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ORIGINAL ARTICLE

The (ir)relevance of the abandoned criterion II for the diagnosis of serrated polyposis syndrome: a retrospective cohort study

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Abstract

The World Health Organization (WHO) recently updated the diagnostic criteria for serrated polyposis syndrome (SPS). One of the three previous diagnostic criteria (criterion II^{2010}) is now abandoned*: ≥ 1 serrated polyp (SP) proximal to the sigmoid in a first-degree relative (FDR) of a patient with SPS.* Individuals fulfilling this abandoned criterion now receive the same surveillance recommendations as all FDRs of patients with SPS. We aimed to compare the incidence of advanced neoplasia (AN) in FDRs with vs. without fulfillment of the abandoned criterion II^{2010}. We retrospectively recruited FDRs of patients with SPS who underwent a colonoscopy, and stratified them according to fulfilment of criterion II^{2010} at baseline. Our primary and secondary outcomes were AN incidence during surveillance and at baseline, respectively. We included 224 FDRs of patients with SPS, of whom 36 (16%) fulfilled criterion II^{2010} at baseline. One hundred and five underwent surveillance after baseline. Criterion II^{2010}-positive FDRs were at increased risk of AN, both during surveillance (hazard ratio 8.94, 95% CI 2.15–37.1, p = .003) as well as at baseline (adjusted odds-ratio 9.30, 95% CI 3.7–23.3, p < .001). FDRs of patients with SPS that underwent colonoscopy and fulfilled the abandoned criterion II^{2010} for SPS diagnosis were at increased risk of AN at baseline and during surveillance in this small, retrospective cohort study. Our results should be interpreted with caution but suggest that adherence to surveillance recommendations for all FDRs of patients with SPS is important, especially for those that would have fulfilled the now abandoned criterion II^{2010}.

Introduction

Serrated polyposis syndrome (SPS) is characterized by the presence of numerous serrated polyps (SPs), and is associated with an increased colorectal cancer (CRC) risk [1–3]. A genetic basis of the syndrome has not been identified and so the diagnosis is based solely on clinical criteria, which have been redefined several over the past decades [4–6]. Due to a scarcity of supporting data these clinical criteria can be considered somewhat arbitrary. As such, one particular clinical criterion (2010′s criterion II) has been topic of continuous debate ever since its introduction [4]. The WHO's 2010 clinical criteria [4] included (I) *at least five SPs proximal to the sigmoid colon, with two or more of these being > 10 mm;* (II) *any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative (FDR) with serrated polyposis syndrome*, or (III) *> 20 serrated polyps of any size, but distributed throughout the colon*. Recently, the World Health Organization (WHO) published the updated 2019 clinical criteria for SPS diagnosis, abandoning this controversial

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second criterion [7]. The updated 2019 criteria now only include two diagnostic criteria: (I) ≥ *5 serrated lesions/polyps proximal to the rectum, all being* ≥ *5 mm in size, with* ≥ *2 being* ≥ *10 mm in size;* or (II) > *20 serrated lesions/polyps of any size distributed throughout the large bowel, with* ≥ *5 being proximal to the rectum*.

Unfortunately, the debate about the 2010′s criterion II has been held mostly 'offline' and has seen limited empirical support due to an almost complete lack of evidence on patients fulfilling this criterion. This lack of evidence, in turn, has been a result of the consistent exclusion of criterion II patients from most recent cohort studies, which extensively described CRC risk and risk-factors in criterion I and/or III patients, but not in criterion II patients [1, 2, 8–10].

Thus, evidence supporting both the introduction of criterion II in 2010, as well its abandonment in 2019, is lacking. Nevertheless, there are two important rational arguments to support the abandonment. First, the presence of a serrated polyp proximal to the sigmoid in a FDR of a patient with SPS might often be a manifestation of a naturally occurring serrated polyp, rather than a manifestation of a polyposis syndrome. After all, with a prevalence of 4.7–12.2%, serrated polyps proximal to the descending colon are common in healthy individuals without SPS [11–13]. The prevalence of SPs proximal to the sigmoid, following the WHO's definition of proximal, is probably even somewhat higher. Exposing all such cases to the stringent endoscopic surveillance regimens imposed on 'true' serrated polyposis patients might lead to overtreatment. Second, *all* FDRs of patients with SPS are recommended to undergo regular endoscopic surveillance (mostly 5 yearly) according to several guidelines and experts [8, 10, 14–17]. Such recommendations are based on several studies demonstrating an increased CRC risk in first-degree relatives of patients with SPS [16–18]. Therefore, even after abandonment of criterion II, all criterion II individuals who would formerly have been diagnosed with SPS will still receive regular endoscopic surveillance if these recommendations are obeyed, simply because they are by definition FDRs of a patients with SPS.

The clinical implication of abandonment of criterion II is that those who were formerly diagnosed with SPS based on criterion II only, will no longer be considered 'true' SPS, and will fall under the same recommendations as all other FDRs of patients with SPS. Although we and many others support the WHO's decision to abandon 2010's criterion II, this decision would ideally have been supported by cohort studies demonstrating that, indeed, criterion II patients harbor a similar CRC risk compared to other FDRs of patients with SPS. Such studies are unfortunately lacking. In an attempt to bridge this empirical gap, we carried out this first retrospective cohort study focusing on patients fulfilling the abandoned WHO's 2010 criterion II.

Methods

To prevent confusion between WHO's 2010 and updated 2019 criteria, we have superscripted '$^{2010\prime}$ or '$^{2019\prime}$ each time one of the WHO's criteria is mentioned, referring to the 2010 WHO guideline [4] and 2019 WHO guideline [6], respectively.

Study aim

We aimed to compare risk of advanced neoplasia (AN) in FDRs of patients with vs. *without* fulfillment of criterion II^{2010}.

Study design and population

We retrospectively collected a cohort of FDRs of patients with SPS and fulfilled WHO criterion I^{2010} and/or III^{2010} [4]. Probands were identified through patient records in the participating Spanish, British and Dutch hospitals and their FDRs who had undergone at least one colonoscopy were included in the study. Because of the retrospective nature of this study, the Institutional Review Board (IRB) of the Academic Medical Center (AMC) in Amsterdam decided that this study did not fall under the legislation regarding Medical Research Involving Human Subjects ACT (WMO).

Inclusion criteria

All FDRs (siblings, children or parents) of index SPS cases were eligible for inclusion if they underwent at least one colonoscopy in their lifetime. We excluded all FDRs with known CRC-related germline mutations or an inflammatory bowel disease. We also excluded FDRs that fulfilled WHO criteria I^{2010} and/or III^{2010} at baseline colonoscopy. FDRs were divided into two groups according to their fulfillment of criterion II^{2010} at baseline, allowing us to compare II^{2010}-positive FDRs vs. II^{2010}-negative FDRs.

Outcome parameters

Our primary endpoint was the risk AN encountered during surveillance colonoscopies after baseline, comparing II^{2010}-positive vs. II^{2010}-negative FDRs. Secondary endpoints were polyp burden at baseline in II^{2010}-positive vs. II^{2010}-negative FDRs, and progression into 'true' SPS phenotype (i.e. fulfillment of WHO criterion I^{2010} and/or III^{2010}) based on cumulative polyp count during consecutive surveillance colonoscopies.

Serrated polyps were divided into three subtypes: sessile serrated lesion (SSL) with or without dysplasia,

hyperplastic polyp (HP) and traditional serrated adenoma (TSA). Advanced SPs (ASPs) were defined SPs ≥ 10 mm in diameter, with dysplasia (any grade) or TSAs. Advanced adenomas (AAs) were defined as adenomas ≥ 10 mm in diameter, with high-grade dysplasia (HGD) and/or a villous component of ≥ 25%. Advanced neoplasia was defined as any ASP, AA or CRC.

Statistical analyses

Baseline characteristics were compared using independent samples t-tests, Chi-squared tests, Fisher's exact tests and Mann–Whitney *U* tests, where appropriate. Risk of AN during surveillance was calculated using Kaplan–Meier survival analyses and expressed as cumulative hazard and 5-year cumulative incidence. FDRs were censored at the date of their most recent colonoscopy. The AN hazard for criterion II^{2010}-positive and II^{2010}-negative FDRs was compared in univariate and multivariable Cox-regression analyses and expressed as hazard ratio (HR). Baseline polyp burden was compared between criterion II^{2010}-positive and II^{2010}-negative FDRs with univariate and multivariable logistic regression analyses. Co-variates for multivariable Cox- and logistic regression analyses were selected based on baseline differences between the two groups (age, gender and smoking status). We restricted the number of variables for multivariable analyses to 1 variable per 10 events to prevent overfitting in our dataset [19].

Survival curves were produced using RStudio version 1.1.453 (Integrated Development for R. RStudio, Inc., Boston, MA, USA) with Survminer package version 0.4.3. All other analyses were performed using Statistical Package for Social Sciences (SPSS) version 24 (IBM, Somers, New York, USA).

Results

Baseline characteristics

Two hundred and twenty four FDRs fulfilled our inclusion criteria. At baseline, 36 (16%) were II^{2010}-positive and 188 (84%) were II^{2010}-negative. The mean age at the time of baseline colonoscopy was 50 years (± 13), and 42% were male (Table 1). The majority (65%) of FDRs was a sibling to the index patient, while 29% was a child and 4.9% was a parent of the proband. The indication of baseline colonoscopy was familial screening in 184 (82%), symptoms in 27 (12%) and population screening in 3 (1.3%) individuals. Age, gender and reason for baseline colonoscopy did not differ between II^{2010}-positive and II^{2010}-negative FDRs. Smoking or former smoking was more common within II^{2010}-positive FDRs (44% vs. 20%, p = .006), although smoking status was missing for 54% of included individuals.

Of the 224 included FDRs, 105 underwent one or more surveillance colonoscopies after baseline, of whom 15 (13%) were II^{2010}-positive and 90 (78%) were II^{2010}-negative. The median follow-up duration was 5.3 years (IQR 2.9–7.7), and was slightly longer for II^{2010}-negative than II^{2010}-positive FDRs (3.5 vs. 5.6 years, p = .026). In this subcohort of 105 FDRs, II^{2010}-positives were slightly older at baseline (54 vs. 49 years, p = .13), and were more often (former) smokers (47% vs. 24%, p = .070).

Advanced neoplasia during surveillance

The risk of AN during surveillance could be assessed in the subcohort of 105 patients who underwent surveillance colonoscopies after baseline. None of the included patients developed CRC during surveillance. AN during surveillance occurred in 9/90 II^{2010}-negative (10%) FDRs; four had an AA, four had an ASP and one had both an AA and an ASP. In comparison, AN occurred in 4/15 (27%) II^{2010}-positive FDRs; three had an ASP while one had both an AA and an ASP (Table 2).

The cumulative 5-year incidence of AN during surveillance was 7.2% (95% CI 1.4–12.6%, Fig. 1a). The 5-year cumulative AN incidence was significantly higher for criterion II^{2010}-positive FDRs (30.4%, 95%CI 0–51.5%) than for II^{2010}-negative FDRs (3.2%, 95% CI 0–7.4%) (Fig. 1b & Table 2), with a corresponding univariate HR of 8.94 (95% CI 2.15–37.1, p = .003). Because only 13 events occurred in our cohort, no multivariable regression analysis could be performed.

Polyp burden at baseline

CRC prevalence and polyp burden at baseline could be assessed in the entire cohort of 224 patients. None of the II^{2010}-positive FDRs presented with CRC at baseline colonoscopy (0%, 95% CI 0–9.7%), compared to 4 of the 188 II^{2010}-negative FDRs (2.1%, 95% CI 0.58–5.4%; Table 3). Thirteen out of 36 II^{2010}-positive (39%) FDRs presented with AN at baseline colonoscopy, compared to 11 of the 188 II^{2010}-negative (5.9%) FDRs (OR 10.2, 95% CI 4.1–25, p < .001; Table 3). Adjusted for age at baseline colonoscopy, this difference remained statistically significant (OR 9.30, 95% CI 3.7–23.3, p < .001). Aside from overall AN incidence, both advanced SPs (11/36, 31% vs. 0/188, 0%; p < .001) as well as advanced adenomas (7/36, 19% vs. 11/188, 5.9%; p = .01) were more common in II^{2010}-positive than II^{2010}-negative FDRs (Table 3).

Table 1 Baseline characteristics stratified according to fulfilment of WHO's criterion II[2010] for SPS diagnosis at baseline colonoscopy

All patients (n = 224)				
	Overall (n = 224)	Criterion II[2010]-positive FDR (n = 36)	Criterion II[2010]-negative FDR (n = 188)	P-value
Age at index colonoscopy, mean (SD)	50 (13)	53 (12)	50 (13)	.11
Male, n (%)	95 (42%)	16 (44%)	79 (42%)	.86
Relation to index patient				
Sibling	145 (65%)	23 (64%)	122 (65%)	.97
Parent	11 (4.9%)	2 (5.6%)	9 (4.7%)	
Child	65 (29%)	11 (31%)	54 (29%)	
Unknown	3 (1.3%)	0	3 (1.6%)	
Reason index colonoscopy				
Familial screening	184 (82%)	31 (86%)	153 (81%)	.66
Community screening	3 (1.3%)	1 (2.8%)	2 (1.1%)	
Symptoms	27 (12%)	3 (8.3%)	24 (13%)	
Other/unknown	10 (4.5%)	1 (2.8%)	9 (4.8%)	
Smoking history				
Previous/current smoker	54 (24%)	16 (44%)	38 (20%)	.006
Never smoker	49 (22%)	4 (11%)	45 (24%)	
No information	121 (54%)	16 (44%)	105 (56%)	
Subcohort of patients with one or more surveillance colonoscopies after index (n = 105)				
	Overall (n = 105)	Criterion II[2010]-positive FDR (n = 15)	Criterion II[2010]-negative FDR (n = 90)	
Age at index colonoscopy, mean (SD)	50 (12.7)	54 (11.7)	49 (12.1)	.13
Male, n (%)	44 (42%)	7 (47%)	37 (41%)	.71
Relation to index patient				
Sibling	80 (76%)	12 (80%)	68 (76%)	.95
Parent	6 (5.7%)	1 (6.7%)	5 (5.6%)	
Child	18 (17%)	2 (13%)	16 (18%)	
Unknown	1 (1%)	0%	1 (1.1%)	
Reason index colonoscopy				
Familial screening	89 (85%)	14 (93%)	75 (83%)	.29
Community screening	2 (1.9%)	1 (6.7%)	1 (1.1%)	
Symptoms	9 (8.6%)	0%	9 (10%)	
Other/unknown	5 (4.8%)	0%	5 (5.5%)	
Smoking history				
Previous/current smoker	29 (28%)	7 (47%)	22 (24%)	.070
Never smoker	29 (28%)	2 (13%)	27 (30%)	
No information	47 (45%)	6 (40%)	41 (46%)	
Number of surveillance colonoscopies after baseline				
1 Colonoscopy	51 (49%)	5 (33%)	46 (51%)	.18
2 Colonoscopies	24 (23%)	3 (20%)	21 (23%)	
3 Colonoscopies	13 (12%)	4 (27%)	9 (10%)	
4 Colonoscopies	5 (4.8%)	1 (6.7%)	4 (4.4%)	
5 Colonoscopies	5 (4.8%)	2 (13%)	3 (3.3%)	
> 5 Colonoscopies	7 (6.7%)	0 (0%)	7 (7.8%)	
Median interval (years) between surveillance colonoscopies (IQR)	1.91 (1.09–2.59)	1.49 (1.10–2.27)	1.97 (1.09–2.72)	
Number of surveillance colonoscopies, median (IQR)	2 (1–3)	2 (1–3)	1 (1–3)	.18
Median follow-up duration after baseline, years (IQR)	5.3 (2.9–7.7)	3.5 (1.3–6.0)	5.6 (3.1–8.4)	.026

Characteristics of the entire cohort are presented in the upper half of the table; the baseline characteristics of the subcohort of patients with surveillance colonoscopies are presented in the bottom half of the table

FDR first-degree relative; *SD* standard deviation; *IQR* interquartile range

Table 2 Cox regression analysis of advanced neoplasia during surveillance, comparing first-degree relatives of patients with SPS with vs. without fulfillment of WHO's criterion II^{2010} for SPS diagnosis

		Cumulative 5-year AN incidence	Unadjusted HR (95% CI)	P-value
AN detected during surveillance, n (%)				
II^{2010}-negative	9/90 (10%)	7.2% (1.4–12.6%)	1.00	
II^{2010}-positive	4/15 (27%)	26.4% (8.0–41.1%)	8.94 (2.15–37.1)	0.003

AN advanced neoplasia *HR* hazard ratio

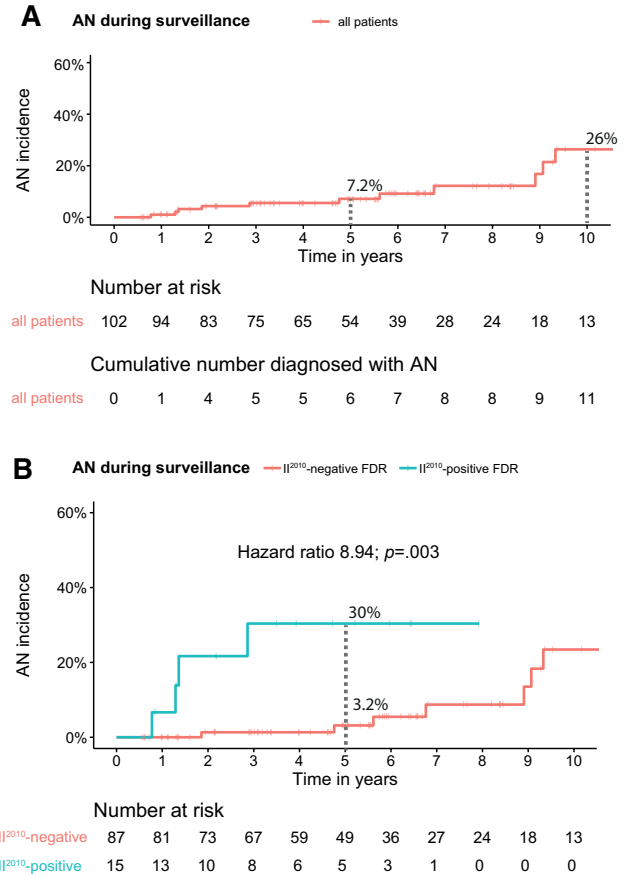

Fig. 1 Cumulative hazard curve for advanced neoplasia during surveillance for all first-degree relatives (**a**), and stratified by fulfillment of WHO criterion II^{2010} (**b**). *AN* advanced neoplasia; *FDR* first-degree relative

Progression to fulfillment of WHO criterion I^{2010} and/or III^{2010} during surveillance

Progression to WHO criterion I^{2010} and/or III^{2010} positive SPS during surveillance could be assessed in the subcohort of 105 individuals who underwent surveillance after baseline. A total of five patients (2.2%) developed sufficient numbers of polyps over time to fulfill criterion I^{2010} and/or III^{2010}. This occurred more often in criterion II^{2010}-positive FDRs (3/15, 20%) than in II^{2010}-negative FDRs (2/90, 2.2%, Fisher's Exact p = .03). Detailed patient characteristics and polyp burden at baseline and during surveillance are displayed in supplementary Table 1.

Fulfillment of WHO criterion II^{2010} during surveillance

Among the 90 FDRs who were II^{2010}-negative at baseline and underwent subsequent surveillance, 20 (22.2%) were diagnosed with a SP proximal to the sigmoid during follow-up, thus fulfilling WHO criterion II^{2010}. Compared to the 70 FDRs who did not fulfill II^{2010} during surveillance, those who did were at increased risk for AN (HR adjusted for age at baseline 7.1, 95% CI 1.34 = 37.6, p = .021). Based on the 49 FDRs for whom smoking history was known, FDRs that fulfilled criterion II^{2010} during surveillance were significantly more often (former) smokers than FDRs who did not fulfill II^{2010} during surveillance (73.3% vs. 32.4%, p = .012).

Discussion

Based on the updated WHO criteria in 2019, patients that were formerly diagnosed with SPS based on criterion II^{2010} are no longer considered to have SPS anymore. Therefore, these individuals now receive surveillance recommendations identical to all other FDRs of patients with SPS [8, 14–17, 20]. However, in this retrospective international multi-center cohort we show that those FDRs that fulfill the WHO criterion II^{2010} seem to be at increased risk of developing AN during surveillance (HR 8.94, p = .003) as compared to WHO criterion II^{2010} negative FDR. In addition, we demonstrate that II^{2010}-positive FDRs more often presented with AN at baseline colonoscopy (adjusted OR 9.30, p < .001). Furthermore, 22.2% of FDRs who were II^{2010}-negative at baseline and underwent surveillance, fulfilled II^{2010} at a later stage based on polyps removed during surveillance. Those who did were at increased risk of AN during surveillance (p = .021). Lastly, and perhaps not surprisingly, FDRs that were II^{2010}-positive at baseline were more likely to acquire enough polyps to fulfill WHO criterion I^{2010} and/or III^{2010}

Table 3 Logistic regression analysis of findings at index colonoscopy, comparing first-degree relatives of patients with SPS with vs. without fulfillment of WHO's criterion II^{2010} for SPS diagnosis

		Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)[a]	P-value
CRC detected at baseline colonoscopy, n (%)					
II^{2010}-negative	4/188 (2.1%)				
II^{2010}-positive	0/36	n/a[b]	.37[b]	n/a[b]	n/a[b]
AN detected at baseline colonoscopy, n (%)					
II^{2010}-negative	11/188 (5.9%)	1.00		1.00	
II^{2010}-positive	14/36 (39%)	10.2 (4.1–25)	< .001	9.30 (3.7–23.3)	< .001
ASP detected at baseline colonoscopy, n (%)					
II^{2010}-negative	0/188 (0%)				
II^{2010}-positive	11/36 (31%)	n/a[b]	< .001[b]	n/a[b]	n/a[b]
AA detected at baseline colonoscopy, n (%)					
II^{2010}-negative	11/188 (5.9%)	1.00		1.00	
II^{2010}-positive	7/36 (19%)	3.88 (1.39–10.83)	.010	3.43 (1.21–9.68)	.020

OR odds ratio; *CRC* colorectal cancer; *AN* advanced neoplasia; *ASP* advanced serrated polyp; *AA* advanced adenoma

[a]Adjusted for age at index colonoscopy

[b]Logistic regression analysis not possible because no events occurred in one of the strata; p-value calculated using Chi-squared test

during surveillance. This demonstrates the concept of 'SPS in evolution': since SPS diagnosis is based on cumulative metachronous polyp count, patients that will later be diagnosed with SPS I^{2010} and/or III^{2010} might first fulfill only criterion II^{2010}. Although several important limitations have to be taken into account, these results suggest that criterion II^{2010}-positive patients might in fact be at increased AN risk as compared to criterion II^{2010}-negative FDRs.

There are several potential explanations for this difference. First of all, proximal SPs are strong predictors of metachronous AN in a non-SPS population [21, 22]. This creates an important á priori difference: criterion II^{2010}-positive FDRs have, by definition, proximal SPs at baseline while II^{2010}-negative FDRs, by definition, do not. Erichsen and colleagues demonstrated an OR of 12.42 for future CRC development after baseline resection of a proximal SP, while Schreiner and colleagues reported an OR of 3.37 for metachronous AN after resection of proximal SPs. Since II^{2010}-positive FDRs presented with proximal SPs at baseline while II^{2010}-negatives did not, the increased metachronous AN risk seems comparable with the data in literature on metachronous risk after resection of sporadic SPs. This explanation implies that the increased risk of metachronous AN in II^{2010}-positive FDRs might rather be a result of the predictive value of baseline proximal SPs for metachronous AN, which would also be seen in an average-risk population with proximal SPs at baseline. Second, criterion II^{2010}-positive FDRs more often had advanced adenomas at baseline than II^{2010}-negatives (19% vs. 5.9%, adjusted p = .020). Anderson and colleagues recently reported that metachronous AN during surveillance was most common in patients with synchronous high-risk adenomas and serrated polyps at baseline colonoscopy [23]. This combination of baseline SPs and high-risk adenomas was much more common among II^{2010}-positives, further increasing their a priori risk of metachronous AN. A final possible explanation for the observed difference between II^{2010}-positive and negative FDRs is the difference in smoking behavior. II^{2010}-positive FDRs were more often (former) smokers, and FDRs who were II^{2010}-negative at baseline but later fulfilled II^{2010} were far more likely to be (former) smokers. Since smoking is a known risk-factor for AN, our results also imply that smoking might be a risk-factor for both fulfillment of II^{2010} as well as development of metachronous AN in FDRs of patients with SPS [24].

Several limitations in our study design and sample size have to be acknowledged to enable proper interpretation of the data. First, the number of included patients was small. Most notably, our primary outcome measure could be assessed in 105 patients, of whom only 15 were criterion II^{2010} positive. This small sample-size unfortunately impeded multivariable Cox-regression analyses, despite important baseline differences between the II^{2010}-negative and positive groups with regard to smoking behavior and age. Criterion II^{2010}-positive FDRs more often had a history of smoking (44% vs. 20%, p = .006) and were of older age at baseline (53 years vs. 50 years, p = .11). Since smoking behavior could not be adjusted for due to our small sample-size and high proportion of missing data, this confounder might have significantly influenced our results. Second, we report as secondary outcome measures ASP incidence at baseline and fulfilment of WHO I and/or III during surveillance. However, since the II^{2010} positive group was defined by the presence of one or more proximal SPs at baseline,

this group was by definition at increased risk of both ASPs at baseline and fulfilment of WHO I and/or III during surveillance. Although we feel these outcome measures are informative and relevant to report, this 'circularity' should be kept in mind when interpreting these outcome measures. Furthermore, due to the retrospective design of this study, only FDRs who underwent surveillance colonoscopy after baseline could be included in our primary analysis. This might have led to a selection-bias towards high-risk patients, since surveillance is more likely to be provided to those FDRs who were considered to be at risk of metachronous neoplasia. Due to the retrospective design patients also did not receive colonoscopies at identical surveillance intervals, data were missing and quality parameters were more difficult to interpret.

To our opinion these limitations illustrate how complicated studying criterion II^{2010} is, which is probably why no previous studies have focused on this group of patients. Adequate study design is complicated and acquiring sufficient numbers of FDRs is difficult, even in a large collaborative network. In the absence of superior prospective studies, however, we think our study has several noteworthy strengths that make our data clinically useful. First, since neither introduction nor abandonment of criterion II^{2010} has been supported by convincing evidence, empirical data on this group of patients was urgently needed. We are the first to provide such data. Second, this study was performed within five high volume expert centers in three different countries, which increases external validity of the data.

Due to the above-mentioned limitations, results from this study should be interpreted with caution and, to our opinion, do not encourage a debate about re-introduction of criterion II^{2010} as a separate SPS diagnostic criterion. We believe adequate CRC prevention can be provided for both criterion II^{2010}-positive as well as II^{2010}-negative FDRs by adhering to the currently recommended regular endoscopic surveillance for *all* FDRs of patients with SPS (most guidelines: 5 yearly). In case (advanced) lesions are detected, surveillance should be adjusted if indicated according to the current post-polypectomy guidelines.

In conclusion, FDRs of patients with SPS that would have fulfilled the abandoned criterion II^{2010} for SPS diagnosis might have a higher risk of AN during surveillance than FDRs not fulfilling criterion II^{2010}, although firm conclusions are impeded by our small and retrospective study design. As is applicable to all FDRs of patients with SPS, regular endoscopic surveillance should be provided to prevent CRC [8, 10, 14–17]. Future prospective studies are needed to validate our findings.

Authors contribution AGCB, JEGI, and ED: study conception & design. AGCB, JEGI, DR-A, SC, FB, JJK, and SAR: acquisition of data. AGCB: drafting of the manuscript and statistical analysis. All authors: analysis & interpretation of data, critical revision of the manuscript for intellectual content, technical & logistical support.

Conflict of interest The author FB have endoscopic equipment on loan of Fujifilm, and he received an honorarium for consultancy from Sysmex, and speaker's fee from Norgine. The author MP received research grant from Fujifilm, received consultancy fee from Norgine and speaker's fee from Olympus, Norgine, Casen Recordati and Janssen. The author ED have endoscopic equipment on loan of Olympus and FujiFilm, receive a research grant from FujiFilm and he received a honorarium for consultancy from FujiFilm, Tillots and Olympus and a speakers' fee from Olympus and Roche.

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