

Early-Stage Colon Cancer Surveillance: Pattern and Timing of Recurrence and the Role of 5-Year Surveillance

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Keywords

Colon cancer · Early stage · Recurrence · Surveillance

Abstract

Introduction: Colorectal cancer is the third most prevalent cancer among both men and women with 80% of patients having localized disease enabling curative treatments. Given the low recurrence rate in early-stage disease, there is a growing interest in reviewing follow-up protocols. The aim of this study was to assess the frequency and timing of recurrence in early-stage colon cancer, as well as recurrence patterns. **Methods:** The data from all patients with colon adenocarcinoma consecutively treated with surgery at the Instituto Português de Oncologia do Porto, EPE, between January 2013 and December 2016, were retrospectively reviewed. **Results:** A total of 1,372 patients with colon cancer were submitted to surgery during the study period. From this group, 51.4% ($n = 705$) were early-stage colon cancers. Regarding the pathological stage, 3.5% were stage 0, 37.4% were stage I and 59.1% were stage II. The overall recurrence rate was 6.7%. When considering the group of patients without risk factors, the recurrence rate was 5.6%. The majority of recurrences occurred in the first 3 years of follow-up. The recurrence was diagnosed in the majority of patients through carcinoembryonic antigen elevation, followed by

imaging exams. The presence of one or more risk factors (high nuclear grade, vascular invasion, extramural venous invasion, and perineural invasion) showed a statistically significant association with recurrence rate. **Conclusion:** The recurrence rate was low in early-stage colon cancer, with the majority of recurrences occurring in the first 3 years. Our study results show that surveillance should be tailored according to individual risk factors.

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Vigilância do cancro do cólon em estadios iniciais: padrão de recorrência e o papel da vigilância até aos 5 anos

Palavras Chave

Cancro do cólon · Estadio inicial · Recorrência · Vigilância

Resumo

Introdução: O cancro do cólon é o terceiro cancro mais prevalente tanto em mulheres como em homens. Cerca de 80% têm doença localizada ao diagnóstico, permitindo o tratamento curativo. Considerando a baixa taxa de recorrência em doentes com estadios iniciais, existe

uma necessidade de rever os critérios e protocolos de vigilância. O objetivo do estudo é avaliar a frequência e padrão de recorrência em doentes com cancro do cólon em estadios iniciais. **Métodos:** Foram analisados retrospectivamente todos os doentes diagnosticados com adenocarcinoma do cólon tratados com cirurgia no Instituto Português de Oncologia do Porto, EPE, entre Janeiro de 2013 e Dezembro de 2016. **Resultados:** Durante este período, foram submetidos a cirurgia um total de 1,372 doentes com diagnóstico de cancro do cólon. Neste grupo, 51.4% ($n = 705$) têm tumores em estadio inicial ao diagnóstico. Considerando o estadio patológico, 3.5% são estadio 0, 37.4% são estadio I e 59.1% estadio II. A taxa de recorrência global foi de 6.7%. Quando analisamos o grupo sem fatores de mau prognóstico, a taxa de recorrência foi de 5.6%. A maioria dos casos de recorrência ocorreu nos primeiros 3 anos de vigilância, sendo que a recorrência foi diagnosticada, na maior parte dos casos, por aumento do CEA, seguido de exames de imagem. A presença de um ou mais fatores de risco (alto grau nuclear, invasão vascular, invasão venosa extramural e invasão perineural) mostrou uma associação estatisticamente significativa com a taxa de recorrência. **Conclusão:** Em conclusão, a taxa de recorrência é baixa no cancro do cólon em estadios iniciais, com a maioria dos casos de recorrência a ocorrer nos primeiros 3 anos de vigilância. O presente estudo demonstra a importância da individualização da vigilância em função dos fatores de risco individuais.

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both women and men. In general, the lifetime probability of developing CRC is approximately 1 in 23 for men and 1 in 26 for women [1]. Approximately 80% of these patients present with localized disease and the majority undergo curative treatment [2]. Intensive surveillance is routinely recommended for these patients [2–4].

Considering the incidence of this pathology, patients with CRC represent one of the largest groups of cancer survivors, requiring an important number of hospital appointments during follow-up [5]. Between 30 and 50% of all patients treated with localized disease will eventually recur and die of the disease [6]. The goal of intensive follow-up protocols is the early detection of recurrence, in

order to provide the possibility of a treatment with curative intent [5, 7].

The risk of recurrence is higher with higher stage disease and 85% of recurrences develop during the first 2.5 years after surgery. Patients who are disease free at 5 years have a recurrence risk of less than 5%. The timing and pattern of recurrence are stage dependent [8].

The majority of surveillance protocols include clinical evaluation, carcinoembryonic antigen measurement, chest-abdominal-pelvic CT scan, as well as colonoscopy every 3–5 years starting 1 year after surgery or earlier if the diagnostic colonoscopy was not complete. The time interval between consultations and exams gradually widens throughout the surveillance [7, 9]. Considering the low recurrence rate in the early stages and the resources required for follow-up in the hospital setting, there has been a growing interest in reviewing follow-up protocols.

The aim of this study was to assess the frequency and timing of recurrences in early-stage colon cancer. Additionally, we aimed to analyze the recurrence patterns and diagnostic approaches as secondary goals.

Materials and Methods

The data from all patients with colon adenocarcinoma consecutively treated with surgery at the Instituto Português de Oncologia do Porto, EPE, between January 2013 and December 2016, were retrospectively reviewed. The enrollment period was chosen to ensure a minimum of 5 years follow-up for all patients.

In our institution, surveillance is conducted during the first 2 years with clinical assessment and tumor marker evaluation every 3–4 months, plus thoraco-abdomino-pelvic CT scans annually. Colonoscopy is performed 1 year after surgery (earlier in cases of incomplete colonoscopy at diagnosis) and 3 years after. After the fifth year of surveillance, the patient is discharged from hospital-level follow-up and transits to monitoring at the primary care center.

Inclusion criteria were adult patients (≥ 18 years old) submitted to surgery with curative intent, with an early clinical stage colon cancer (defined by the authors as stages 0, I, and II according to AJCC TNM classification), with lesions proximal to 15 cm from the dentate line in colonoscopy and histologic confirmation of adenocarcinoma. Exclusion criteria were stages III and IV at diagnosis, surgery for recurrent disease, genetic syndromes associated with higher risk of colon cancer, extracolonic synchronous tumors, and lack of surveillance data (due to loss of follow-up or death within 30 days of surgery).

Data regarding demographic features, treatments, histologic characteristics of the tumor, follow-up, and disease recurrence were recorded. The descriptive analysis of categorical variables was presented with frequency tables and continuous variables were presented using median and interquartile range (IQR).

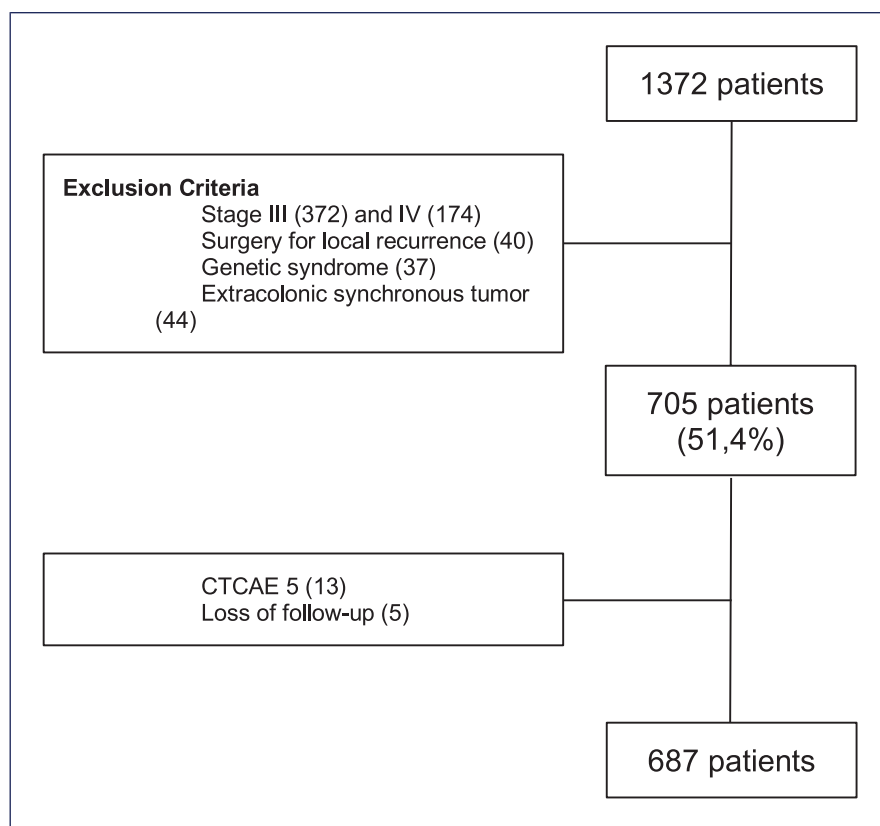


Fig. 1. Distribution of patients applying exclusion criteria.

A univariate analysis was carried out using χ^2 tests in order to test the association between known prognostic factors (independent variables) and the risk of recurrence (dependent variable). The analyzed independent variables were the location of the tumor (right colon defined as lesions proximal to the mid-point of the transverse colon vs. left colon defined as all lesions distal to the midpoint of the transverse colon), surgical approach (open vs. laparoscopic), 30-day surgical morbidity (classified according to the common terminology criteria for adverse events (CTCAE) version 5.0), and histologic characteristics such as pT, nuclear grade, vascular invasion, extramural venous invasion (EMVI), perineural invasion, and a number of lymph nodes retrieved in the surgical specimen (analyzed using both 12 as a cutoff point since it is the guideline-recommended minimum number of lymph nodes to be removed, as well as 19 since it was the median of lymph nodes removed in the surgical specimens in our patient sample). The association between ≥ 1 prognostic factor (high nuclear grade, vascular invasion, EMVI, or perineural invasion) and risk of recurrence was also tested since these are the major factors used to decide adjuvant chemotherapy indication. Only factors that achieved statistical significance in the univariate analysis were used to build the multivariate analysis model, through a Cox regression model, with hazard ratio (HR) and the respective 95% confidence intervals (95% CI) reported. Survival analysis was performed using Kaplan-Meier's survival curves and life tables. A p value < 0.05 was considered statistically significant and statistical analysis was performed using SPSS® version 26.0 software.

Results

A total of 1,372 patients with colon cancer were submitted to surgery during the study period. A total of 546 patients were staged as III or IV and were excluded from the study. Additionally, in 44 patients, synchronous extracolonic cancer was diagnosed and another 37 patients had a genetic syndrome associated with higher risk of colon cancer, excluding all of these patients from this analysis. Of the 705 patients remaining, 5 were lost to follow-up and 13 died within 30 days after surgery (mortality rate 1.8%) (shown in Fig. 1, 2).

Of the 687 patients included, 43.8% (301) corresponded to female patients, with a median age of 68 years old (IQR 15). The characteristics of the surgical treatment are described in Table 1. The majority of patients were submitted to elective surgery (99%; $n = 680$). The most common approach was laparotomy (73.1%; $n = 502$) and the most common procedures were right colectomy (43.8%; $n = 301$) and sigmoidectomy (39.9%; $n = 274$). The major complication rate, defined as CTCAE 3/4 was 9.5% ($n = 65$).

Regarding the pathological stage, 3.5% ($n = 24$) were stage 0, 37.4% ($n = 257$) were stage I, and 59.1% ($n = 406$)

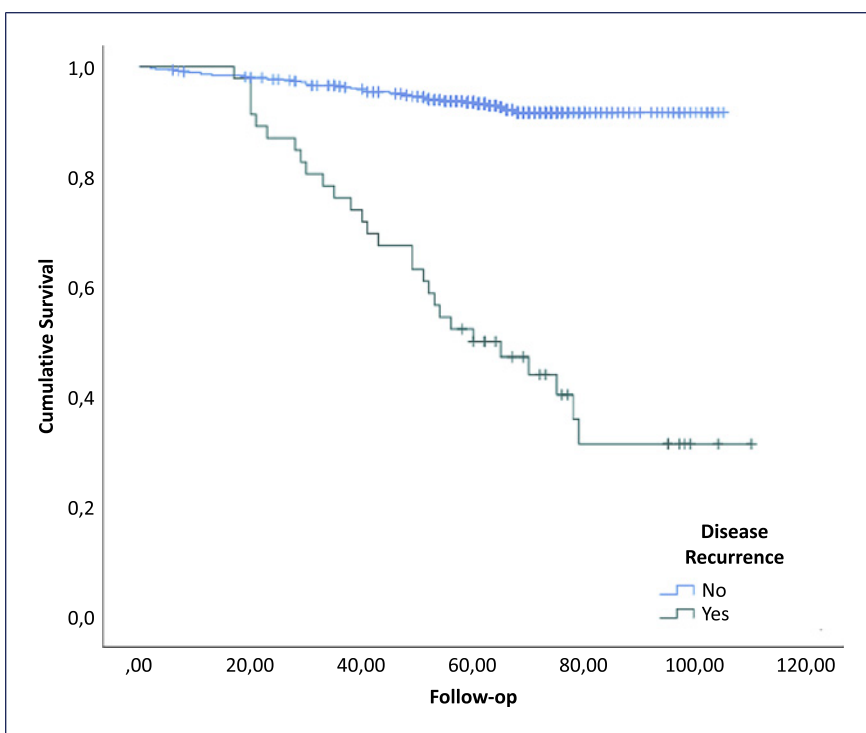


Fig. 2. Overall survival comparing the groups with and without recurrence.

Table 1. Demographic characteristics of the study cohort

Variables	n (%)
Type of surgery	
Elective	680 (99)
Urgent	7 (1)
Surgical approach	
Laparotomy	502 (73.1)
Laparoscopy	185 (26.9)
Surgical procedure	
Right hemicolectomy	301 (43.8)
Sigmoidectomy	274 (39.9)
Left hemicolectomy	85 (12.4)
Transverse colectomy	16 (2.3)
Subtotal/total colectomy	11 (1.6%)
Surgical morbidity	
CTCAE 0	563 (82%)
CTCAE 1	5 (0.7%)
CTCAE 2	54 (7.9%)
CTCAE 3	44 (6.4%)
CTCAE 4	21 (3.1%)

were stage II. Within the stage II patients, the majority were stage IIA (53.4%; $n = 367$), followed by stage IIB in 3.8% ($n = 26$) and stage IIC in 1.9% ($n = 13$). All resections were pathologic R0. Considering the grade,

54.1% ($n = 372$) were in grade 1, 33.5% ($n = 230$) in grade 2, and 4.2% ($n = 29$) in grade 3. Examining other histological features, 18.5% ($n = 127$) had vascular invasion, 9.2% ($n = 63$) had EMVI and 10.8% ($n = 74$) had perineural invasion. Ten percent ($n = 69$) of the patients were submitted to adjuvant chemotherapy. The histological characteristics of the surgical specimens are described in Table 2.

The median follow-up time was 62 months (IQR 12). The overall recurrence rate was 6.7% ($n = 46$). When considering the group of patients without risk factors ($n = 390$), the recurrence rate was 5.6% ($n = 22$). The majority of recurrences (73.9%, $n = 34$) occurred in the first 3 years of follow-up, 21.7% ($n = 10$) between the third and fifth years of follow-up and 4.4% ($n = 2$) after the fifth year of follow-up.

Figure 3 enables the observation of survival curves based on the diagnostic stage. It can be noted that stage 0 initially exhibits a better prognosis, but over time, it becomes comparable to stage I. Additionally, stage IIA tends to align more closely with stage I than with other subgroups within stage II.

Considering each stage group, among the patients in stage 0 ($n = 24$), the median follow-up was 61.5 months and no cases of recurrence were observed. The stage I group had 257 patients with a median follow-up time of 62 months. Within this subgroup, a total of 3.9% of

Table 2. Histological descriptive characteristics of the study cohort

Variables	n (%)
Pathologic tumor staging (n = 687)	
Stage 0	24 (3.5%)
Stage I	257 (37.4)
Stage IIA	367 (53.4)
Stage IIB	26 (3.8)
Stage IIC	13 (1.9)
Tumor grade (n = 631)	
1	372 (58.9)
2	230 (36.5)
3	29 (4.6)
Vascular invasion (n = 671)	
No	544 (81.1)
Yes	127 (18.9)
EMVI (n = 646)	
No	583 (90.2)
Yes	63 (9.8)
Perineural invasion (n = 639)	
No	565 (88.4)
Yes	74 (11.6)

patients relapsed ($n = 10$). Among those, 1.6% ($n = 4$) recurred within the first 3 years, 1.9% ($n = 5$) between the third and fifth year of follow-up, and only one after the fifth year. The median time until recurrence was 36 months. The stage II group comprised 406 patients, with a median follow-up of 61.5 months. Within this subgroup, the recurrence rate was 8.9% ($n = 36$). Among them, 7.6% ($n = 31$) recurred within the first 3 years, 1% ($n = 4$) between the third and fifth year of follow-up, and only one after the fifth year. The median time to recurrence was 14.5 months Table 3.

In regards to the pattern of recurrence, 71.7% ($n = 33$) of patients had distant metastasis, 26.1% ($n = 12$) loco-regional disease, and 2.2% ($n = 1$) both local and distant recurrence. The recurrence was diagnosed in the majority of patients through carcinoembryonic antigen elevation (54.3%; $n = 25$), followed by imaging exams in 32.6% ($n = 15$), colonoscopy in 10.9% ($n = 5$), and clinical evaluation in 1 patient (2.25%). Considering the treatment for recurrent disease, 52.2% ($n = 24$) of the patients were submitted to surgical treatment, 28.3% ($n = 13$) to systemic treatment, and 19.6% ($n = 9$) to support care.

An evaluation of prognostic factors for recurrence was made in stages I and II patients ($n = 663$). EMVI, perineural invasion, pT, and the presence of one or

Table 3. Characteristics of recurrent disease

Variables	n (%)
Pattern of recurrence	
Distant metastasis	33 (71.7)
Loco-regional metastasis	12 (26.1)
Local and distant metastasis	1 (2.2)
Diagnostic method	
CEA elevation	25 (54.3)
Imaging exams	15 (32.6)
Colonoscopy	5 (10.9)
Clinical evaluation	1 (2.25)
Treatment	
Surgical treatment	24 (52.2)
Systemic treatment	13 (28.3)
Supportive care	9 (19.6)
CEA, carcinoembryonic antigen.	

more risk factors were statistically significant in the univariate analysis. In the multivariate analysis, the presence of EMVI did not show statistical significance (HR = 1.753, $p = 0.194$, 95% CI [0.751–4.092]). Conversely, perineural invasion demonstrated a statistically significant association with recurrence (HR = 2.298, $p = 0.037$, 95% CI [1.052–5.016]). Although the pT stage did not reach statistical significance ($p = 0.124$), a noticeable relationship was observed between higher pT stages and an increased risk of relapse (shown in Table 4). Upon comparing the overall survival between the group of patients with recurrence and the group that remained recurrence-free, a notable observation is the significantly higher overall survival in the recurrence-free group.

Discussion

The aim of this study was to assess the frequency and timing of recurrences in early-stage colon cancer. In our study sample, the overall recurrence rate was 6.7%, with the majority of patients (73.9%) being diagnosed in the first 3 years of follow-up. We analyzed the recurrence in each stage group, and in stage 0, no cases of recurrence were observed, as was expected according to the literature. In stage I, the relapse rate was 3.9%, and in stage II, the relapse rate was 8.9%. In our cohort, the proportion of early-stage colon cancer was 51.4%, which is higher compared to the 37% reported in the literature, especially considering that our center is a tertiary care facility, where a higher number of advanced cases would be expected

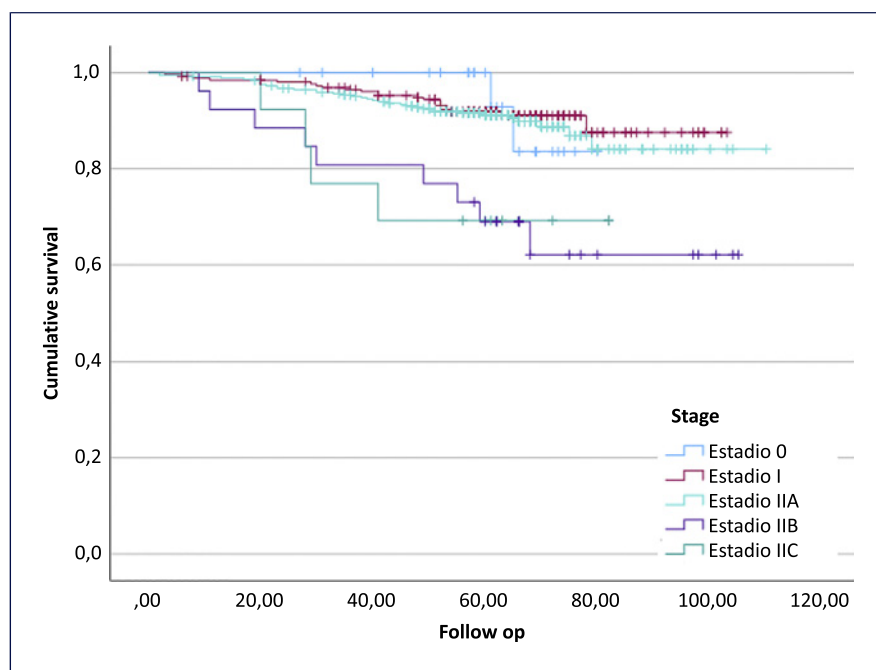


Fig. 3. Overall survival comparing the stages 0, I, and II at diagnosis.

Table 4. Univariate and multivariate analysis of prognostic factors for recurrence

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Surgical approach (open approach)	1.336 (0.649–2.752)	<i>p</i> = 0.432		
Tumor localization	1.146 (0.612–2.145)	<i>p</i> = 0.670		
Surgical complications	0.539 (0.274–1.057)	<i>p</i> = 0.072		
Tumor grade		<i>p</i> = 0.376		
1	1			
2	1.850 (0.240–14.238)			
3	2.692 (0.348–20.846)			
Vascular invasion	0.523 (0.270–1.012)	<i>p</i> = 0.054		
EMVI	0.394 (0.180–0.863)	<i>p</i> = 0.020	1.753 (0.751–4.092)	<i>p</i> = 0.194
Perineural invasion	0.378 (0.182–0.783)	<i>p</i> = 0.009	2.298 (1.052–5.016)	<i>p</i> = 0.037
Mucinous tumor	1.611 (0.704–3.683)	<i>p</i> = 0.259		
pT		<i>p</i> = 0.009		<i>p</i> = 0.124
T1	1		1	
T2	0.168 (0.036–0.775)		0.457 (0.118–1.760)	
T3	0.104 (0.020–0.531)		1.040 (0.379–2.852)	
T4a	0.275 (0.072–1.058)		1.583 (0.342–7.334)	
T4b	0.794 (0.157–4.000)		4.087 (0.832–20.076)	
Number of lymph nodes (>12)	0.835 (0.344–2.024)	<i>p</i> = 0.689		
Number of lymph nodes (>19)	0.808 (0.441–1.477)	<i>p</i> = 0.488		
≥1 risk factor	2.371 (1.224–4.592)	<i>p</i> < 0.010		

CI, confidence interval; HR, hazard ratio; *n*, number.

[10]. In Portugal, there is a national guideline, provided by the Directorate-General of Health, recommending screening based on colonoscopy and fecal blood testing for asymptomatic individuals aged between 50 and 74 years, but there is no nationwide covered program. Some geographical areas are covered by an organized screening program, similar to the scenario in Northern Portugal, which had an annual population coverage of 69% in 2021, and this effective coverage may explain the higher rate of early cases represented in our study [11–13].

Despite the occurrence of local recurrence and distant metastasis following curative surgery remaining a significant concern and being associated with poor prognosis, this high proportion of early cases raises the question of the burden associated with intensive and long-term surveillance in these patients [9]. According to existing literature, the risk of recurrence for stages I to III colon cancer ranges from 30 to 40%, with the occurrence of relapse being dependent on the stage of the disease at diagnosis [9]. In our population, the relapse rate of stage I patients was 3.9%, lower than the 5% described in the literature [5]. Within the stage II subgroup, the relapse rate was 8.9%, as expected higher than in stage I, but still lower than the rates reported in the literature (10–20%) [5]. These low recurrence numbers may question the need for intense surveillance protocols in early-stage colon cancer.

Several recommendations regarding post-treatment surveillance for CRC have been published and endorsed by professional societies. According to NCCN, the surveillance program is, in fact, stage dependent. In stage I patients, there is no need for other exams beyond colonoscopy. In stage II, a more intensive surveillance protocol is advised, with clinical evaluation and tumor seric markers every 3–6 months for the first 2 years and every 6 months between the third and fifth year, as well as a CT scan annually for the first 5 years [8]. Other societies, such as ESMO and ASCO guidelines, suggest similar timings for follow-up exams [5, 14].

While these conventional guidelines advocate for rigorous surveillance, emerging data suggest that less intensive approaches are not inferior. In the “Colofol Randomized Clinical Trial,” approximately 2,500 patients with stages II and III colon cancer were studied, and it was found that more or less intensive surveillance had no impact on overall survival [3]. Synder et al. [4] revealed that the difference between the intensity of surveillance did not have an impact on recurrence, resectability of the recurrent disease, and overall survival. Notably, the literature reveals that increased

postoperative CRC follow-up, from 2 to 5 examinations over 3 years of post-surgery with 5 years of follow-up, did not yield significant differences in 5-year overall mortality or CRC-specific mortality rates [2]. In a scenario involving a diverse group of patients who could potentially benefit from more intensive surveillance, there is a notable focus on developing strategies better tailored to individual risk levels. Although the high-intensity follow-up group detected CRC-specific recurrences earlier, this did not lead to reduced mortality rates [2–4].

Another important point concerns the timing of recurrence. Our results demonstrated that the vast majority of relapses occur within the first 3 years after surgery (73.9%), with a low percentage occurring between the third and fifth years of follow-up. This difference was even more pronounced in the stage II subgroup, where despite a higher percentage of relapse, these occurred earlier (median time to recurrence of 14.5 months). These findings allow us to infer that the highest risk period lies within the first 3 years of surveillance. These data may lead us to consider the possibility of reducing the hospital follow-up time.

An acknowledgment has also to be made regarding the low rate of adjuvant chemotherapy in this group. This can be explained by the fact that, during the study period, histologic factors were not yet used as criteria for adjuvant treatment (specifically undifferentiated tumor, lymphovascular and perineural invasion, and microsatellite instability) [8].

In our study, factors impacting recurrence in the univariate analysis were EMVI and perineural invasion, stage, and the presence of at least one risk factor. In the multivariate analysis, only perineural invasion was found to be statistically significant. These findings in a group with a low rate of adjuvant chemotherapy allow us to confirm that histologic factors such as lymphovascular and perineural invasion have an impact on the risk of recurrence and should be used to aid in the decision regarding adjuvant treatments, as reported in recent literature [9]. In patients without risk factors, the recurrence rate was 5.6%, increasing to 8.8% in patients with at least one risk factor. Therefore, these adverse prognostic factors may not only be used to guide treatment decisions but also to tailor follow-up programs in patients with early-stage disease. In patients without risk factors for recurrence and with early-stage colon cancer, the risk of recurrence is very low and it is in this group that the decrease in intensity of follow-up could have a significant impact at a hospital level.

Our findings challenge the need for intense surveillance in early-stage patients, as the low recurrence rates observed question the benefits of such protocols, emphasizing the importance of finding a balanced approach considering both clinical needs and economic considerations [2, 9]. They also emphasize the need to develop risk scores that can be used to identify patients who require more intensive surveillance. The future of surveillance seems to be moving toward a more personalized, risk-based approach that takes into account individual patient and disease characteristics.

The study's strengths include having a substantial sample size, being conducted with a group of patients treated in a tertiary center with standardized treatment by experienced teams and using real-world data. The limitations encompass its retrospective design, being conducted in a single center, lack of emergency surgery cases, and the time period not yet encompassing a significant laparoscopy rate.

Conclusion

The recurrence rate is low in early-stage colon cancer, with the majority of recurrences occurring within the first 3 years. Histologic factors have a significant impact on recurrence and may allow a less intense follow-up regimen in these patients. Therefore, these results suggest that long-term follow-up plans should be tailored according to individual risk factors, taking into account multiple disease factors, which may have not only an economic impact but also on the patient's quality of life.

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Statement of Ethics

All procedures in this study were in accordance with the ethical standards and with the Helsinki Declaration of 1964. All patients at our institution sign a consent form on admission allowing their data to be used. The Ethics Committee approved the present work. The ethics opinion document has the following identification: Parecer CES. 109/024.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Paula Ferreira Pinto and Mariana Peyroteo: design of the work; acquisition, analysis, interpretation of data; and writing of the manuscript. Catarina Baía, Mariana Marques, and Maria João Cardoso: drafting of the work and acquisition of data. José Flávio Videira and Joaquim Abreu de Sousa: revision of the manuscript and acceptance for publication.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article (and/or) its supplementary materials.

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