multiple urologic cancers: 15 bladder + prostate cancer, 10 bladder + kidney cancer, 8 prostate + kidney cancer and 3 bilateral kidney cancers. Associations of urological cancer with another cancer, either previously or after the urologic cancer were encountered in 40 patients (breast, lung, skin, lymphoma, colorectal, melanoma, gastric, thyroid, larynx, endometrial, cervical, liver, adrenal, osteosarcoma and rhinopharynx cancer). The average age of the patients was 65.32 years (48 to 87 years). The index tumor most frequently encountered was prostate cancer, followed by kidney and bladder cancer. Twelve patients (33.33%) had synchronous tumors: 6 with bladder + prostate cancers (16.66%), 3 (8.33%) with bladder + kidney cancer and 3 with kidney + prostate can-

cer (8.33%). Many patients had associated cardiovascular, respiratory, hepatic, cerebral diseases and diabetes. The diagnosis was established by clinical examinations with laboratory findings and paraclinical investigations (CT, abdominal and endoscopic ultrasound, MRI, bone scintigraphy, PET-CT, bladder cystoscopy, endorectal prostate biopsies). The treatment consisted in surgery, radical or palliative interventions (classic radical nephrectomy or robotic assisted nephrectomy with a da Vinci surgical robot, partial nephrectomy, transurethral cystoscopic resection, radical cystectomy, radical prostatectomy, bilateral orchidectomy and hormonal treatment) followed by adjuvant therapy or oncological therapy in cases with distant metastases. Bladder cancer was described most frequently, followed by prostate cancer and in the end by renal cancer.

The index and the second primary cancer (mentioned between brackets) for all 217 patients with multiple cancers were: Breast=56 (51); Colorectal=44 (29); Urinary bladder = 22 (23); Prostate=16 (22); Kidney=16 (23); Skin cancer=14 (11); Cervical=7 (2); Melanoma=7 (0); Ovary=5 (4); Lymphoma=4 (7); Leukemia=4 (4); Larynx=4 (0); Gastric=3 (6); Liver=3 (1); Pulmonary=3 (8); Sarcoma=3 (0); Testicular=2 (1); Endometrial=2 (8); Vaginal=1 (1); Brain=1; Thyroid=0 (5); Bone=0 (1); Rhinopharynx=0 (1). We may observe that the most frequent index tumors were located in the breast, followed by colorectum, bladder, kidneys, prostate and skin cancers.

The second cancer appeared after a median period of 6.5 years, the 25 and 75 percentiles were 4 and 11 years respectively. The third cancer appeared after a median time of 4 years, the 25 and 75 percentiles being of 7 years and 8.5 years.

Discussions

In 2008, Romania had an incidence for all cancers of 240.6/100,000 (37386 cases) in men, with a mortality rate of 171.4 (27,439 deaths); in women the incidence rate was 179.6 (32,876 cases) with a mortality rate (3) of 91.8 (18,862 deaths).

In 1889 Theodor Billroth [cited by Varty et al. (4)] published for the first time the clinical case of a patient diagnosed with two primitive malignant tumors, the first one a spinocellular carcinoma of the right ear and the second one a gastric carcinoma. Only in 1932 were multiple malignant tumors classified by Warren and Gates (5). The incidence of synchronous malignant breast tumors may vary [0.3%-9%], being increased with the use of mammography (in some studies it is reported to be 5 times greater (6,7)). Metachronous malignant tumors are more frequently diagnosed, their incidence rates varying between 1 and 89%. In our series we had a small number of patients with synchronous cancers and the rest of them with metachronous malignant tumors, the great majority with 2 cancers, many with 3 tumors (9) and a few of them with more than 4 tumors. Some of the most frequent synchronous malignant tumors are breast cancers, mostly because of the use of mammography as a screening method. Usually the metachronous breast malignant lesions were discovered because of the follow-up of the first malignant tumor

diagnosed. This may explain why most of the clinical cases with multiple malignant breast cancers are in early stages of the malignancy, which can offer a better survival. Not all synchronous breast malignant lesions were diagnosed preoperatively, in some cases it was a surprise after the surgical treatment of a supposed benign breast tumor.

Not only the risk for the contralateral breast was increased in a SEER (Surveillance, Epidemiology and End Results) study concerning 182,057 patients diagnosed with a breast invasive carcinoma and irradiated between 1973 to 2000, but also for the lungs, esophagus, pleura, bones and soft tissues (10); they found 15,498 second solid primary cancers, including 6,491 contralateral breast cancers. Our patients underwent neo-adjuvant and/or adjuvant treatment, including radiotherapy and chemotherapy depending on the stage of the malignant breast tumors, as well as hormonal therapy (Tamoxifen).

We have to mention that the malignant tumors appeared after the second primary cancer were not considered as individual observations, but as number of cases already taken into account. Women with a breast cancer have a 2-6 fold increased risk to develop another breast cancer in the contralateral breast, in comparison with women diagnosed with any other cancer (11). Lobular carcinomas tend to develop a contralateral cancer 2.6 times more frequent than invasive ductal carcinomas in the first 6 months after the diagnosis of the in situ carcinoma (12). It is well-known that lobular carcinomas are multicentric. 31.91% of our patients had a lobular carcinoma, 57.45% an invasive ductal carcinoma and 10.64% other types. After a breast cancer, apart from the risk for the contralateral breast (13,14), ovarian, endometrial (15,16), melanoma, thyroid (18), lung (19,20,21), colon cancer and leukemia (22,23) may appear.

New South Wales Central Cancer Registry (24) revealed an increased risk between 1972-1991 to develop a second primary after a colon cancer: small bowel cancers in both sexes, prostate and kidney cancer in men, breast, endometrial, ovarian cancer and thyroid cancer in women. After a rectal cancer, the risk is increased for another colon, prostate and pancreas cancer. In Japan (25) other primaries are described as well (stomach, lung, prostate, larynx, liver, esophagus and urinary bladder in men; uterus, stomach, breast, and liver in women). We had associations of colorectal malignant tumors with prostate, stomach, pancreas, breast, skin and especially with kidney cancer. Also, in the colorectal synchronous cancers group there were patients diagnosed with pancreatic cancer and prostate cancer, as other new primaries.

High dose radiotherapy for cervical cancer (26) offers an increased risk for bladder, rectal, vaginal, bone, endometrial, colon, gastric cancer, non-Hodgkin lymphoma and leukemia. Radiotherapy for a prostate cancer (26% of the patients are irradiated) determines an increased risk for a second primary rectal cancer (27,28), colon cancer (29), bladder cancer (30, 31). Also, after radiotherapy for colon cancer in men under 50 years an increased risk to develop a prostate cancer was observed, but a decreased risk for the same cancer after radiotherapy for rectal cancer (32).

Bladder cancer was observed more frequently in women

with a previous breast, ovarian, or cervical cancer, than in men previously diagnosed with a lung, gastric or larynx cancer; a longer period (16 to 25 years) to develop a bladder cancer was noticed in patients with testicular cancer, cervical and endometrial cancer (33). Bladder cancer was found more frequently in our patients as well, followed by kidney and prostate cancer, but usually the urological cancers were not the first tumor diagnosed.

As mentioned in other studies (34) we had synchronous and metachronous malignant tumors, with and without metastases, part of them being removed in the same surgical session or later, in another one (35).

Conclusions

Even if the analysis of these patients with multiple malignant tumors was not performed on a significant sample of affected population, it represents the activity of a university hospital and may offer a piece of the giant puzzle that is cancer disease. We had patients diagnosed with many urological tumors, which is in accordance with an increased incidence of these malignant tumors. In women, we noticed a large number of patients who developed multiple breast cancers, and in some of them, where a long survival was obtained, the third primary malignant tumour or even the fourth appeared. Published data revealed an increased risk to develop a second primary cancer especially in younger patients, so there is an obvious need for a good surveillance of the patients diagnosed with a cancer. As long as the life expectancy is greater due to an early diagnosis of cancer and to radical therapies for it, we will have more and more patients who will survive and a part of them will develop new malignant tumors. Fortunately, as a result of well-conducted periodical controls, we will in time discover the new primary, if there is one, and this will offer a good chance for patients to survive.

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