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Timing of First Surveillance Colonoscopy after Curative Resection of Colorectal Cancer

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Abstract

Aim: To determine the optimal time to first surveillance, to evaluate potential risk factors.

Background: Endoscopic Surveillance after Colorectal Cancer (CRC) resection enables early detection of recurrence and prophylactic resection of polyps. There is no agreement regarding the timing of first colonoscopy after CRC resection.

Methods: A retrospective data analysis of 246 CRC patients who underwent curative surgical resection between 2007 to 2013, and had at least one postoperative colonoscopy conducted up to 3 years from surgery. Demographic, disease and endoscopic-associated variables were recorded.

Results: The prevalence of pathological findings was higher among patients performing late (18 to 36 months) surveillance colonoscopy (39.6%) compared to the early (up to 18 months) surveillance group (21.5%) ($p<0.005$). The Receiver Operator Characteristic (ROC) analysis revealed optimal cut-off time for postoperative first surveillance colonoscopy at 17.5 months. Patients who had pathological findings were older at diagnosis compared to disease-free patients.

Conclusion: Older age and higher grade at presentation are risk factors for the presence of pathological findings on first surveillance colonoscopy. A relation between time to first surveillance colonoscopy and presence of pathological findings has been markedly highlighted. First surveillance colonoscopy was found to be optimal at 17.5 months post operation. The need to agreed guidelines is eminent.

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Introduction

Colorectal Cancer (CRC) is one of the most common cancers worldwide, although country - specific incidences vary markedly [1]. CRC survivors are at a 30% to 50% risk for local recurrences and second primary cancers after curative resection [2,3]. Findings regarding risk factors for postoperative tumor recurrence are inconclusive and often contradictive [4-6]. Synchronous CRC, age above 60 and diabetes mellitus were suggested as prognostic factors [7,8]. Recurrences are treated better if found in the asymptomatic patients therefore, postoperative patients should undergo a surveillance strategy which includes laboratory testing, radiographic imaging and endoscopic surveillance [9]. Surveillance colonoscopy should detect local anastomotic recurrence, metachronous CRC and premalignant polyps [10]. Despite the importance of endoscopic surveillance as a preventive strategy, little consensus or consistency is found between professional society guidelines regarding the timing of initial colonoscopy after resection of CRC; the British Society of Gastroenterology recommends an initial follow-up colonoscopy at 5 years [11]. The 2005 Australian National Health & Medical Research Council (NHMRC) guidelines recommend surveillance colonoscopy every 3 to 5 years after CRC surgery [12]. On the other hand, the American Cancer Society and the US Multi-Society Task Force guidelines, as well as the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend colonoscopy at 1 year following surgery [2,13,14]. The discrepancy of guidelines is reflected in variation of practice among clinicians [10]. Israeli Gastroenterology Association recommends initial surveillance colonoscopy at one year after curative surgery, followed by 3 and 5 years checkups thereafter. The reasoning for one year post resection surveillance relays on the assumption that genetic susceptibility may give rise to early subsequent lesions and considers the possibility of perioperative missed lesions [10]. Determining an optimal surveillance for CRC survivors is necessary because of the significant burden on patients, physicians, and health care system [15]. The difference between one three or five years first post-

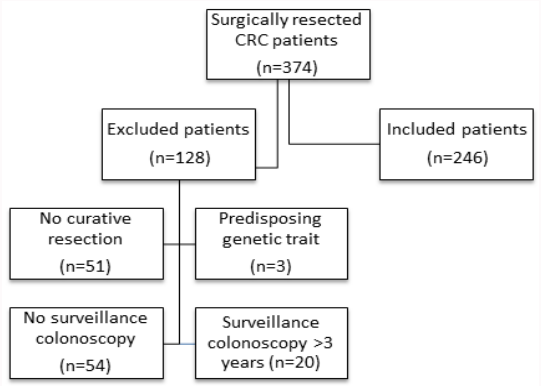

Figure 1: Study population- screened, excluded and included patients of the overall screened CRC patients who were surgically resected, 128 were excluded. Overall 246 patients met the inclusion criteria.

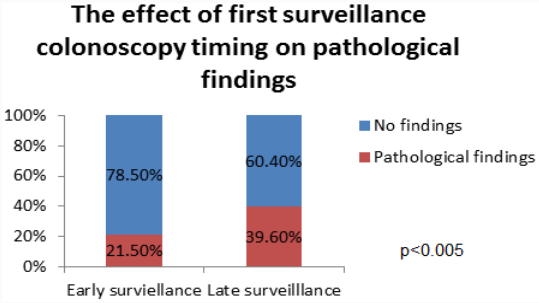

Figure 2: The effect of first surveillance colonoscopy timing on pathological findings.

surgical colonoscopy significantly influences the already overloaded endoscopic services. Bearing in mind that efficacy, risks and cost-effectiveness of an early colonoscopy in improving life-expectancy of CRC patients are questionable extending the time to first surveillance colonoscopy may be safe and might help conserving valuable resources and improve compliance [10,16-20]. Guidelines variations represent no solid evidence for the right time for first surveillance colonoscopy. In the lack of clarity regarding the responsible physician for CRC patients' surveillance program, i.e. primary physician, gastroenterologist, oncologist or surgeon, patients' compliance and actual surveillance timing may differ. This study quantifies the yield of first surveillance colonoscopy and investigates the proper post-surgery interval. Various parameters were correlated to patient outcomes in order to better understand impact on prognosis and potentially to point on subpopulation that might benefit from more intense surveillance.

Materials and Methods

Study design

We retrospectively analyzed data from 374 consecutive patients who underwent surgical resection for colorectal cancer between the years 2007 and 2013 at the Hillel Yaffe Medical Center (HYMC).

Study population

The study included adult colorectal cancer patients over the age of 18, who underwent curative surgical resection and had documented pre-operative colonoscopy and pathology and at least one postoperative colonoscopy within 3 years after the operation. Patients with an identified genetic trait predisposing to colorectal cancer (familial adenomatous polyposis, Lynch syndrome), inflammatory bowel disease and those who underwent total proctocolectomy were excluded. 246 patients met inclusion criteria and were eligible for our study (Figure 1). The study was approved by the Institutional Ethics Board and was conducted according to the principles expressed in the Declaration of Helsinki.

Data source

A database of CRC patients in years 2007 to 2013 was extracted from pathology, surgery and gastroenterology institution's files: Medical data included age at presentation, gender, tumor location and surgical reports. Pathology data included colonoscopies findings analysis and surgical specimen results that enabled determining tumor staging according to the American Joint Committee on Cancer classification [21]. Endoscopy data included perioperative and postoperative colonoscopy results.

Data analysis

In order to study the influence of surveillance colonoscopy timing on disease free survival – patients were divided into two groups: early surveillance group was comprised of patients who had their first surveillance colonoscopy up to 18 months after surgery and the late surveillance group of patients who had first colonoscopy 18 to 36 months after surgery. The prevalence of pathological findings was recorded. A statistical hypotheses test was applied to exam the influence of timing of first surveillance colonoscopy on disease-free survival. Furthermore, analysis was applied to find the best cutoff in timing of surveillance colonoscopy to differentiate between patients with or without significant pathological findings. A second analysis estimated the influence of independent potential risk factors among the examined demographic, disease-associated and endoscopic variables on disease-free survival.

Statistical analysis

The association between two qualitative categorical variables was assessed by the Chi-square, χ^2 test and the Fisher's Exact Test (FET). Comparison of quantitative variables between two groups was carried out using the two sample t-test. For the comparison of two different time groups and the presence of significant findings the statistical significance is 5% (one tailed). All other comparisons were two tailed. The Receiver operator characteristic (ROC) analysis was applied to find the best cut off in timing of test to differentiate between patients with/without significant findings. Univariate analyses were performed to estimate the independent potential quantitative and qualitative risk factors that influence disease-free survival. The statistical significance was 5% (two tailed). The variables found to be significantly associated with disease-free survival in the univariate analysis were entered into a multivariate logistic regression model to test their simultaneous effect. Statistical analysis was done using SPSS (v18) software (Chicago, IL).

Results

Patient's characteristics

The clinical characteristics of all 246 patients included in this study and of the two compared surveillance colonoscopy groups, early and late, are presented in Table 1. Surveillance groups were compared by independent samples t-tests, χ^2 and Fishers' Exact tests. Early surveillance group included significantly more patients in CRC stage 3 at diagnosis. The prevalence of pathological findings was higher among patients in the late surveillance colonoscopy group, (44 patients, 39.6%) compared to patients in the early surveillance group

Table 1: Background characteristics of patients.

	All sample (n=246)	Early surveillance colonoscopy <18 months (n=135)	Late surveillance colonoscopy 18-36 months (n=111)	P- values[1]
Age at diagnosis (years)[2]	65.57 ± 11.89	65.02 ± 12.30	66.23 ± 11.41	0.43
Time to surveillance (months)[3]	19.53 ± 12.61	12.12 ± 2.74	28.54 ± 4.00	0.00
Gender - male (%)	119 (48.4)	64 (47.4)	55 (49.5)	0.74
Stage (%)				0.00
1	86 (35)	44 (32.6)	42 (37.8)	
2	83 (33.7)	43 (31.9)	40 (36)	
3	72 (29.3)	45 (33.3)	27 (24.3)	
4	5 (2)	3 (2.2)	2 (1.8)	
Grade (%)				0.73*
High	75 (30.5)	37 (27.4)	38 (34.2)	
Low	100 (40.7)	52 (38.5)	48 (43.2)	
Unknown	71 (28.9)	46 (34.1)	25 (22.5)	
Location (%)				0.09
Right colon	63 (25.6)	34 (25.2)	29 (26.1)	
Transverse colon	19 (7.7)	7 (5.2)	12 (10.8)	
Left colon	98 (39.8)	62 (45.9)	36 (32.4)	
Rectum	66 (26.8)	32 (23.7)	34 (30.6)	
Findings in surveillance (%)				0.00
None	173 (70.3)	106 (78.5)	67 (60.4)	
Premalignant	58 (23.6)	25 (18.5)	33 (29.7)	
Malignant anastomotic recurrence	4 (1.6)	1 (0.7)	3 (2.7)	
Malignant metachronous cancer	11 (4.5)	3 (2.2)	8 (7.2)	

*Patients whom their tumor grade was unknown were excluded from the analysis
[1]Significant p-values are defined as <0.05 in comparison between the early and late surveillance groups
[2]Presented as mean age in years with the standard deviation
[3]Presented as mean time from surgery to surveillance in months with the standard deviation

(29 patients, 21.5%) ($\chi^2(1)=9.62$, $p<0.005$ (Figure 2). Prevalence of malignant (early surveillance: 4 patients, 13.8%; late surveillance: 11 patients, 25%; $\chi^2(1)=1.34$, $p>0.05$) and premalignant findings did not differ between the two surveillance groups (Figure 3). The Receiver Operator Characteristic (ROC) analysis was conducted in order to find the best cutoff of first surveillance colonoscopy timing that differentiates between patients with or without pathological findings. The optimal cut-off time was defined as the point in which specificity and sensitivity were highest. Cutoff was identified as the value of 17.5 months post-surgery (Figure 4). The effect of Clinicopathological characteristics on prognosis: (Table 2).

Age: The age at diagnosis correlated significantly with pathological findings on first surveillance colonoscopy. Patients who had pathological findings were older at diagnosis compared to disease-free patients (p=0.03) (Figure 5A).

Gender: No significant relationship was found between pathological findings and gender ($\chi^2(1)=1.06$, $p>0.05$.

Tumor location: No relationship was found between presence of pathological findings on surveillance and tumor location at diagnosis ($\chi^2(3)=0.27$, p=0.96.

Grade: Tumor grade at diagnosis correlated significantly with pathological findings on surveillance ($\chi^2(1)=10.62$, p=0.001). Most patients who were found disease-free in the surveillance had a low-grade tumor at diagnosis (71 patients, 67% of disease-free patients),

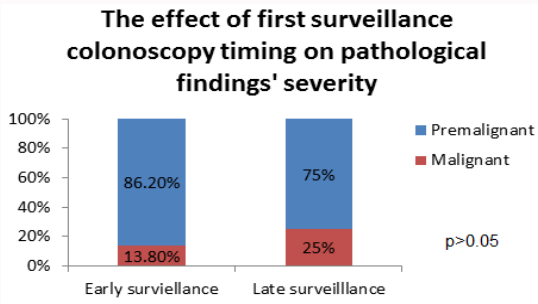

Figure 3: The effect of first surveillance colonoscopy timing on pathological findings' severity.

while most of the patients with pathological findings had a high-grade tumor at diagnosis (40 patients, 58% of patients with pathological findings) (Figure 5B).

Stage at diagnosis

The presence of pathological findings on surveillance colonoscopy significantly related to tumor stage at diagnosis (p<0.001). However, the significant difference between groups in tumor stage was attributed to an unexpected finding; in stage 4, expected to be a more prone stage for producing pathological findings, all five patients were part of disease-free group in the surveillance colonoscopy. When these 5 patients were excluded, the effect of stage became insignificant

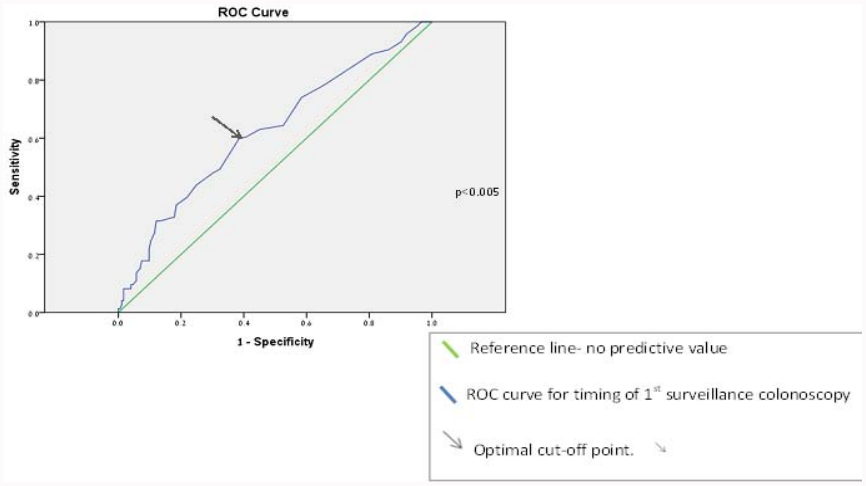

Figure 4: ROC curve for timing to first surveillance after CRC resection: Area under the ROC curve for timing of first surveillance colonoscopy (blue line) was found to be significant although with low effect on pathological findings- 0.62 (SE=0.04, p<0.005, 95% CI 0.54-0.70). The optimal cut off time (arrow) was 17.50 months (Sensitivity =0.60, Specificity =0.61).

Table 2: Clinicopathological parameters and their associations to pathological findings.

	Patients with pathological findings (n=73)	Disease free patients (n=173)	P- values[1]
Age at diagnosis (years)[2]	68.05 ± 10.97	64.52 ± 12.14	0.03
Time to surveillance (months)[3]	23.33 ± 15.32	17.92 ± 10.94	0.01
Gender - male (%)	39 (53.4)	80 (46.2)	0.30
Stage (%)			0.00*
1	28 (38.4)	58 (33.5)	
2	20 (27.4)	63 (36.4)	
3	25 (34.2)	47 (27.2)	
4	0 (0)	5 (2.9)	
Grade (%)			
High	40 (54.8)	35 (20.2)	0.00**
Low	29 (39.7)	71 (41)	
Unknown	4 (5.5)	67 (38.7)	
Location (%)			0.96
Right colon	18 (24.7)	45 (26)	
Transverse colon	6 (8.2)	13 (7.5)	
Left colon	28 (38.4)	70 (40.5)	
Rectum	21 (28.8)	45 (26)	

*When patients in stage 4 were excluded, p=0.30
**Patients whom their tumor grade was unknown were excluded from the analysis
[1]Significant p-values are defined as <0.05 in comparison between pathological findings and disease-free on surveillance colonoscopy
[2]Presented as mean age in years with the standard deviation
[3]Presented as mean time from surgery to surveillance in months with the standard deviation

($\chi^2(2)=2.39$, p-value =0.30 Therefore we decided to relate to stage at diagnosis as an insignificant prognostic factor.

Timing of first surveillance colonoscopy

Time from surgery to first surveillance did correlate significantly with more pathological findings (t(244)= -3.12, p<0.05). Patients who performed the surveillance later had more pathological findings compared to disease-free patients (p-value =0.01) (Figure 5C). Age at diagnosis, tumor grade at diagnosis and time to surveillance did not correlate with severity of pathological findings and did not distinguish between patients with premalignant and malignant findings, (age: t(71)=1.54, p>0.05 (Figure 6A); grade: $\chi^2(1)=0.08$, p>0.05 (Figure 6B); time to surveillance: t(71)=-1.77, p>0.05 (Figure 6C). The simultaneous effect of age at diagnosis, time to surveillance and tumor grade on surveillance results was tested by a binary logistic regression analysis. Results are presented in Table 3. All three variables had a significant contribution to prediction. The risk of pathological findings in surveillance was higher when the patient was older at diagnosis, the surveillance was done later, and the tumor grade at diagnosis was higher. The tumor grade contribution was the highest in this model.

Discussion

Surveillance colonoscopy following curative CRC resection

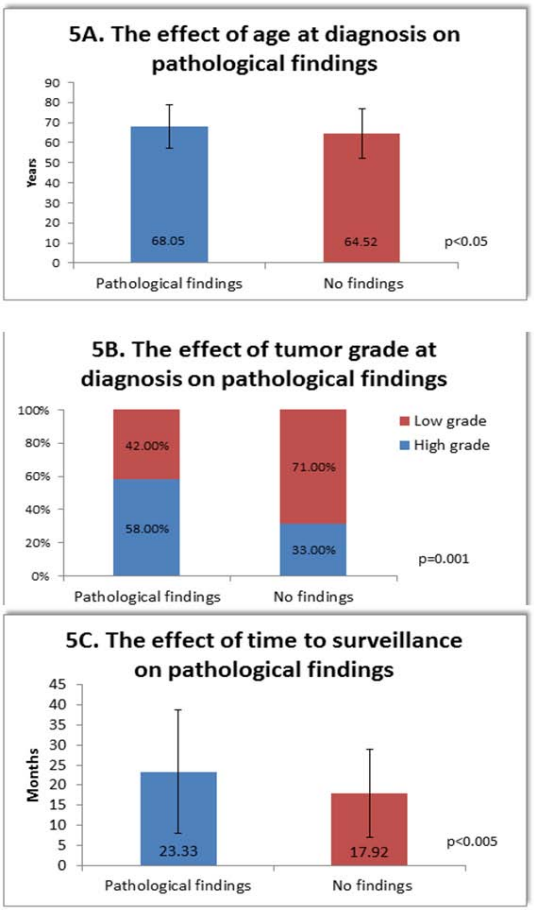

Figure 5: Differences between patients with and without pathological findings on surveillance by means of age at diagnosis, tumor grade at diagnosis and time to surveillance: **A)** The effect of age at diagnosis on pathological findings (presented as average ages in years), **B)** The effect of tumor grade at diagnosis on pathological findings, **C)** The effect of time to surveillance on pathological findings (presented as average months).

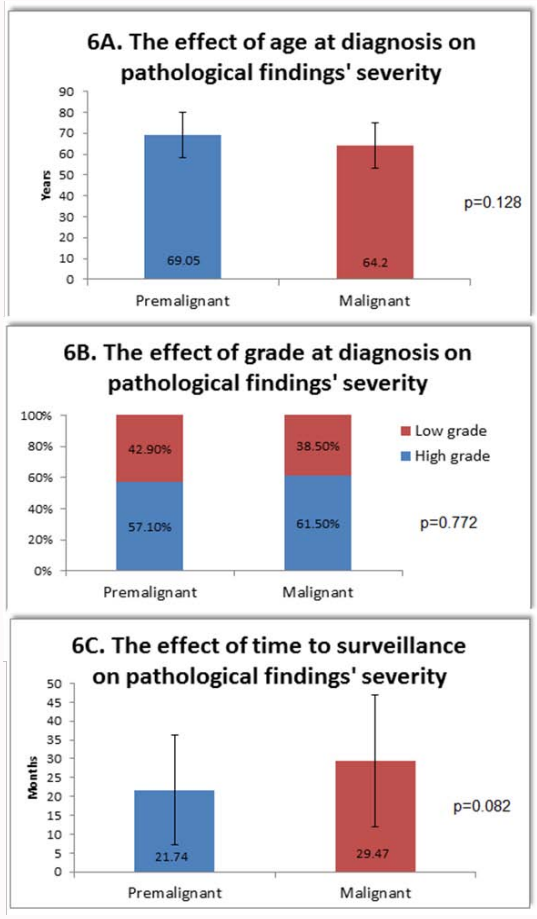

Figure 6: Differences between patients with premalignant and malignant findings by means of age at diagnosis, tumor grade at diagnosis and time to surveillance: Patients were divided by having premalignant vs. malignant findings at first surveillance colonoscopy. The measured parameters were significantly insignificant (All p-values>0.05) **A)** The effect of age at diagnosis on pathological findings' severity, **B)** The effect of grade at diagnosis on pathological findings' severity, **C)** The effect of time to surveillance on pathological findings' severity.

is intended to achieve early detection of metachronous or local anastomotic cancers and to discover and remove pre-malignant lesions, thus lowering the risk of subsequent cancer formation [11]. Investigation of the optimal interval between CRC resection and first surveillance colonoscopy is valuable, but timing of first surveillance colonoscopy is widely variable among recommendations and individual practice [2,10-14,22,23]. Some randomized controlled trials had demonstrated earlier detection of local recurrence with intensive early colonoscopy and an improved survival, while others had shown no, or little, benefit from early colonoscopy [17,19,24-26]. Several studies concluded that extending the time to first colonoscopy appears to be safe and would help conserve valuable resources [10,27]. This study investigated outcomes of post-surgery surveillance colonoscopy in 246 CRC patients who met inclusion criteria. We found that early surveillance group (colonoscopy <18 months) consisted of more patients with advanced tumor stage at diagnosis, a difference that might be explained by a tendency of physicians to instruct surveillance more strictly in patients with higher stages of disease. Pathological findings were significantly higher among patients in the late surveillance colonoscopy group (colonoscopy at 18-36 months) (39.6%) compared to early surveillance group (21.5%) (p<0.005). The number of pathological findings is higher in this study than in the published data of 3% and 12% pathological findings at 18 months and 3 years, respectively [7,8,28]. This might be related to country-specific variations of disease and recurrence rates or a result of selected population bias with demographics-related genetic susceptibility and life style influences [1,29]. Although late surveillance group had more patients with malignant findings (11 patients, 25% malignant), compared to the early surveillance group (4 patients, 13.8% malignant), the difference was not statistically significant ($\chi^2(1)=1.34$, $p>0.05$). We therefore conclude that in the measured periods, the timing of colonoscopy did not statistically influence pathological findings severity. A study which compared 0 to 2 years *vs.* 3 to 5 years post-surgical surveillance colonoscopy found equal number of malignant findings in the two time periods [11]. The optimal timing of colonoscopy in our study has been investigated by ROC analysis method, which consists of each patient's information and calculates the optimal spot of highest sensitivity and specificity. The optimal interval for first post resection surveillance colonoscopy was 17.5 months. From the area under the curve (AUC-0.62) we learned that other risk factors other than time also play a role in pathological outcomes. In contrast to other studies that suggested extending the time to first colonoscopy is safe our findings of a significant pathology in early surveillance colonoscopy support the

Table 3: Regression analysis results.

	B (SE)	Wald	p	Odds Ratio
Age at diagnosis	0.03 (0.01)	4.4	0.04	1.03
Time to surveillance	0.02 (0.01)	2.64	0.01	1.02
Tumor grade	-1.03 (0.33)	9.76	0	0.36

R^2=0.14, $\chi^2(3)$=19.56, p<0.001

guidelines of early detection regardless of complications and cost-effectiveness considerations [10,17,19,26,27]. Parameters of age at diagnosis, tumor grade and timing of first surveillance colonoscopy correlated significantly with pathological findings on surveillance colonoscopy but not with the findings' severity. Patients who had pathological findings were older at diagnosis compared to disease-free patients. This finding is supported in other reports of age related post-surgery premalignant findings with no relation to recurrence of malignancy [4,8,30,31]. It is known that premalignant findings are age-related even in a healthy, non-cancerous population. Most patients who were found disease-free in the surveillance had a low-grade tumor at diagnosis while most of the patients with pathological findings had a high-grade tumor at diagnosis. This is widely supported in literature, whereas histologic high-grade subtypes known to have a significant impact on malignant recurrence and prognosis but no role in relation to premalignant findings [4,8,32]. On a binary logistic regression analysis all three prognostic factors had a significant contribution to the prediction while tumor grade contribution was the highest. Nevertheless, more prognostic factors are still to be found in order to improve stratifying risk for pathological findings and allow surveillance to be tailored to a patient's susceptibility. Gender, tumor location and tumor stage had no influence on pathological findings evolution. These are supported by other researches: Gender was found irrelevant right- and left-sided colon cancers carry same prognosis when present with loco regional disease and tumor stage was not a prognostic factor for post-operative malignant or premalignant findings [4,8,9,33]. Only about half of the patients complied with the local clinical guidelines of one year post-operative colonoscopy. 135 patients managed to have their first surveillance colonoscopy at up to 18 months from surgery. However, 111 patients had theirs at 18 to 36 months, 20 had a first colonoscopy over 3 years after surgery and 54 patients did not have a postoperative surveillance colonoscopy or were lost to follow up. Hence about half of patients underwent a less intensive surveillance colonoscopy program. Similar proportions were found in a study conducted on US population with less than half of Medicaid-insured CRC survivors received a colonoscopy in up to 18 months after colorectal resection [34]. These findings stress the need for uniform, more established, guidelines that will serve the foundation for better enforcement of recommendations. Improvements in screening in this high-risk population should be the target of future interventions to reduce the probability of recurrence.

Conclusion

Relying on a single-center experience this research may have selected population bias and demographic limitations. Nevertheless, the link between time to first surveillance colonoscopy and presence of pathological findings has been markedly highlighted. Significant findings, both in their number and severity, were present in the early surveillance colonoscopy group. The optimal time for post-operative first surveillance colonoscopy was found to be 17.5 months. Advanced age and high tumor grade at presentation should be considered as risk factors for pathological finding on surveillance, although more risk factors are yet to be found in order to enable a further personalized surveillance approach. In order to improve patients' compliance an agreement on guidelines is important.

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