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ORIGINAL ARTICLE

Sporadic versus inflammatory bowel disease-related colorectal adenocarcinoma: lessons learned from a single institution experience

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Summary

Purpose: *Inflammatory bowel disease (IBD) - related colorectal adenocarcinoma (CAC) is known to impose a less favorable prognosis than its sporadic counterpart. The determining factor in the prognosis of IBD patients is the early endoscopic detection of commonly occult pre-cancerous lesions. This retrospective study attempted to highlight the distinctive features of IBD-related CAC, as well as the importance of implementing an acceptable surveillance protocol in IBD patients.*

Methods*: The medical records and biopsies of all IBD patients undergoing surgery and of surgical patients with sporadic CAC, admitted in the 5-year period 2010-2014, were examined. Overall, 26 clinicopathological parameters were collected and compared between the two groups.*

Results: *A total of 370 patients with sporadic CAC and 103 patients with IBD were included in the study, of which 8.7% (9/103) proved to have CAC. Cancer in IBD patients appeared at a younger age, had a larger maximum diameter and was more likely to have multiple synchronous locations and a signet-ring cell differentiation ($p<0.05$). Only 25% of IBD patients with CAC had previously followed correct surveillance.*

Conclusions: *The aggressive features of IBD-related CAC, as well as the rising incidence of poorly-surveilled IBD patients that eventually progress to cancer, reflect the necessity of establishing dedicated IBD centers for their optimal follow-up.*

Key words: *cancer, colitis, surveillance*

Introduction

IBD has long been proven to increase the risk for CAC, accounting for 1-2% of all CAC cases. Although ulcerative colitis (UC) was initially thought to provoke the highest risk, colonic Crohn's disease (CD) has been shown to be almost equivalent. The overall risk of cancer can be best estimated through population-based studies. However, there has been a discrepancy in the relative risk among different studies throughout the years [1]. The risk of CAC seems to have decreased over time [2,3] , probably owing to more efficient treatment, earlier surgical operations, better adherence to surveillance protocols, and more correct processing of studies.

Risk factors for IBD-related CAC

Several factors have been confirmed to increase the likelihood of IBD patients to develop cancer; however, the degree of the risk varies among studies [4]. Presence of primary sclerosing cholangitis (PSC) appears to be an important risk factor (OR 4.09; 95% CI, 2.89-5.76 [5,6]), and is associated with an earlier age of developing cancer (9% after 10 years, 31% after 20 years, and 50%

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after 25 years of disease [7]). Longer duration of disease also increases the risk for CAC (0.6% after 10 years, 5.4% after 20 years, and 7.5% after 30 years [8]), though there have been many cases of early CAC (developing before 8-10 years from diagnosis). The extent of disease and degree of inflammation increase the risk, with a standardized incidence ratio (SIR) 5.6 for pancolitis [9]. Young age of onset of IBD raises the lifetime risk; however, patients who are diagnosed with IBD at an older age are associated with early CAC [10]. Family history of CAC and male gender of patients are also associated risk factors [11].

Precancerous lesions in IBD

Dysplasia in IBD can be focal or multifocal, low intermediate or high grade, and may appear adjacent or distant to an underlying carcinoma, but always develops in areas of inflammation [12]. Precancerous lesions in IBD (dysplasia-associated lesions or masses, DALM) can have a versatile appearance, either resembling to a sporadic adenoma (adenoma-like DALM or adenoma-like mass (ALM)), or having non polypoid features, varying from a patchy or plaque-like shape to a nodular or wart-like formation (non-adenoma-like DALM). Both of these types of DALM have a similar endoscopic appearance, making their discrimination sometimes impossible [13].

ALMs are endoscopically identical to sporadic adenomas, having a pedunculated or sessile appearance and no flat component [4]. Synchronous adenomatous lesions (SAL) are another term describing sporadic adenomatous lesions found elsewhere from a synchronous cancer, within or between areas of inflammation, with no adjacent dysplasia [14]. Their histological and molecular similarities led to the conclusion that ALMs represent sporadic adenomas arising from areas of inflamed colon, and, therefore, complete polypectomy regardless of grade of dysplasia is an adequate treatment, with low risk of cancer development [15,16].

Non-adenoma-like DALM is a much more sinister dysplastic lesion, as it is considered to be not only a precursor but also a marker for a synchronous or a metachronous CAC. The discovery of such a lesion in an IBD patient is found to be linked with cancer in more than 50% of cases, making it an indication for a total proctocolectomy with ileoanal pouch, irrespective of its grade [17]. Therefore, the endoscopic discrimination between ALM and non-adenoma-like DALM is critical for the correct management of the IBD patient.

Sporadic vs IBD-related CAC

Both sporadic and IBD-related CAC have a similar dysplasia-to-cancer sequence, similar frequency of major chromosomal abnormalities [18], and usually arise from the surface epithelium rather than from crypts [19]. However, the sequence of mutations has been shown to differ, with p53 mutations occurring early in the course of carcinogenesis in IBD patients, and APC mutations occurring late (probably accounting for the non-polypoid form of IBD cancers) [20]. Cancer in IBD patients is more likely to be diagnosed at an advanced stage [21], probably owing to the fact that they are more often of mucinous or signet-ring cell type, and more likely to consist of multiple synchronous cancers, compared to sporadic cases.

Despite the pathological differences, IBD-related cancer has been shown to have a similar 5-year survival rate post-diagnosis and similar local recurrence risk with sporadic CAC [22]. However, cancer in IBD patients has a higher mortality rate [23], and appears at a younger age (<50 years) compared to sporadic (>65 years) [22]. In fact, cancer in CD seems to appear earlier in the course than in UC (CD mean duration of disease: 16±8 years vs UC: 22±11 years) and has a poorer prognosis [24].

Surveillance recommendations

Such are the similarities between UC and CD that have led to the decision of equal guidelines for the follow-up of patients [25]. Careful colonoscopic surveillance is crucial for preventing CAC and diagnosing early dysplastic lesions.

Due to its subtle gross appearance, non-adenoma-like DALM is frequently missed even by experienced endoscopists [26]. For many years, the best surveillance method for IBD patients has been obtaining multiple random biopsies every 10cm from the entire colon, as well as from every macroscopically visible lesion. This method apart from being inefficient is still prone to miss some important occult lesions.

There are no uniform guidelines amongst the gastroenterological societies worldwide for the surveillance of IBD patients [27]. Most of them recommend that surveillance colonoscopy should begin at year 8 since the onset of symptoms in the case of pancolitis, or at year 15 in left colon colitis, and be repeated in 1-5 years depending on the patient's risk factors [28].

Purpose of the study

In this retrospective study, an effort has been attempted to delineate the distinctive features of IBD-related CAC vs sporadic CAC, and to compare the rates of IBD-related CAC currently observed in the Aretaieion University Hospital of Athens, Athens, Greece, with those observed in worldwide centers, highlighting the importance of adherence to a uniform surveillance protocol.

Methods

In this study included were all the cases of primary CAC and of IBD that were diagnosed from colectomies performed between January 1st 2010 and October 31st 2014 in the Aretaieion University Hospital of Athens. Aretaieion University Hospital is an institution considered a nationwide referral center for IBD surgical treatment.

Endoscopic biopsies, polyp resections, segmental sigmoid or rectal resections, complementary resections, *in situ* CAC, enterectomies, colectomies post neo-adjuvant chemotherapy or radiotherapy, cases with hereditary syndromes such as FAP, and patients whose records could not be retrieved were excluded from our study.

Since there is no electronic database of the patients admitted in our hospital, a strenuous search through the Pathology Department's past biopsies had to be performed. A total of 751 biopsies performed in this 5-year period were examined, of which 473 met the inclusion criteria of the study.

Indications for the colectomies performed in the IBD group were either the endoscopic detection of dysplasia or the failure of medical treatment to control symptoms. All colectomies were performed by senior surgeons of the hospital's surgical unit.

The biopsies collected were interpreted by the chief of the Pathology Department. The patient gender, age at the time of diagnosis and of surgery, as well as the location, size, macroscopic and microscopic features of the sporadic and IBD-related CACs were all carefully registered. Each IBD patient was classified according to the Montreal Classification [29]. Additionally, the medical records of the IBD-related CAC patients was further examined for the presence of PSC, family history of IBD or CAC, and the kind of treatment and follow-up schema applied post-diagnosis. Overall, 26 parameters were examined. Since this was a retrospective study, no informed consent was required.

Statistics

Percentages were calculated for categorical variables and were compared with z-test. Continuous variables were described using the mean value and were compared with unpaired t-test. For each analysis, a p value of <0.05 was considered to be statistically significant.

Table 1. Comparison of findings between sporadic and IBD-related CACs

	Sporadic CAC	*IBD- CAC*
Number of patients	370	9
CD		2
UC		7
Gender, % (No. of pts)		
Male	58.1 (215/370)	77.8 (7/9)
Female	41.9 (155/370)	22.2 (2/9)
Mean age, years (range)		
All	71.1 (34-95)	51.9 (34-80)
Males	70.6 (38-95)	50.4 (37-67)
Females	72.3 (34-95)	57 (34-80)
Mean maximum diameter, cm (range)	4.64 (0.2-11)	6.14 (1.5-18)
Lymph node involvement, % (No. of pts)	48.1 (178/370)	44.4 (4/9)
Multiple synchronous locations, % (No. of pts)	2.4 (9/370)	22.2 (2/9) Both in UC
Total number of neoplasms	380	11
Complete involvement of colonic circumference, % (No. of pts)	34.2 (130/380)	18.2 (2/11)
Complete invasion of colonic wall, % (No. of pts)	81.6 (310/380)	72.7 (8/11)
Location, % (No. of pts)		
Terminal ileum	1.6 (6/370)	0
Cecum	14.3 (53/370)	11.1 (1/9)
Appendix	1 (3/370)	0
Ascending	17 (63/370)	33.3 (3/9)
Hepatic flexure	5.1 (19/370)	11.1 (1/9)
Transverse	7 (26/370)	11.1 (1/9)
Splenic flexure	1.9 (7/370)	0
Descending	4.9 (18/370)	0
Sigmoid	35.9 (133/370)	44.4 (4/9)
Rectum	24.9 (92/370)	44.4 (4/9)
Anus	1 (3/370)	22.2 (2/9)
Grade of differentiation, % (No. of pts)		
High	28.7 (109/380)	18.2 (2/11)
Medium	56.1 (213/380)	27.3 (3/11)
Low	14.5 (55/380)	54.5 (6/11)
Signet-ring cell	1.8 (7/380)	36.4 (4/11)
Mucinous	4.5 (17/380)	27.3 (3/11)
Macroscopic features, % (No. of pts)		
Ulcerative	56.1 (213/380)	54.5 (6/11)
Necrotic	14.5 (55/380)	0
Polypoid	38.4 (146/380)	18.2 (2/11)
Plate-shaped	11.1 (42/380)	0

For abbreviation see text

Results

Sporadic vs IBD – related CAC (Table 1)

In the 5-year period of 2010-2014, 370 patients had sporadic CAC and 103 had IBD (CD/UC=62/41, ratio=1.5), of which 9 (8.7%) had IBD-related CAC (2 had CD [25%] and 7 had UC [75%]).

The number of patients with CD that had a colectomy was significantly higher than of those with UC ($p<0.05$).

The mean patient age with IBD-related CAC was significantly lower (95% CI -26.71,-11.75) compared with patients with sporadic CAC, by about 20 years. The number of males with sporadic CAC was significantly higher ($p<0.05$) than of females. The mean age at surgery per gender did not show any statistically significant difference.

In the 370 patients with sporadic CAC, 380 cancers were found, compared to 11 cancers found in the 9 patients of the IBD group. The percentage of multiple synchronous locations was significantly higher ($p<0.05$) in the IBD group (22.2 vs 2.4%), as was the mean maximum diameter of neoplasms, by about 1.5cm (95% CI 0.254,2.734).

IBD tumors were more likely to have low differentiation. In particular, signet-cell type of CAC was significantly more common in IBD cancers ($p<0.05$). Most IBD and sporadic CAC involved the rectosigmoid. All cancers were visible macroscopically.

IBD – related CAC features (Table 2)

The mean overall duration of IBD before cancer development was 13.8 years (21.5 years for CD and 11.6 years for UC). Two out of 9 patients (22.2%) developed early CAC (occurring within 8-10 years from diagnosis). Well above half of the patients (66.7%) were subjected to conservative medical treatment for their disease prior to surgery. Two out of 9 patients had concomitant PSC (both with UC), one of which developed early CAC. None had a family history of CAC or IBD. Regular surveillance colonoscopy was performed in 25% of the patients; none had undergone a novel- technique colonoscopy.

From the patients with IBD but not CAC, 2 cases with dysplasia, 1 carcinoid of the appendix and 2 adenomas were found.

Discussion

Despite the relatively small number of patients in our study, many facts concerning sporadic and IBD-related CAC proved to be in line with the current knowledge.

Failed surveillance

One main aspect of the present study was to calculate the percentage of cancers found in colectomies performed on IBD patients in our center in the 5-year period 2010-2014. Few retrospective studies focusing on this matter are based on surgical specimens; most studies found in the literature are based on endoscopic biopsies. This is the first such study to be performed in Greece [30], from an institution considered a nationwide referral center for IBD surgical treatment. The

Table 2. Parameters examined in IBD patients with cancer

Parameters	*Total IBD-CAC*	*UC-CAC*	*CD-CAC*
Mean duration of disease (years)	13.8	11.6	21.5
Mean age of onset of IBD (years)	38	40.9	28.5
Extent of inflammation, % (No. of pts) (according to Montreal classification)		Pancolitis (E3): 85.7 (6/7)	Colonic and perianal with penetrating behavior (L2 pB3): 100 (2/2)
Prior medical therapy, % (No. of pts)	66.7 (6/9)	71.4 (5/7)	50 (1/2)
PSC, % (No. of pts)	22.2 (2/9)	28.6 (2/7)	0
Family history	0	0	0
Correct surveillance[1]	25 (2/8)	33.3 (2/6)	0
Pre-op endoscopic diagnosis of CAC	45.5 (5/11)	33.3 (3/9)	100 (2/2)
Adjacent dysplasia	77.8 (7/9)	85.7 (6/7)	50 (1/2)
Synchronous adenomatous lesions (SALs)	33.3% (3/9)	28.6% (2/7)	50% (1/2)

[1]the denominator is 8 instead of 9 because IBD and CAC diagnosis were concurrent in one single patient. For abbreviations see text

Table 3. Studies presenting percentage of CAC found in colectomized IBD patients and comparison with the present study's rate

Year of publication	*Authors*	*Disease examined*	*IBD patients with cancer / Total IBD patients undergoing surgery*	*Country of study*	*Statistically significant difference to this study's percentage (z-test)*
1994	Von Herbay et al.[31]	UC	6.6% (20/301)	Germany	
1996	Shelton et al [32]	UC	5.1% (25/493)	USA	
2000	Gorfine et al [33]	UC	6.4% (38/590)	USA	
2006	Maykel et al [34]	CD	2.7% (6/222)	USA	p<0.05
2013	Scaringi et al [35]	CD	3.5% (11/313)	Italy	
2013	Matsuoka et al [36]	UC	6.5% (83/1274)	Japan	
2014	Murphy et al [37]	UC	2.3% (49/2130)	USA	p<0.05

For abbreviations see text

percentage of cancer cases amongst IBC patients that underwent surgery found in our study (8.7%) is interestingly higher compared to other studies of the same kind, and is also proved to be significantly increased compared to two studies of the last decade (Table 3).

This high percentage, though computed in a relatively small sample, can be attributed to the dramatically poor adherence of IBD patients to the surveillance recommendations. An acceptable surveillance can be determined based on four factors: timing of initial screening colonoscopy, intervals, extent of colon investigated, and number of biopsies obtained [38]. Based on these determinants (except for the latter, which was impossible to be retrieved from the patient records), only 2/8 of our IBD-CAC patients (25%, patient no.1 and no.2, both of which with concomitant PSC) had previously adhered to the recommended protocol of follow-up. Fifty percent (4/8) had false surveillance, and it is interesting to see in what way. Patient no.3 with UC began surveillance at the right timing; however it consisted only of rectosigmoidoscopy, and eventually he developed a right-sided CAC. Patients no.4 and no.5 had their first surveillance colonoscopy 17 and 12 years post-IBD diagnosis, respectively. Patient no.6 had never undertaken a colonoscopy post-diagnosis, and presented with symptomatic CAC. On the other hand, 2/8 (25%) of our IBD-CAC patients followed an over-intensive surveillance. Patient no.7 had a yearly colonoscopy right after IBD diagnosis, and patient no.8 had a colonoscopy once every 2 years for the first 10 years from diagnosis. Patient no.9 did not undertake any surveillance because IBD and CAC diagnosis were concurrent.

The determining factor in the prognosis of IBD patients is the early detection of dysplasia. In fact, only 5/11 of the neoplasms in our IBD patients had been detected from endoscopic biopsy. Three out of 11 were diagnosed as DALM and eventually were proved to be cancer.

This discrepancy in surveillance, finely depicted in these 8 IBD patients who eventually developed CAC, reflects the disorderly notion of the correct follow-up that predominates in Greece. The absence of dedicated IBD centers that would promote the establishment of national guidelines or even the adherence to foreign recommendations appears to be critical for the prognosis of IBD patients. Given the harsh economic status that exists in the country, as well as in many countries worldwide, an efficient and cost-effective way of surveillance would prove beneficial both for the healthcare system and for the patient [39].

An ideal move forward in the management of IBD patients would be the integration of the novel techniques in endoscopy, such as chromoendoscopy, magnification endoscopy and confocal laser endomicroscopy. The concept behind these is the use of a dye, such as indigo carmine, to enhance the detection of non-polypoid lesions that would otherwise be left undetected. Studies have already proved the superiority of these techniques to white light microscopy [40,41], and have led to their usage in advanced healthcare centers, aspiring for an early detection and better prognosis of CAC in IBD patients. Currently in Greece they are used only in few hospitals. However, studies examining their cost-effectiveness have proved them to be less costly than common endoscopy [42], validating the necessity of them to be introduced in the public sector.

IBD patients remain inadequately educated concerning their disease and its complications [43]. Therefore, it is the duty of the health com-

munity to educate them in being aware of their ideal management, even post-surgery. If the prior colectomy resulted in a CAC diagnosis, the risk of recurrence within the pouch may reach up to 25% [44]. If there was no prior neoplasia, frequent surveillance of the pouch is considered unnecessary, even in the presence of PSC. However, biopsies should be obtained, as well as in the case of recurrent pouchitis [45,46].

Signet-ring cell CAC

What triggered the initiation of this study was the observation of the increasing frequency in the diagnosis of signet-ring cell type CAC in the colectomized IBD patients of our center (36.4 vs 1.8% in sporadic CAC). In general, the vast majority of signet-ring cancers are known to arise from the stomach, the rest arising from other sites such as breast, gallbladder, pancreas, urinary bladder, colon, and prostate [47]. Although the molecular pathology of signet-ring cancers is beginning to be unveiled [48], their association with IBD still remains peculiar, given that they generally account for less than 1% of all colorectal cancers [49]. Despite the rarity in their occurrence, their clinical importance is significant, as they tend to develop at a younger age, show a worse tumor grade, appear at a more advanced stage and have a much poorer prognosis compared to sporadic CAC (5-year survival: 9.4%) [50,51]. It has also been noted that signet-ring type of CAC metastasizes predominantly to the peritoneum and the ovaries, and is less likely to spread to the liver and lungs [52]. Since the incidence of signet-ring CAC is on the rise [53], a link to a possible explanation is yet to be found.

Limitations

This study describes a single institution experience, using a relatively small sample size of a selected patient population. Due to its retrospective design, the staging and survival of the patients were not explored.

Conclusion

The present study attempted to corroborate the current knowledge that IBD-related CAC is a special type of cancer, with specific features that tend to impose a less favorable prognosis than its sporadic counterpart. It is highly stressed that healthcare systems should provide IBD patients with the best of prevention through dedicated IBD centers which implement updated surveillance protocols that are both cost-effective and optimal for the IBD patient follow-up.

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References

1. Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis 2013;19:789-799.
2. Jess T, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology, 2012;143:375-381.
3. Lichtenstein GR. Reduction of colorectal cancer risk in patients with Crohn's disease. Rev Gastroenterol Disord 2002;2 (Suppl 2) :S16-24.
4. Rutter M. Importance of Nonpolypoid (Flat and Depressed) Colorectal Neoplasms in Screening for CRC in Patients with IBD. Gastrointest Endosc Clin N Am 2014;24:327-335.
5. Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. Gastrointest Endosc 2002;56:48-54.
6. Lindström L, Lapidus A, Ost A, Bergquist A. Increased risk of colorectal cancer and dysplasia in patients with Crohn's colitis and primary sclerosing cholangitis. Dis Colon Rectum 2011;54:1392-1397.
7. Velayos FS, Loftus EV, Jess T et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. Gastroenterology 2006;130:1941-1949.
8. Lakatos L, Mester G, Erdelyi Z et al. Risk factors for ulcerative colitis-associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: results of a population-based study. Inflamm Bowel Dis 2006;12:205-211.
9. Soderlund S, Brandt L, Lapidus A et al. Decreasing time-trends of colorectal cancer in a large cohort of patients with inflammatory bowel disease. Gastroenterology 2009;136:1561-1567.
10. Baars JE, Kuipers EJ, van Haastert M, Nicolaï JJ, Poen AC, van der Woude CJ. Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey. J Gastroenterol 2012;47:1308-1322.
11. Askling J, Dickman PW, Karlen P et al. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. Gastroenterology 2009;120:1356-1362.
12. Svrcek M, Cosnes J, Beaugerie L et al. Colorectal neoplasia in Crohn's colitis: a retrospective comparative study with ulcerative colitis. Histopathology 2007;50:574-583.
13. Chen Y X, Qiao L. Adenoma-like and non-adenoma-like dysplasia-associated lesion or mass in ulcerative colitis. J Dig Dis 2013;14:157-159.
14. Rubio CA, Slezak P. The unique pathology of nonpolypoid colorectal neoplasia in IBD. Gastrointest Endosc Clin N Am 2014;24:455-468.
15. Quinn AM, Farraye FA, Naini BV et al. Polypectomy is adequate treatment for adenoma-like dysplastic lesions (DALMs) in Crohn's disease. Inflamm Bowel Dis 2013;19:1186-1193.
16. Vieth M, Behrens H, Stolte M. Sporadic adenoma in ulcerative colitis: endoscopic resection is an adequate treatment. Gut 2006;55:1151-1155.
17. Mescoli C, Frego M, Rugge M. Pathology of dysplasia and cancer in inflammatory bowel disease. Ann Ital Chir 2011;82:11-18.
18. Breynaert C, Vermeire S, Rutgeerts P, Van Assche G. Dysplasia and colorectal cancer in inflammatory bowel disease: a result of inflammation or an intrinsic risk? Acta Gastroenterol Belg 2008;71:367-372.
19. Shih le-M, Wang TL, Traverso G et al. Top-down morphogenesis of colorectal tumors. Proc Natl Acad Sci USA 2001;98:2640-2645.
20. Rhodes JM, Campbell BJ. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. Trends Mol Med 2002;8:10-16.
21. Kiran RP, Khoury W, Church JM, Lavery IC, Fazio VW, Remzi FH. Colorectal cancer complicating inflammatory bowel disease: similarities and differences between Crohn's and ulcerative colitis based on three decades of experience. Ann Surg 2010;252:330-335.
22. Dyson JK, Rutter MD. Colorectal cancer in inflammatory bowel disease: what is the real magnitude of the risk? World J Gastroenterol 2012;18:3839-3848.
23. Herszenyi L, Miheller P, Tulassay Z. Carcinogenesis in Inflammatory Bowel Disease. Dig Dis 2007;25:267-269.
24. Ouaïssi M, Maggiori L, Alves A et al. Colorectal cancer complicating inflammatory bowel disease: a comparative study of Crohn's disease vs ulcerative colitis in 34 patients. Colorectal Dis 2011;13:684-688.
25. Colorectal adenocarcinoma in Crohn's disease. Ann Surg 1996;223:186-193.
26. Kulaylat MN, Dayton MT. Ulcerative Colitis and Cancer. J Surg Onc 2010;101:706-712.
27. Mooiweer E, van der Meulen AE, van Bodegraven AA et al. Neoplasia yield and colonoscopic workload of surveillance regimes for colorectal cancer in colitis patients: a retrospective study comparing the performance of the updated AGA and BSG guidelines. Inflamm Bowel Dis 2013;19:2603-2610.
28. Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010;138:746-774.
29. Satsangi J, Silverberg MS, Vermeire S, Colombel J-F. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749-753.
30. Katsanos KH, Stamou P, Tatsioni A et al. Prevalence of inflammatory bowel disease related dysplasia and cancer in 1500 colonoscopies from a referral center in northwestern Greece. J Crohns Colitis 2011;5:19-23.
31. von Herbay A, Herfarth C, Otto HF. Cancer and dys-

plasia in ulcerative colitis: a histologic study of 301 surgical specimen. Z Gastroenterol 1994;32:382-388.

32. Shelton AA, Lehman RE, Schrock TR, Welton ML. Retrospective review of colorectal cancer in ulcerative colitis at a tertiary center. Arch Surg 1996;131:806-810; discussion 810-1.
33. Gorfine SR, Bauer JJ, Harris MT, Kreel I. Dysplasia complicating chronic ulcerative colitis: is immediate colectomy warranted? Dis Colon Rectum 2000;43:1575-1581.
34. Maykel JA, Hagerman G, Mellgren AF et al. Crohn's colitis: the incidence of dysplasia and adenocarcinoma in surgical patients. Dis Colon Rectum 2006;49:950-957.
35. Scaringi S, Di Martino C, Zambonin D et al. Colorectal cancer and Crohn's colitis: clinical implications from 313 surgical patients. World J Surg 2013;37:902-910.
36. Matsuoka H, Ikeuchi H, Uchino M et al. Clinicopathological features of ulcerative colitis-associated colorectal cancer pointing to efficiency of surveillance colonoscopy in a large retrospective Japanese cohort. Int J Colorectal Dis 2013;28:829-834.
37. Murphy J, Kalkbrenner KA, Pemberton JH et al. Dysplasia in ulcerative colitis as a predictor of unsuspected synchronous colorectal cancer. Dis Colon Rectum 2014;57:993-998.
38. Kottachchi D, Yung D, Marshall JK. Adherence to guidelines for surveillance colonoscopy in patients with ulcerative colitis at a Canadian quaternary care hospital. Can J Gastroenterol 2009;23:613-617.
39. Bernstein CN, Papineau N, Zajaczkowski J, Rawsthorne P, Okrusko G, Blanchard JF. Direct hospital costs for patients with inflammatory bowel disease in a Canadian tertiary care university hospital. Am J Gastroenterol 2000;95:677-683.
40. Subramanian V, Mannath J, Ragunath K, Hawkey CJ. Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease. Aliment Pharmacol Ther 2011;33:304-312.
41. Subramanian V, Ramappa V, Telakis E et al. Comparison of high definition with standard white light endoscopy for detection of dysplastic lesions during surveillance colonoscopy in patients with colonic inflammatory bowel disease. Inflamm Bowel Dis 2013;19:350-355.
42. Konijeti GG, Shrime MG, Ananthakrishnan AN, Chan AT. Cost-effectiveness analysis of chromoendoscopy for colorectal cancer surveillance in patients with ulcerative colitis. Gastrointest Endosc 2014;79:455-465.
43. Baars JE, Siegel CA, van't Spijker A, Markus T, Kuipers EJ, van der Woude CJ. Inflammatory bowel disease-patients are insufficiently educated about the basic characteristics of their disease and the associated risk of colorectal cancer. Dig Liver Dis 2010;42:777-784.
44. Derikx LA, Kievit W, Drenth JP et al. Prior colorectal neoplasia is associated with increased risk of ileoanal pouch neoplasia in patients with inflammatory bowel disease. Gastroenterology 2014;146:119-128.
45. Imam MH, Eaton JE, Puckett JS et al. Neoplasia in the ileoanal pouch following colectomy in patients with ulcerative colitis and primary sclerosing cholangitis. J Crohns Colitis 2014;1;8:1294-1299.
46. Um JW, M'Koma AE. Pouch-related dysplasia and adenocarcinoma following restorative proctocolectomy for ulcerative colitis. Tech Coloproctol 2011;15:7-16.
47. Yokota T, Kunii Y, Teshima S et al. Signet ring cell carcinoma of the stomach: a clinicopathological comparison with the other histological types. Tohoku J Exp Med 1998;186:121-130.
48. Fukui Y. Mechanisms behind signet ring cell carcinoma formation. Biochem Biophys Res Commun 2014;450:1231-1233.
49. Psathakis D, Schiedeck TH, Krug F, Oevermann E, Kujath P, Bruch HP. Ordinary colorectal adenocarcinoma vs. primary colorectal signet-ring cell carcinoma: study matched for age, gender, grade, and stage. Dis Colon Rectum 1999;42:1618-1625.
50. Nitsche U, Zimmermann A, Späth C et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann Surg 2013;258:775-782.
51. Makino T, Tsujinaka T, Mishima H et al. Primary signet-ring cell carcinoma of the colon and rectum: report of eight cases and review of 154 Japanese cases. Hepatogastroenterology 2006;53:845-849.
52. Pande R, Sunga A, Levea C et al. Significance of signet-ring cells in patients with colorectal cancer. Dis Colon Rectum 2008;51:50-55.
53. Kang H, O'Connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum 2005;48:1161-1168.