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METACHRONOUS COLORECTAL TUMORS IN PATIENTS WITH REGULAR COLONOSCOPIC FOLLOW-EXAMINATIONS

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Summary. *Metachronous colorectal tumors are common colonoscopic finding. Metachronous colorectal adenomas are detected in 20-70.3% of patients, but metachronous colorectal carcinoma (CRC) in 0.5-9% patiens. In this prospective study, 120 patients (80 male, 40 female, mean age 57.9, range 31-77) were evaluated for metachronous tumors after colonoscopic polypectomy for benign single/multiple colorectal tumors or colorectal surgery for CRC. There were 34 (28.33%) patients in whom 58 metachronous tumors (benign and malignant) were detected 12-48 months after previous intervention, localised in different colorectal segments. Metachronous tumors were more frequent in patients with initial multiple tumors than in patients with initial single colorectal tumor. Most of the tumors were found within 24 months from colonoscopic polypectomy or colorectal surgery. It is supposed that initial advanced adenoma and malignant alterated adenoma could be adittional risk factors for development of metachronous adenoma. Metachronous CRC were detected in 6.47-7.69% metachronous tumors in patients originating from different initial groups. Regular colonoscopic follow-up examinations after colonoscopic polypectomy or colorectal surgery for CRC are required. Follow-up colonoscopies may detect colorectal adenomas with different degrees of dysplastic changes, but colonoscopic polypectomy may prevent transformation of adenoma to CRC (adenoma - carcinoma sequence). In the same time follow-up colonoscopies may detect metachronous CRC in early stage, when prognosis after colorectal surgery is much better than after colorectal surgery for advanced metachronous CRC.*

Key words: *Metachronous adenoma, metachronous CRC, colonoscopy, colonoscopic polypectomy*

Introduction

Metachronous (interval, asynchronous) colorectal tumors are defined as a primary colorectal tumors developed 6-12 months after previous colorectal surgery for colorectal carcinoma (CRC) or colonoscopic polypectomy for colorectal polyps (1,2). Metachronous adenomas are detected in 20-70.3% patients after polypectomy. Incidence of metachronous adenomas is 20-60% after removing of single colorectal adenoma (3-10), but 30-70.3% after removing of multiple colorectal adenomas (4,5,9,11). The highest incidence of metachronous adenomas was observed in patients with villous structure of adenomas (12), making villous component of adenoma as a predictor for recurrence of adenoma (13).

Annual incidence rate of metachronous adenoma has been decreased from 0.3-0.4 in the first year after polypectomy to 0.1-0.15 in the next years (14). In the first year after colonoscopic polypectomy metachronous adenomas are detected in 31.8% patients, in the second in 45.2%, but in the third year in 52.6% patients. Metachronous adenomas are less than 10 mm in diameter within two years after polypectomy (4).

New colorectal adenomas tend to be clustered in the same segments as previously removed adenomas (15). In 13-48% patients metachronous adenomas were detected at the same site as previously removed adenomas (4). It is considered that 10% of metachronous adenomas were missed adenomas (10). Secondary metachronous adenomas tend to develop in 30% patients with metachronous colorectal adenomas.

After CRC operation there is a higher risk for development of metachronous adenomas and metachronous CRC (16).

Incidence of metachronous CRC is 0.5-9% (16-39). Metachronous CRC makes 1,6% from a total of resected patients due to CRC (25,40,41). Incidence of metachronous CRC is underestimated because many patients refused to operate on follow-up examinations after resection of initial CRC (27). The average time for detecting metachronous CRC is 7-11 years (25,35,42, 43), range 1-35 years (2,25,29,31,35,42,44-46). Some metachronous CRC were missed synchronous CRC. Within first year after colorectal surgery due to CRC "metachronous" CRC were detected in 24% patients

(22), but within two years in 19-38.6% patients (36,47,48). Early metachronous CRC, detected within three years from colorectal surgery due to CRC were observed in 28.57% of patients developing metachronous CRC (32). Some authors consider that early metachronous CRC were missed synchronous CRC (49).

Colonoscopy is the best diagnostic method for detecting metachronous CRC (50). There are some opinions that during colonoscopy for initial CRC, cancer cells may be implanted in the mucosa of the proximal large bowel segments with possibility for hematogenous or lymphomatogenous spreading (51). Complete preoperative colonoscopy in patients with CRC enables identification of all benign and malignant colorectal tumors with removing of adenomas. Corresponding colonoscopic follow-up programm of patients after colorectal surgery for CRC could be reduced incidence rate of metachronous CRC.

The aim of this study was to evaluate some characteristics of metachronous colorectal tumors (benign and malignant) in patients with regular colonoscopic follow up after colorectal surgery for CRC or after colonosopic polypectomy for colorecatal adenomas.

Patients and Methods

This prospective study was performed in 120 patients (80 male, 40 female, mean age 57.9; range 31-77) after removing of all colorectal adenomas or after colorectal surgery for CRC. Complete colonoscopy to cecum was done in all patients, or within 6 months after colorectal surgery for CRC. and clean colon (colon without tumors) was obtained after 6 months from polypectomy or colorectal surgery. Patients were regularly followed-up in period of 6 months up to 48 months after the clean colon was obtained.

Colonoscopies were performed with Olympus colonoscope types: CF 20HI and CF 30HI. Metachronous colorectal polyps were completely removed by standard or "piece meal" polypectomy techniques. Sessile colorectal polyps, diamters up to 4 mm were removed by hot biopsy forceps (FD 1L), but larger polyps by snare ectomy, using Olympus standard diathermic snares: SD-6 and SD 9/11 and Olympus elestrosurgical unit PSD 2E. Mucosal lesions suspected on malignant tumors were multiply biopsed (4-6) by standard bioptic forceps FB 23K, FB 24K and FB 25K. Classic HE (hematoxilin-eozin) staining for confirmation of pathohistologic processes and histochemic's stainings (AB-PAS, HID/AB) for mucins were used too.

For statistical analysis Student's t test and χ^2 test were applied.

Results

Nature and number of initial tumors are shown in table 1.

Table 1. Nature and number of initial colorectal tumors

Nature of tumor	Single	Synchronous	Total
Benign	16 (32%)	36 (51.43%)	52 (43.33%)
Malignant	34 (68%)	7 (10.0%)	41 (34.17%)
Benign + malignant	-	27 (38.57%)	27 (22.50%)
Total	50 (100%)	70 (100%)	120 (100%)

Control colonoscopies detected metachronous tumors in 34 (28.33%) patients. Metachronous tumors were observed in 3 (18.75%) patients after polypectomy of single, but in 13 (36.11%) patients after polypectomy of multiple colorectal polyps ($p>0,05$). Total of 30.76% metachronous tumors were detected after colonoscopic polypectomy of colorectal polyps.

Frequency of metachronous tumors is higher if previously removed adenomas had advanced pathologic characteristics (diameter more than a 10 mm, severe dysplasia, villous structure of adenoma), and it was observed in 25% patients with initial single and in 37.5% patients with initial multiple adenomas.

In 6 (17.64%) patients metachronous tumors were found in the follow-up period after colorectal surgery for single CRC, but in 2 (28.57%) after large bowel resection due to synchronous CRC. Total of 19.51% metachronous tumors were observed after colorectal surgery due to single or synchronous CRC.

There was not significant difference between frequency of metachronous tumors after polypectomy or after colorectal surgery for CRC ($p>0,05$).

In mixed subgroups of synchronous tumors (initial single or synchronous CRC and single or synchronous aadenomas) metachronous tumors were represented with the next frequency: in 33.33% patients with initial single CRC and single adenoma, 44.44% in patients with initial single CRC and multiple adenomas, but in a half of two patients with synchronous CRC and synchronous adenomas. Total of 37.03% metachronous adenomas were found in patients with different number and/or nature of colorectal tumors.

In 34 patients follow-up colonoscopies detected 58 metachronous tumors, mean 1.71; range 1-8 tumors (Table 2).

Table 2. Number of metachronous tumors

Number of tumors per pts.	Patients		Total of tumors per pts.
	No	%	
1	22	64.70	22
2	8	23.52	16
3	2	5.88	6
6	1	2.95	6
8	1	2.95	8
Total	34	100%	58

Most of patients had single metachronous tumor (statistically significant difference in relation to patients with two or more metachronous tumors, $p<0.001$).

Single metachronous adenoma were observed in patients with inital: single adenoma, single CRC, synchronous CRC, single CRC associated with multiple

adenomas and patients with synchronous adenomas.

Metachronous tumors were found in 9 (18%) patients with initial single but in 25 (35.71%) patients with initial synchronous tumors ($p<0.001$).

Metachronous tumors were diagnosed 12-48 months, mean 21.18 after removing of initial tumors (Table 3).

Table 3. Time interval's of detection of metachronous tumors

Time interval (months)	Patients	
	No	%
12	15	25.86
18	14	24.14
24	15	25.86
30	10	17.24
36	2	3.45
48	2	3.45
Total	58	100.00

Time interval of metachronous tumors detection is: 12-48 months, mean 23.02 for patients with initail single adenoma, 12-36 months, mean 18.85 for patients with initial CRC, but 12-36 months, mean 21.69 for patients with initial benign and malignant tumors.

Metachronous tumors were detected 18-48 months, mean 30.0 after polypectomy of single adenoma, but 12-30 months, mean 21.21 after removing of multiple colorectal adenomas.

Half of patients with Dukes A CRC, 19.04% with Dukes B, and 12.5% patients with Dukes C CRC were developed metachronous CRC.

Within 24 months from intervention we observed 77.73% of all metachronous tumors after initial polypectomy, 85.72% after colorectal surgery due to CRC, but 84.60 % after surgery for associated benign and malignant colorectal tumors (Table 4).

Table 4. Initial nature of tumors and time interval's of diagnostic's of metachronous tumors

Time intervals (months)	Benign		Malignant		Benign + Malignant	
	No	%	No	%	No	%
12	4	12.90	8	57.15	3	23.07
18	10	32.25	1	7.14	3	23.07
24	7	22.58	3	21.43	5	38.46
30	9	29.03	1	7.14	-	-
36	-	-	-	-	2	15.40
48	1	3.24	1	7.14	-	-
Total	31	100.00	14	100.00	13	100.00

Observed differences were not statistically significant ($p>0.05$).

Analysis of metachronous tumors distribution in relation to initial nature of tumor (benign, malignant, benign and malignant) showed that metachronous tumors were the most frequent in the initial benign tumor group, statistically significant differences in relation to initial malignant tumor group, $p<0.05$ (Fig. 1).

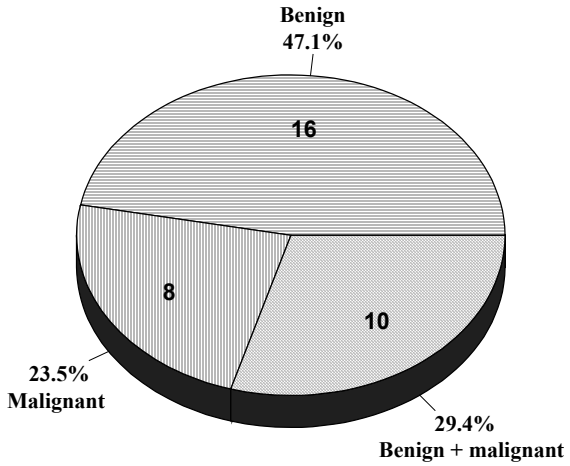

Fig. 1. Frequency of initial tumor nature in patients developing metachronous tumors

Metachronous tumor was found in 42.85% patients after polypectomy of malignant alterated adenoma.

In 25 (35.71%) patients, with different histologic structure of initial synchronous colorectal tumors, metachronous colorectal tumors were found. Multiple adenomas group was the most frequent type of initial synchronous tumors developing metachronous tumors (Table 5).

Table 5. Incidence of metachronous tumors in patients with different synchronous tumors

Nature of synchronous tumors	Patients	Metachronous tumours		Incidence
	No	No	%	
Multiple polyps	36	13	52	36.11
Multiple CRC	7	2	8	28.57
CRC + polyp	14	5	20	35.71
CRC + multiple polyps	10	4	16	40.00
Multiple CRC + multiple polyps	2	1	4	50.00
Multiple CRC + polyp	1	-	-	-
Total	70	25	100	

Synchronous-metachronous tumors were diagnosed in 8% patients with initial solitary but in 11.42% patients with initial synchronous tumors ($p>0.05$), in 9.61% patients with initial benign, 9.75% patients with initial CRC, and in 12.5% patients with initial benign and CRC.

Half of patients were developed metachronous tumors in rectum and sigmoid (Table 6). Total of metachronous tumors of rectum and sigmoid were statistically more frequent finding than metachronous tumors of the right colon (ascending and cecum), $p<0.01$.

Metachronous tumors in patients with initial single or multiple adenomas tend to develop in the same anatomic segment (81.25%).

It was observed, in relation to initial nature of tumors in patients developing metachronous tumors, that metachronous tumors of the left colon and rectum were more frequent than metachronous tumors of the right colon in the initial benign tumors group ($p<0.05$),

and in the group with initial malignant tumors group, p<0.01).

Table 6. Localisation of metachronous tumors

Localisation	Patients		Tumors		Average
	No	%	No	%	
Rectum	8	23.52	15	25.86	1.87±0.72
Sigmoid colon	9	26.48	14	24.14	1.55±0.6
Descending colon	4	11.76	8	13.79	2.00
Transversal colon	6	17.64	11	18.97	1.83±0.74
Ascending colon	4	11.76	7	12.07	1.75±0.64
Cecum	3	8.84	3	5.17	1.00
Total	34	100.00	56	100.00	

Table 7. Histology of metachronous tumors

Histologic structure	Patients	
Tubular adenoma	20	34.48
Tubulovillous adenoma	19	32.76
Villous adenoma	4	6.90
Hyperplastic polyp	8	13.79
Mixed polyp	3	5.17
Adenocarcinoma	4	6.90
Total	58	100.0

Table 8. Histology of metachronous tumors and initial tumor's nature

Histological structure	Benign		Malignant		Benign + Malignant	
	No	%	No	%	No	%
Tubular adenoma	10	32.25	5	35.72	5	38.46
Tubulovillous adenoma	11	35.48	3	21.42	5	38.46
Villous adenoma	3	9.67	-	-	1	7.69
Hyperplastic polyp	4	12.90	3	21.42	1	7.69
Mixed polyp	1	3.23	2	14.29	-	-
Adenocarcinoma	2	6.47	1	7.15	1	7.69
Total	31	100.00	14	100.00	13	100.00

Histologic examinations detected all structures of benign and malignant colorectal tumors, except signet ring cell carcinoma (Table 7).

Metachronous adenomas were dominant histologic finding (74.14%), p<0.001.

Distribution of different histologic structure of metachronous tumors in relation to the initial nature of tumors is presented in table 8.

Metachronous adenomas were more frequent finding in patients with initial benign and malignant tumors than in patients with initial malignant tumors (p<0.01). Metachronous CRC were detected with the almost same frequency in all initial groups (6.47-7.69%).

Dysplasia I was observed in 60.45%, but malignant alteration in 7% metachronous adenomas (Table 9).

Dysplasia I is statistically more frequent than the other grades of dysplastic changes (p<0.001),and it was predominant finding in metachronous tubular adenomas, but dysplasia III and malignant alteration in metachronous villous adenomas.

Pedicle was detected in 34 (62.96%), but broad based polyps in 20 (37.04%) metachronous polyps, p<0.05.

Diameters of the removed metachronous polyps were 3-40 mm, mean 7.46 mm. The average diameter of broad based polyps was 7.9 mm, but pedicle polyps 7.2 mm. The most polyps (79.63%) had diameter up to 10 mm (p<0.001). Diameter's analysis of metachronous tumors in relation to the initial patients group showed that mean diameter of metachronous polyps after removing of benign tumors was 8,36 mm, 5.0 mm after surgery for CRC, but 8.33 mm after colorectal surgery for associated benign and malignant tumors.

Villous metachronous adenomas were larger than tubular metachronous adenomas (p<0.001).

Metachronous colorectal adenomas with advanced features were found 18-30 months after polypectomy of multiple adenomas or after surgery for synchronous CRC associtaed with synchronous adenomas.

Metachronous CRC were detected in patients with initial synchronous CRC or multiple adenomas, 24-48 months after previous intervention.

Discussion

It is well known that most CRC arise in pre-existing adenomas, adenoma-carcinoma sequence (52,53). Winawer et al. recently reported that colonoscopic polypectomy reduces the inicidence of CRC (54). Some Japanesse authors were reported "de novo" CRC (arising in previously normal colorectal mucosa), a new pathogenetic form of CRC (55-57). During the last two decades, colonoscopic polypectomy has been used widely for removal of colorectal polyps. Some studies have reported that after the removal of colorectal adenomas, there is an increased rate (30-70.3%) for development of metachronous colorectal adenomas (3-11,58,59). It is generally accepted that patients who

Table 9. Dysplastic changes of metachronous adenoma

Grade of dysplasia	Tubular		Tubulovillous		Villous		Total	
	No	%	No	%	No	%	No	%
I	16	80.0	10	52.63	-	-	26	60.45
II	4	20.0	5	26.31	1	25.0	10	23.25
III	-	-	2	10.53	2	50.0	4	9.30
Malignant alteration	-	-	2	10.53	1	25.0	3	7.00
Total	20	100.0	19	100.0	4	100.0	43	100.0

have had polypectomy for colonic adenomas need colonoscopic surveillance. Colonoscopy is the procedure of choice for colorectal tumors follow-up (60). The recommendations for colonoscopic surveillance of adenomas have recently been made by National Polyp Study in theUnited States (8), although the exact interval for endoscopic surveillance of patients with colorectal adenomas remains contraversial (61), and vary from intervals of 6 months to several years (62).

It has been established that factors associated with metachronous adenomas are the size and histologic type of the index adenoma, multiplicity of adenomas, family history of CRC, and age of patients (13,58,59).

More than one fourth of patients, in this study, have had asymptomatic metachronous tumors of different nature and size. Tumors were localised in all segments of the large bowel. Frequency of metachronous tumors was higher in the patients with initial benign tumors, than in the patients after colorectal surgery, as same as in the initial multiple adenoma group, and in patients with advanced colorectal adenomas (37.5%), including malignant alterated adenomas (42.85%). Results of this study are broadly similar to those of the other studies (3-11). We suggest that initial advanced adenoma and malignant alterated adenomas could be additional risk factors for metachronous adenoma.

The most of metachronous tumors were observed within 24 months after polypectomy or colorectal surgery (75.86%). Henry et al. have been demonstrated a decrease in recurrence rates after 4 years (5), the same observation as in this study. The finding that most of them were diameters less than 10 mm indicated that they are not overlooked (missed) adenomas, but true metachronous adenomas.

Metachronous tumors tend to be distributed along the large bowel, more frequent in the distal colon and rectum, considering that potential for metachronous tumors varies along the colon.

Adenoma is the most frequent histologic structure of metachronous tumors. Dysplasia I was dominant finding, but dysplasia III and malignant transformation were detected , too.

Malignant alterated adenomas were observed within 48 months from multiple polypectomies of adenomas. Within 24 months from surgery for CRC two other malignant alterated adenomas were found. Detection of metachronous tumors short time after operation in patients with clean colon indicates that metachronous tumors have a higher proliferative and invasive potential than initial tumors. This observation were supported by findings of malignant alterated tubulo-villous adenoma, diameter less than 10 mm, and villous adenoma with dysplasia III, 40 mm in diameter found 24 months after colorectal surgery for synchronous CRC and multiple adenomas.

Diagnostics of metachronous CRC 24-48 months after previous intervention confirmes that regular follow-up colonoscopy should be done in all patients after single or multiple polypectomies or after colorectal surgery for CRC, especially in mentioned period.

It is apparent that those who have metachronous tumors on the second colonoscopy remain at elevated risk for further metachronous adenomas (29%). The data would suggest that those with several negative repeat colonoscopies may revert to a risk of adenomas comparable to the general population and may not require special surveillance (6).

Metachronous colorectal tumors are a common phenomenon in patients after polypectomy or colorectal surgery. Data reported in this study as same as in the literature indicate that metachronous colorectal adenomas usually occur soon after polypectomy, though some may represent polyps missed on the first examination. Periodic surveillance colonoscopy has been recommended after the removal of colorectal adenomas and after colorectal surgery for CRC within 6 months to assess whether the colon has been "cleared". Colorectal tumors detected in this interval were synchronous tumors with initial colorectal tumors. Missinterpretation of these tumors as metachronous will be prevented.

Detection of benign colorectal tumors during the follow up period and colonoscopic polypectomy will prevent genesis of CRC through adenoma-carcinoma sequence (52,53).

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METAHRONI KOLOREKTALNI TUMORI U BOLESNIKA SA PRAVILNIM KONTROLNIM KOLONOSKOPSKIM PREGLEDIMA

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Kratak sadržaj: *Metahroni kolorektalni tumori su čest kolonoskopski nalaz. Metahroni kolorektalni adenomi se otkrivaju u 20-70.3% bolesnika, a metahroni kolorektalni karcinomi (CRC) u 0.5-9% bolesnika. U prospektivnu studiju, nakon kolonoskopske polipektomije benignih solitarnih ili multiplih kolorektalnih tumora ili nakon operacije debelog creva zbog CRC. Uključeno je 120 bolesnika (80 muškaraca i 40 žena, prosečne starosti 57,9 godina, 31-77 godina). U bolesnika su procenjivani metahroni tumori. U 34 (28.33%) bolesnika otkriveno je 58 benignih i malignih kolorektalnih tumora, 12-48 meseci nakon prethodne intervencije sa lokalizacijom u različitim segmentima debelog creva. Metahroni tumori su češći u bolesnika sa inicijalnim multiplim tumorima nego u bolesnika sa inicijalnim solitarnim kolorektalnim tumorima. Većina tumora je otkrivena unutar 24 meseci od kolonoskopske polipektomije ili kolorektalne hirurgije. Predpostavlja se da bi inicijalni uznapredovali adenomi i maligno alterisani adenomi mogli da budu dodatni rizični faktori za razvoj metahronih adenoma. Metahroni CRC su otkriveni u 6.47-7.69% metahronih tumora u bolesnika različitih inicijalnih grupa. Pravilni, kontrolni, kolonoskopski pregledi posle kolonoskopske polipektomije ili kolorektalne hirurgije zbog CRC su neophodni. Kontrolne kolonoskopije mogu da otkriju kolorektalne adenome različitog stepena displastičnih promena, kolonoskopska polipektomija može da spreči transformaciju adenoma u CRC (adenoma-carcinoma sequence). U isto vreme, kontrolne kolonoskopije mogu da otkriju metahrone CRC u ranom stadijumu, kada je posle kolorektalne hirurgije prognoza mnogo bolja nego nakon operacije uznapredovalih metahronih CRC.*

Ključne reči: *Metahroni adenom, metahroni kolorektalni karcinom, kolonoskopija, kolonoskopska polipektomija*

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