# Utilidad del Narrow Band Imaging para el estudio de las enfermedades con alto riesgo de cáncer digestivo

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Tesis doctoral



Departamento de Medicina

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# UTILIDAD DEL NARROW BAND IMAGING PARA EL ESTUDIO DE LAS ENFERMEDADES CON ALTO RIESGO DE CÁNCER DIGESTIVO

Tesis presentada por María López-Cerón Pinilla para optar al grado de Doctor en Medicina

Directores de Tesis:

Dra. Maria Pellisé Urquiza y Dr. Josep Llach Vila

Barcelona, junio de 2013

# AUTORIZACIÓN DEL DIRECTOR DE TESIS

DRA. MARIA PELLISÉ URQUIZA, MÉDICO ESPECIALISTA SENIOR DEL SERVICIO DE GASTROENTEROLOGÍA DEL HOSPITAL CLÍNIC DE BARCELONA,

CERTIFICA:

Que la memoria que lleva por título "Utilidad del Narrow Band Imaging para el estudio de las enfermedades con alto riesgo de cáncer digestivo", presentada por María López-Cerón Pinilla para optar al grado de Doctor en Medicina, ha sido realizada bajo mi dirección. Una vez finalizada, autorizo su presentación para ser juzgada por el tribunal correspondiente. Y para que quede constancia a los efectos oportunos, firmo la presente en

Barcelona a junio de 2013.

Dra. Maria Pellisé Urquiza

## AUTORIZACIÓN DEL DIRECTOR DE TESIS

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JEFE DE LA UNIDAD DE ENDOSCOPIA DIGESTIVA DEL HOSPITAL CLÍNIC DE BARCELONA,

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Dr. Josep Llach Vila

Dedicada a Javi y a Julia,

mis amores

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# Ayudas personales

Los trabajos que constituyen la base de la presente Tesis Doctoral han sido efectuados con el soporte de las siguientes ayudas personales:

# Abreviaturas

**CCR**: cáncer colorrectal

**PAF**: poliposis adenomatosa familiar

**SPS**: síndrome de poliposis serrada

**EII**: enfermedad inflamatoria intestinal

**EAR**: endoscopia de alta resolución

**CCD**: *charged coupled devices*, dispositivos de carga acoplada

**CE**: cromoendoscopia

**NBI**: Narrow Band Imaging

**λ**: longitud de onda

**nm**: nanómetros

**CIMP**: *CpG island methylator phenotype*, fenotipo metilador de islas CpG

**PH**: pólipos hiperplásicos

**ASS**: adenoma serrado sésil

**RR**: riesgo relative

**CU**: colitis ulcerosa

**EC:** enfermedad de Crohn

**NIE:** neoplasia intraepitelial

**mm:** milímetros

# Antecedentes del tema

# 1. Introducción

El cáncer del tubo digestivo es uno de los más prevalentes en la sociedad occidental. En concreto, el cáncer colorrectal (CCR) es el tercer cáncer más frecuente en hombres y el segundo en mujeres de países desarrollados.[1] Este dato contrasta con que el hecho de que los tumores del tubo digestivo son el paradigma de las neoplasias susceptibles de prevención. La herramienta de la que disponemos para ello es la endoscopia digestiva, que permite no sólo diagnosticar, sino extirpar las lesiones precursoras del cáncer.

Tradicionalmente se ha considerado que la lesión fundamental precursora del adenocarcinoma en el tubo digestivo era el adenoma. Así, Vogelstein describió en 1988 la secuencia adenoma – carcinoma, en la que se demuestra que la acumulación secuencial de alteraciones genéticas provoca el desarrollo de adenomas y posteriormente, si continúan acumulándose alteraciones, adenocarcinomas.[2, 3] En el caso del colon esta concepción se ha modificado en los últimos años al constatar que un subgrupo de todos los CCR se desarrolla a partir de un grupo de lesiones diferentes de los adenomas que se han denominado genéricamente pólipos serrados. Esta vía de la carcinogénesis es responsable de un 20-30% de los CCR.[4] El cambio de paradigma en lo que se considera lesión precursora del CCR ha dado lugar una revolución en las estrategias preventivas y en las exploraciones endoscópicas, que actualmente no sólo se dirigen a detectar y resecar los adenomas, sino también los pólipos serrados.

El riesgo de desarrollar cáncer digestivo no es homogéneo en toda la población. En el caso del CCR estos grupos están bien establecidos en población de riesgo bajo, medio y alto.[5] La población de riesgo bajo está compuesta por aquellas personas asintomáticas menores de 50 años sin antecedentes familiares ni personales de adenomas ni CCR; este grupo no es

susceptible de exploraciones endoscópicas. La población de riesgo medio incluye personas de las mismas características, pero mayores de 50 años. Por último, la población de riesgo alto agrupa individuos con patologías que presentan probabilidades muy distintas de desarrollar cáncer. Está constituido fundamentalmente por los siguientes subgrupos: poliposis adenomatosa familiar (PAF), síndrome de poliposis serrada (SPS), enfermedad inflamatoria intestinal (EII) de larga evolución, síndrome de Lynch, o antecedentes personales y/o familiares de adenomas o CCR.[6]

Las actividades preventivas genéricamente se dividen en tres tipos en función del momento en el que actúen. La prevención primaria incluye las medidas dirigidas a disminuir el riesgo de cáncer antes de que éste o las lesiones precursoras aparezcan (por ejemplo, la promoción de hábitos de vida saludables). La prevención secundaria o cribado (*screening*) consiste en la realización de pruebas diagnósticas con la intención de identificar a los individuos con una mayor probabilidad de presentar lesiones precursoras. La prevención terciaria o vigilancia (*surveillance*) representa las exploraciones y los tratamientos que pretenden minimizar el impacto en el individuo a quien ya se ha identificado alguna lesión, ya que estas personas presentan un riesgo mayor de desarrollar otras lesiones metacrónicas.[5] En el caso del cáncer digestivo se ha demostrado que la resección endoscópica de las lesiones precursoras permite prevenir la aparición del mismo y reducir la mortalidad por este motivo.[7] Con este objetivo se han diseñado estrategias de prevención que incluyen la realización de endoscopias digestivas para detectar y extirpar posibles lesiones precursoras con una intensidad que varía en función del riesgo.

Las enfermedades con alto riesgo de desarrollar cáncer digestivo se benefician especialmente de las actividades preventivas endoscópicas. Sin embargo, presentan ciertos rasgos que hacen que la endoscopia convencional proporcione información limitada, por lo que las técnicas de imagen avanzada podrían jugar un papel relevante en el seguimiento de

estos pacientes. En este texto nos centraremos en la PAF, el SPS y la EII de larga evolución, entidades que por sus características requieren un seguimiento endoscópico intensivo y exploraciones exhaustivas.

## 2. Desarrollo de los sistemas de imagen endoscópica y técnicas auxiliares de realce.

En los últimos años la endoscopia digestiva ha experimentado grandes avances que han mejorado la calidad de la imagen y han desarrollado sistemas que permiten "ver lo invisible". El objetivo de las exploraciones endoscópicas es detectar y resecar todas las lesiones precursoras del cáncer, pero esto presenta ciertas dificultades.

En primer lugar, para que una lesión sea detectada, el endoscopista debe identificarla con un cambio grosero en la mucosa gastrointestinal como el pólipo, que en ocasiones no es evidente. Existen lesiones planas o muy similares a la mucosa circundante que pueden pasar desapercibidas al ojo del explorador; e incluso patologías que cursan con cambios tan sutiles que son invisibles y requieren la toma de biopsias aleatorias para poder detectarlos. Por otro lado, las exploraciones endoscópicas no son capaces de detectar absolutamente todas las lesiones: sabemos por estudios con colonoscopias consecutivas que un 22% de pólipos quedan sin diagnosticar en cada exploración[8] y se calcula que aproximadamente la mitad de los CCR de intervalo (aquel diagnosticado entre dos pruebas de cribado o vigilancia) se deben a lesiones no detectadas previamente.[9] Además, el efecto protector de la colonoscopia no se ha demostrado en el CCR derecho.[10, 11] Uno de los factores que intervienen en ello es, posiblemente, la mayor prevalencia de lesiones planas y por tanto más difíciles de detectar en esta localización.

En segundo lugar, una vez biopsiada o resecada la lesión debemos esperar al diagnóstico histológico, lo que también conlleva algunas limitaciones. La muestra requiere un procesamiento con una demora mínima de 24-48 horas, lo que no permite tomar una decisión terapéutica en el momento de la endoscopia. Este hecho es especialmente problemático si la lesión se ha detectado en una biopsia aleatoria de mucosa a simple vista normal, o bien si el margen de la lesión resecada está afecto. Por otro lado, el diagnóstico histológico en ocasiones es controvertido, ya que la concordancia entre los patólogos no es total.[12, 13]

Para intentar superar estas dificultades se han perfeccionado los sistemas de imagen endoscópica y se han desarrollado técnicas auxiliares de realce. A través del aumento de la nitidez y del contraste pretenden, por un lado, mejorar la detección de lesiones precursoras, y por otro, caracterizarlas *in situ*, es decir, predecir su diagnóstico histológico sin necesidad de esperar al procesamiento de la muestra.  Este último concepto se ha denominado "histología virtual" o "biopsia óptica".

Los sistemas de  endoscopia de alta resolución (EAR) o definición permiten una óptima discriminación de pequeños detalles. Esta mejora se ha conseguido mediante el aumento del número de células fotoeléctricas que registran la imagen, que se expresa en píxeles. Las células fotoeléctricas están contenidas en los chips de color CCD (*charged coupled devices*, dispositivos de carga acoplada). Los sistemas EAR han conseguido miniaturizar los CCD, de manera que tienen una capacidad de hasta 1 millón de píxeles a diferencia de los videoendoscopios convencionales, que tienen en torno a 300 000. Dado que con mayor cantidad de píxeles se consigue mayor calidad, la imagen que ofrece la EAR es excelente. Para visualizar una imagen de alta resolución es necesario además que el circuito esté acoplado con videoprocesador y cables de transmisión capaces de tratar imágenes de alta resolución y con un monitor de televisión con mayor número de líneas (1080 frente a las 576 o 720 convencionales), suficiente para recibir la alta densidad de píxeles del CCD.[6, 14, 15]

Otro sistema endoscópico que ayuda a percibir pequeños detalles es la magnificación. Mientras que la resolución se refiere a la nitidez de la imagen, la magnificación consiste en la amplificación de la misma. En algunos modelos de endoscopios de alta resolución se incorpora un zoom digital que agranda los píxeles entre 1,5 y 2 veces perdiendo así resolución. Por el contrario, los sistemas de magnificación óptica amplifican la imagen hasta 150 veces sin pérdida de nitidez.[6, 14, 15] Tanto la EAR como la magnificación se han utilizado para diagnosticar lesiones en el tubo digestivo superior e inferior en combinación con CE.

Además se han desarrollado técnicas auxiliares de realce que aportan información adicional. La cromoendoscopia (CE) es la que se desarrolló en primer lugar y en los países asiáticos forma parte de las herramientas de la práctica clínica rutinaria. Consiste en la aplicación tópica de contrastes (generalmente índigo carmín o azul de metileno) en la mucosa gastrointestinal que permiten resaltar pequeñas irregularidades, delimitando lesiones invisibles por la luz blanca, mejorando la visualización de sus márgenes y ayudando a su caracterización mediante la inspección detallada de su patrón de criptas.[16] Sus aplicaciones clínicas para la detección y caracterización de lesiones en esófago, estómago y colon son bien conocidas[17-19] y representa el referente de las técnicas auxiliares de realce que se han desarrollado posteriormente. A pesar de sus ventajas, no se ha implantado de forma generalizada porque es una técnica laboriosa, que requiere dedicarle tiempo y en ocasiones conlleva cierto grado de suciedad.

En vista de los inconvenientes de la CE se desarrollaron tecnologías que proporcionan información similar, con la ventaja de ser reversibles (se activan y desactivan pulsando un botón), rápidas y limpias. Estos sistemas se han denominado genéricamente de CE digital. El primero en comercializarse fue el sistema Narrow Band Imaging (NBI), de la casa Olympus (Olympus Medical Systems, Tokio, Japón). Posteriormente se diseñaron sistemas capaces de obtener una visión similar mediante el postprocesamiento digital de imágenes, como el

sistema FICE de la casa Fuji (Fujinon, Saitama, Japón) y el sistema i-Scan de la casa Pentax (Pentax, Tokio, Japón).

## 2.1. El sistema Narrow Band Imaging

El sistema NBI es una herramienta endoscópica de realce basada en un filtro que sólo permite el paso de luz en el espectro del verde y del azul. Proporciona una imagen con contrastes que destacan cambios sutiles de la mucosa y permiten observar su estructura íntima y patrón vascular. La microestructura de la superficie mucosa y la microvasculatura se encuentran alteradas en las lesiones neoplásicas del tubo digestivo, por lo que el sistema NBI puede potencialmente mejorar su detección y caracterización.

### 2.1.1. Fundamentos técnicos

Percibimos la luz de un color determinado según su longitud de onda ($\lambda$). La luz blanca visible contiene muchas $\lambda$, es decir, tiene un espectro amplio (400-700 nm). Al iluminar un objeto rojo con luz blanca, este objeto absorbe la luz de todas las longitudes de onda salvo las que están en el rango del rojo, que refleja. La luz reflejada llega al ojo, que lo percibe como rojo. Si iluminamos un objeto rojo con luz verde y azul, absorberá toda la luz y no reflejará nada, por lo que percibiremos el objeto de color negro: este es el fundamento del NBI. En el sistema NBI la lámpara xenón del endoscopio emite luz blanca que pasa a través de un filtro. Así se crea una luz con dos bandas estrechas, es decir, que contienen pocas $\lambda$. La $\lambda$ central de cada banda es de 415 y 540 nm, en el rango del azul y del verde respectivamente (figura 1). La

luz con estas λ es específicamente absorbida por la hemoglobina. Como se ha eliminado el componente rojo, la hemoglobina no refleja ninguna luz. Por tanto, al iluminar la mucosa con NBI los vasos se visualizan en color oscuro, con gran contraste respecto al resto de estructuras mucosas. Al estrechar la anchura de las bandas se incrementa la intensidad de la luz, mejorando también de este modo el contraste. Por otra parte, al tener distintas λ, la luz penetra hasta diferentes profundidades en el tejido, resaltando en distintos colores la red vascular superficial y la profunda. La luz azul tiene una λ corta y destaca por tanto la red vascular superficial, que con NBI se visualiza de color marrón. En cambio la luz verde tiene mayor λ y resalta los vasos mucosos más profundos y los submucosos, que con NBI adquieren un tono cian.[20, 21] La tecnología NBI está comercializada en equipos que incorporan un sistema de imagen de alta resolución, lo que contribuye a aumentar la calidad de la imagen.
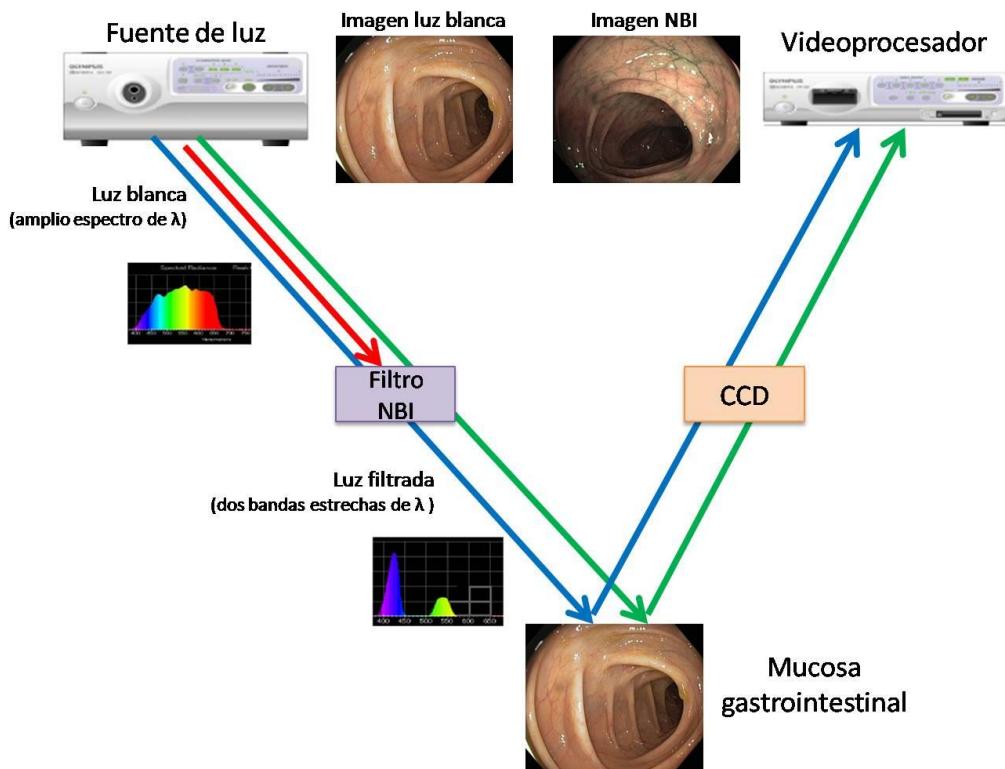


**Figura 1.** Representación esquemática del funcionamiento del sistema Narrow Band Imaging.

## 2.1.2. Contribución del NBI al estudio de las enfermedades del tubo digestivo

Desde su aparición, la tecnología NBI ha sido evaluada en múltiples estudios donde se ha explorado su aportación al manejo de enfermedades digestivas que potencialmente pueden desarrollar lesiones malignas, tanto en el tracto superior como en el inferior.

El esófago de Barrett (EB) es una entidad donde el papel del NBI ha sido ampliamente investigado. Los pacientes con EB son se benefician de un seguimiento endoscópico periódico para despistaje de lesiones displásicas y así evitar su progresión a cáncer. En estas endoscopias se recomienda la toma de biopsias aleatoria de cada cuadrante cada 2 cm, ya que la displasia se presenta en lesiones planas que pasan desapercibidas a la endoscopia convencional.[22] El NBI ha demostrado ser capaz de detectar una mayor proporción de áreas con displasia reduciendo el número de biopsias.[23] Respecto a la caracterización, un metaanálisis que incluyó 2194 lesiones el sistema NBI mostró una capacidad para identificar displasia de alto grado con una alta precisión diagnóstica (sensibilidad 0,94 y especificidad 0,99).[24]

Existen varios estudios que evalúan la capacidad del NBI para identificar y caracterizar lesiones precursoras del cáncer gástrico, así como cáncer gástrico precoz. Se ha comunicado la utilidad del NBI para detectar áreas focales de metaplasia intestinal o displasia,[25, 26] sugiriendo que podría evitar la toma aleatoria de biopsias en las endoscopias de pacientes con gastritis crónica, así como para delimitar lesiones de cáncer gástrico precoz previo al tratamiento.[27] En la literatura japonesa se han comunicado diferentes descripciones de estos rasgos con NBI y magnificación que caracterizan eficazmente la metaplasia intestinal[28, 29] y displasia,[30] además de distinguir en pequeñas lesiones deprimidas la presencia de cáncer precoz frente a gastritis.[31] En la literatura occidental un estudio multicéntrico reciente se validó una clasificación simplificada con NBI sin magnificación que diferenciaba mucosa normal, metaplasia intestinal y displasia con alta precisión.[32]

En el colon el sistema NBI no ha demostrado mejorar la detección de adenomas globalmente frente a la endoscopia de luz blanca,[33-38] sin embargo existen datos que indican que podría identificar más lesiones planas.[39-41] Respecto a la caracterización de lesiones (figura 2), se han diseñado varias clasificaciones basadas en la microestructura del patrón de criptas y la microvascularización.[42-44] La mayoría de estos estudios proceden de la literatura japonesa y se han llevado a cabo con endoscopios de magnificación. Recientemente se ha desarrollado una clasificación simplificada conjunta con autores japoneses y occidentales que es posible aplicar sin magnificación, con resultados prometedores (precisión diagnóstica del 89%).[45, 46]
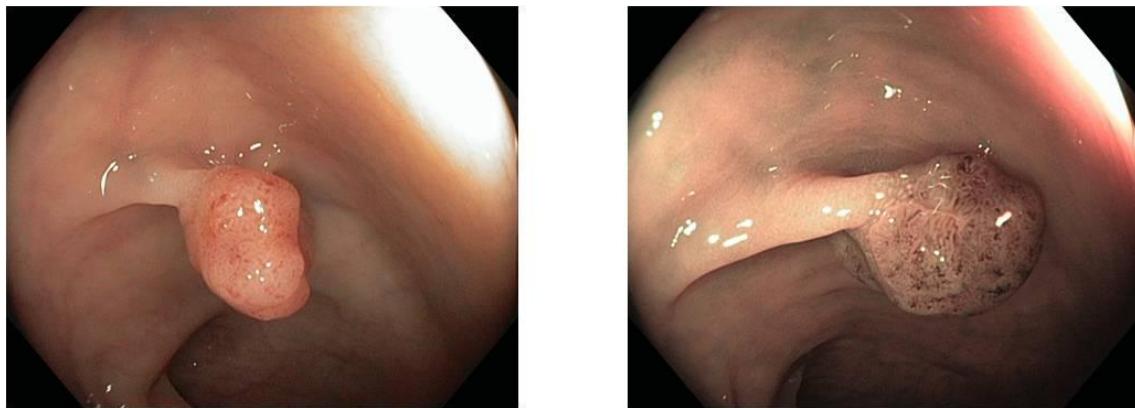


**Figura 2.** Adenoma tubular con displasia de bajo grado en colon. Imagen con luz blanca (izquierda) y NBI (derecha).

La capacidad del NBI para predecir la histología de los pólipos de colon se ha llevado a la práctica clínica evaluando si podría evitar el análisis histológico en lesiones a priori de bajo riesgo y predecir el intervalo de seguimiento inmediatamente después de la colonoscopia, sin necesidad de esperar al diagnóstico histológico. Esta estrategia ha dado buenos resultados en los dos estudios que la han explorado hasta el momento, en los que la recomendación de intervalo de seguimiento coincidió con la que se habría hecho conociendo el diagnóstico

histológico en más de 80% de los casos.[47, 48] El NBI también ha demostrado aplicabilidad clínica al ser capaz de predecir histología hiperplásica en pólipos de rectosigma menores de 5 mm con buena fiabilidad (valor predictivo negativo para adenoma 95-99%),[49, 50] de manera que estos pólipos podrían dejarse *in situ* con seguridad tras examinarlos con NBI.

# 3. Enfermedades con alto riesgo de cáncer digestivo

## 3.1. Poliposis adenomatosa familiar

La PAF clásica es una enfermedad autosómica dominante caracterizada por la presencia de más de cien pólipos en el colon y recto, además de varias manifestaciones extracolónicas y extraintestinales. Su incidencia es de 1 caso por cada 10000 habitantes.[51] Casi todos los pacientes desarrollan CCR a los 40-50 años a no ser que se identifiquen de forma temprana y se traten con colectomía profiláctica.[52] En contraposición a la forma clásica, un 8% de familias con PAF presentan una forma de presentación atenuada, con menos pólipos y desarrollo de CCR a edades más tardías.

La PAF clásica está producida la mayor parte de las veces por una mutación germinal en el gen supresor de tumores *APC* (*adenomatous poliposis coli*). Recientemente se ha descrito que las mutaciones bialélicas del gen *MUTYH* son responsables de un 10% de los casos de PAF clásica.[53] Por otro lado, un 15-20% de los casos con PAF son *de novo*, es decir, sin evidencia clínica o genética de enfermedad en los padres.[54]

Entre las manifestaciones extracolónicas se encuentran los adenomas en intestino delgado (presentes en hasta un 92% de los pacientes con PAF) o estómago (6%) (figura 3) y la poliposis de glándulas fúndicas (47%).[55]
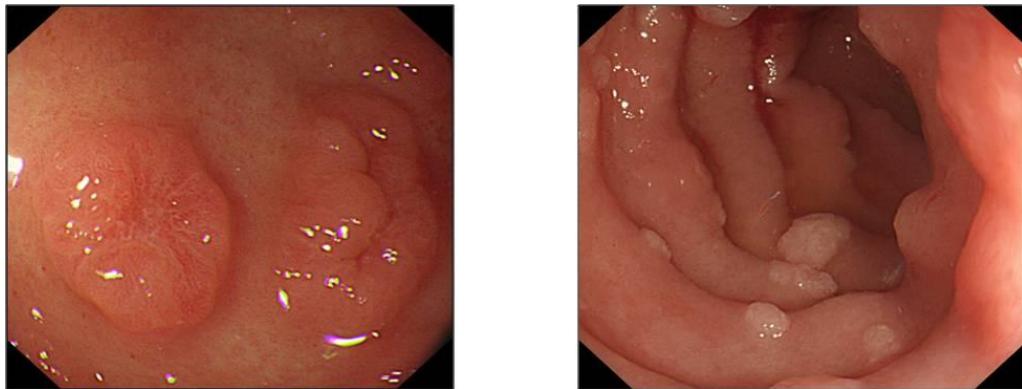


**Figura 3.** Adenomas gástricos (izquierda) y duodenales (derecha) en un paciente con PAF

Las manifestaciones extraintestinales más frecuentes son la hipertrofia congénita del epitelio retiniano (70-80%), quistes epidermoides (50%), osteomas (50-90%) y tumores desmoides (10-15%). También puede asociarse a entidades malignas como el cáncer de tiroides (2-3%), tumores cerebrales (menos del 1%) o hepatoblastomas (1%).[52] Se debe ofrecer consejo genético y análisis de la mutación a todos los pacientes con PAF. El test genético servirá como técnica de diagnóstico presintomático a los familiares de primer grado para seleccionar aquellos que deben incluirse en programas de cribado endoscópico.

El desarrollo de múltiples pólipos en el duodeno es una de las manifestaciones extracolónicas más frecuentes. Está presente en un 65-92% de pacientes, aumentando la prevalencia con la edad.[55-58] También se ha descrito la presencia de pólipos distales al ángulo de Treitz, pero su frecuencia e importancia clínica son mucho menores. Se dan en pacientes con poliposis duodenal importante y se localizan sobre todo en yeyuno.[59, 60] Se ha estimado que a lo largo de su vida un 4-10% de los pacientes con PAF desarrollarán cáncer duodenal.[61, 62]

Esta es la primera causa de mortalidad en estos pacientes desde la implantación de la colectomía profiláctica.[63]

La clasificación de Spigelman,[64] descrita en 1989, se utiliza actualmente en todo el mundo para estimar la probabilidad de desarrollar cáncer duodenal en pacientes con PAF. Tiene en cuenta el número de pólipos, su tamaño, el diagnóstico histológico y el grado de displasia (tabla 1). Por cada categoría se obtienen de 1 a 3 puntos, que se suman para obtener un valor global. Esta puntuación coloca al paciente en cuatro posibles estadios, de menor a mayor gravedad en función del riesgo de desarrollar cáncer duodenal.

De acuerdo con esto, se han establecido estrategias de vigilancia y/o tratamiento. Se recomienda realizar la primera endoscopia de cribado entre los 25-30 años y posteriormente ajustar según el estadio[52] (tabla 2). Dado que la región ampular es un lugar especialmente proclive a la formación de adenomas[56] se aconseja explorarla con un endoscopio de visión lateral o duodenoscopio, especialmente en estadios avanzados.[52] En caso de afectación ampular, se recomienda realizar ecoendoscopia para evaluar la afectación locorregional.

| Criterios | Puntuación | | |
| --- | --- | --- | --- |
| | 1 punto | 2 puntos | 3 puntos |
| Número | 1-4 | 5-20 | >20 |
| Tamaño | 1-4 mm | 5-10 mm | >10 mm |
| Histología | adenoma tubular | adenoma tubulovelloso | adenoma velloso |
| Displasia | bajo grado | ---- | alto grado |
| Estadio 0: 0 puntos; Estadio I: 1-4 puntos; Estadio II: 5-6 puntos; Estadio III: 7-8 puntos; Estadio IV: 9-12 puntos | | | |

**Tabla 1.** Clasificación de Spigelman modificada[59, 64, 65] para la estadificación de la adenomatosis duodenal. De acuerdo con la clasificación de Viena[66] no se tiene en cuenta la categoría displasia moderada.

| Estadio de Spigelman | Intervalo de vigilancia | Riesgo de cáncer duodenal |
|:---:|:---:|:---:|
| 0-I | 5 años | 0% |
| II | 3 años | 2,3% |
| III | 1-2 años | 2,4% |
| IV | 3 meses<br>Considerar ecoendoscopia y cirugía profiláctica | 36,4% |

**Tabla 2.** Intervalo recomendado de las endoscopias de vigilancia del tracto digestivo superior en pacientes con poliposis duodenal en función de la clasificación de Spigelman y del riesgo estimado de cáncer duodenal.[52, 67]

Sin embargo, la clasificación de Spigelman no ha demostrado un valor predictivo tan bueno como el esperado. Se han descrito casos de cáncer duodenal en pacientes con estadio II y III, así como regresión del estadio en las endoscopias subsiguientes.[58, 67, 68] Otro inconveniente de la clasificación de Spigelman radica en que no considera la región ampular. Por otro lado, en los últimos años se ha producido un importante desarrollo de la tecnología endoscópica que ha mejorado la calidad de la imagen.[14] El impacto de estos avances en la clasificación de Spigelman no se ha evaluado, ya que podrían aumentar la detección de lesiones sin que ello supusiera necesariamente un aumento del riesgo.

Hasta la fecha, sólo se ha investigado el papel de la CE en la detección de los pólipos duodenales. Existen dos estudios al respecto: uno de ellos mostró un aumento de detección de lesiones por parte de la CE[69], pero estos datos no se confirmaron en el segundo, donde el uso de CE resultó en un aumento clínicamente no significativo de la cantidad de adenomas duodenales detectados.[70] Dado que este estudio se realizó con un equipo de alta resolución, los autores interpretaron que la CE tiene menos que ofrecer en este escenario, ya que la imagen de alta resolución podría mejorar la detección de lesiones por sí sola.

Además de adenomas duodenales, los pacientes con PAF tienen tendencia a desarrollar pólipos gástricos. Generalmente se trata de pólipos de glándulas fúndicas, cuyo comportamiento es benigno incluso cuando son numerosos.[71] También existe mayor tendencia a desarrollar adenomas, que representan un 10% de los pólipos gástricos en pacientes con PAF.[64, 72] En estudios asiáticos se ha comunicado un riesgo de desarrollar cáncer gástrico 3-4 veces mayor que la población general,[73, 74] pero este dato no se ha constatado en Occidente.

## 3.2. Síndrome de poliposis serrada

El SPS, anteriormente denominado síndrome de poliposis hiperplásica, es un término recientemente acuñado para designar a una condición que predispone al CCR y que se caracteriza por la presencia de pólipos serrados múltiples o con tamaño significativo a lo largo de todo el colon. La profundización en el conocimiento de los pólipos serrados ha dado lugar a una revolución en el concepto de la carcinogénesis colorrectal. La creencia tradicional se basaba en la existencia de dos tipos fundamentales de pólipos en el colon: pólipos hiperplásicos y adenomas. Se pensaba que los pólipos hiperplásicos carecían de relevancia clínica y que todos los CCR se originaban en adenomas de colon. Así, la secuencia adenoma-carcinoma describe que la acumulación de alteraciones genéticas favorece el paso de mucosa normal a adenoma y de adenoma a cáncer.[2, 3] Sin embargo, en los últimos años se ha definido histológicamente el grupo de los pólipos serrados, que incluye los pólipos hiperplásicos, los adenomas serrados sésiles y los adenomas serrados tradicionales.[75] Hoy en día existe evidencia histológica y molecular de que los pólipos serrados también tienen potencial de malignización y de que la vía serrada de la carcinogénesis puede ser responsable de hasta un 30% de todos los CCR.[4]

A diferencia de la vía clásica, la vía serrada se caracteriza por el silenciamiento epigenético de genes (es decir, sin cambio en la secuencia de nucleótidos) mediante la metilación de sus regiones promotoras. Este fenómeno se conoce como fenotipo metilador de islas CpG (*CpG island methylator phenotype*, CIMP). Si los genes silenciados son genes supresores de tumores, ello contribuye al desarrollo de cáncer. Los CCR que se desarrollan a través de esta vía presentan además mutaciones tempranas en los protooncogenes *BRAF* y *KRAS* y pueden cursar con silenciamiento epigenético del promotor del gen *MLH1*. La función de este gen es reparar los errores que se producen al replicar el ADN; si no se permite su expresión se producirán errores al replicar la secuencia de DNA, especialmente en las zonas donde las series de nucelótidos son repetitivas (microsatélites).[4] Esta circunstancia se denomina inestabilidad de microsatélites.

Los pólipos serrados son un grupo heterogéneo de lesiones que tienen en común la apariencia histológica "en dientes de sierra". Los pólipos hiperplásicos (PH) son el tipo más frecuente (80-90% de todas las lesiones serradas) y se encuentran sobre todo en el recto y sigma. Histológicamente se caracterizan por presentar los cambios serrados en el tercio superior de las criptas, que tienen una apariencia recta, y nunca contienen displasia.[76] Aunque existen pocos datos al respecto, los PH parecen presentar un comportamiento benigno con bajo o nulo riesgo de degeneración maligna.[77] Los adenomas o pólipos serrados sésiles (ASS) representan el 15-20% de los pólipos serrados y se localizan fundamentalmente en el colon derecho. Se caracterizan por criptas ensanchadas y/o ramificadas en su base, con forma de L o T invertida. En sus estadios precoces los ASS no tienen displasia, pero este rasgo aparece en la progresión hacia carcinoma.[76] Por este motivo, un ASS con displasia se considera una lesión de alto riesgo.[78] Por último, los adenomas serrados tradicionales son muy poco frecuentes y se localizan sobre todo en el colon izquierdo. Presentan una arquitectura histológica similar a la de los PH, pero con cambios displásicos.[76] Se consideran también lesiones premalignas, como

mínimo al mismo nivel que los ASS.[78, 79]A pesar de que estas definiciones han sido establecidas con el consenso de patólogos existe una importante variabilidad interobservador.[80]

La apariencia endoscópica de los pólipos serrados ha sido descrita de forma relativamente reciente, paralela al desarrollo de los endoscopios y mejoría en la calidad de la imagen. A diferencia de los adenomas serrados tradicionales, que tienen una morfología sésil o pediculada y son eritematosos, los ASS y PH tienen una apariencia endoscópica muy similar (figura 4).[81]
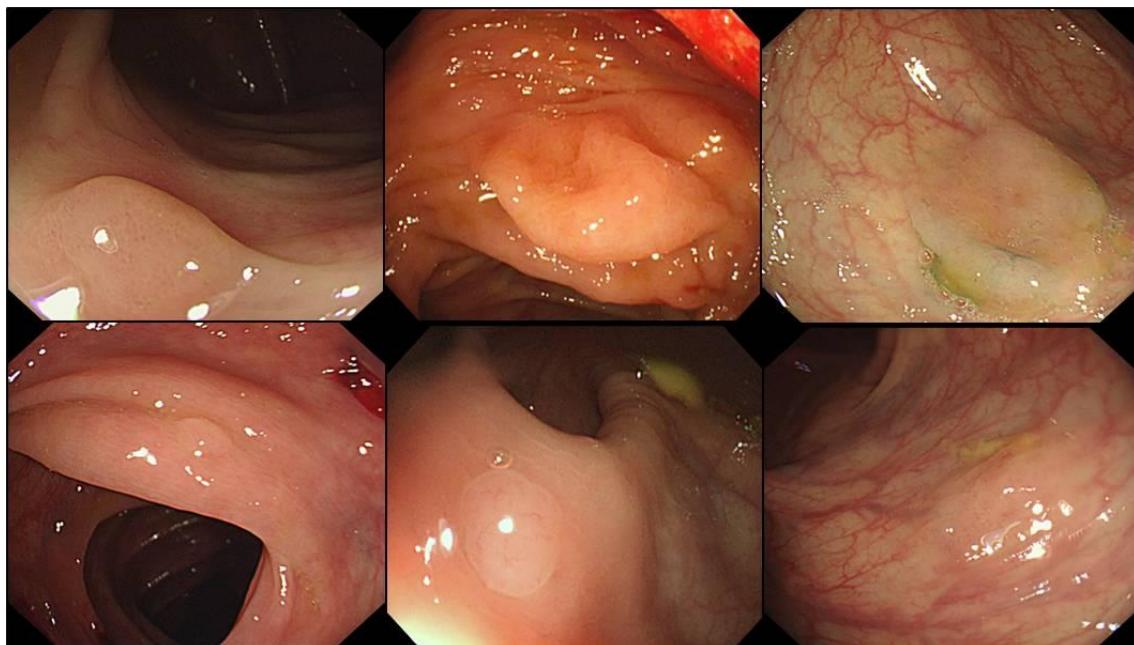


**Figura 4.** Adenomas serrados sésiles (arriba) y pólipos hiperplásicos (abajo) de colon. Ambas lesiones presentan una apariencia endoscópica similar.

Suele tratarse de lesiones sésiles o planas y pálidas, en ocasiones mal delimitadas, que pueden confundirse con un pliegue engrosado, por lo que su identificación es más difícil. La gran variabilidad interendoscopista en la tasa de detección de pólipos serrados ilustra este

hecho, con cifras que varían desde el 0 al 31%.[82] Los ASS tienen un tamaño medio mayor que

los PH y en muchas ocasiones existe una capa de moco recubriendo su superficie.[78, 83] Algunos

autores han descrito rasgos que podrían identificar ASS, como el patrón de criptas II-O visible

con endoscopia de magnificación y cromoendoscopia.[84] Hasta el momento no se han publicado

estudios que investiguen las características de los pólipos serrados con otras técnicas de

imagen endoscópica, como el NBI o la autofluorescencia.

Dado su potencial demostrado de transformación maligna, se recomienda resecar

todos los pólipos serrados detectados endoscópicamente, con la única excepción de los PH

diminutos (≤ 5 mm) del recto y sigma, que se siguen considerando inofensivos.[78] Existen datos

que relacionan los pólipos serrados con el CCR de intervalo[4, 85] (definido como aquel que se

diagnostica entre dos pruebas de cribado o vigilancia), hecho que pone de manifiesto la

importancia de una adecuada identificación y resección de estas lesiones. Por otro lado, la

dificultad en su detección y su falta de reconocimiento endoscópico hasta ahora podría jugar

un papel, junto con otros factores, en la ausencia de protección de CCR derecho por parte de

la colonoscopia.[10, 11]

En 2010 la Organización Mundial de la Salud redefinió los criterios diagnósticos del

SPS:[75] 1) al menos 5 pólipos serrados proximales al sigma con 2 o más mayores de 1 cm; o 2)

cualquier número de pólipos serrados proximales al sigma en un individuo con antecedentes

familiares de primer grado de SPS; o 3) más de 20 pólipos serrados de cualquier tamaño a lo

largo de todo el colon. Esta entidad predispone al desarrollo de CCR con un riesgo aún no bien

definido. Existen múltiples descripciones de SPS con CCR sincrónico[86-88] y en un estudio

retrospectivo se encontró una incidencia acumulada a los 5 años de seguimiento de 6,5%.[89] Se

desconoce la alteración genética responsable y si es hereditaria, pero se ha comunicado cierta

agregación familiar: en un estudio retrospectivo se comunicó un riesgo relativo de 5,4 de CCR

en los familiares de primer grado de pacientes con SPS.[90] Además existe una clara asociación

con el hábito tabáquico.[91] La lesión característica del SPS es el ASS, pero la coexistencia de adenomas es habitual (11-69%).[89, 90, 92] La edad media al diagnóstico es de entre 40 y 60 años y no parece existir una predilección por ningún género.[89, 93] Se han descrito 3 formas de presentación del SPS: en la primera predominan las lesiones grandes en el colon derecho (48%), la segunda presenta pequeños pólipos en el colon izquierdo (16%) y la tercera muestra un patrón de distribución mixto (37%).[93]

El papel de las nuevas tecnologías endoscópicas en el diagnóstico del SPS ha sido poco explorado. En un estudio con 22 pacientes diagnosticados de SPS a quienes se practicaron colonoscopias consecutivas con luz blanca de alta resolución y Narrow Band Imaging (NBI) en orden aleatorizado, el NBI mostró una mejora en la detección de lesiones, con una tasa de pólipos no detectados del 10% frente a la luz blanca, de 36%.[94] Un estudio piloto del mismo grupo no encontró utilidad al NBI ni a la autofluorescencia para diferenciar ASS de PH en pacientes con SPS.[95]

## 3.3. Enfermedad inflamatoria intestinal de larga evolución

Los pacientes con EII de larga evolución tienen un riesgo incrementado de desarrollar CCR a lo largo de su vida. La magnitud exacta del riesgo es desconocida, ya que existen importantes variaciones en los estudios realizados hasta la fecha. En estudios poblacionales históricos se ha encontrado un número mayor de casos que el esperado, con un riesgo 2,4 y 1,9 veces mayor que en la población general en la colitis ulcerosa (CU) y en la enfermedad de Crohn (EC) respectivamente.[96, 97] Sin embargo, estudios recientes indican un descenso en la incidencia de CCR relacionado con EII, con cifras generales que asemejan el riesgo al de la

población general.[98] Este hecho se ha relacionado, entre otros factores, con un mejor control de la enfermedad.[99]

La carcinogénesis en estos pacientes es consecuencia del proceso inflamatorio crónico. No se conoce bien el mecanismo, pero se cree que el estrés oxidativo y las citocinas inflamatorias puede afectar la regulación de procesos y genes que previenen la carcinogénesis. Como en el CCR esporádico, la aparición del cáncer relacionado con la EII se debe a la acumulación secuencial de alteraciones genéticas, pero siguen una vía diferente.[100] Por ejemplo pueden ocurrir en distintos momentos del proceso, como la pérdida del gen *APC*: es un evento precoz en el CCR esporádico, pero se da en estadios tardíos en el CCR relacionado con la EII.[101] Otro fenómeno característico de la carcinogénesis en la EII es que las alteraciones genéticas pueden encontrarse en la mucosa inflamada antes de la aparición histológica de displasia o cáncer. Un estudio encontró ausencia del gen supresor de tumores *p53* en mucosa con inflamación crónica del 50% de pacientes y en el 50-85% de tumores asociados a colitis.[102]

Se han descrito varios factores de riesgo que favorecen la aparición de CCR en estos pacientes. Un metaanálisis demostró un aumento del riesgo de CCR en función del tiempo de evolución de la CU, que iba desde un 2% a los 10 años hasta un 18% a los 30 años.[103] Si bien se ha comunicado una incidencia global decreciente de CCR en pacientes con EII, el mismo estudio poblacional que señaló este hecho observó que el riesgo sigue incrementado en cierto tipo de pacientes: aquellos con CU diagnosticada en la infancia o adolescencia presentaron un riesgo relativo (RR) de 43,8 y los pacientes con colangitis esclerosante primaria un RR de 9,13.[98] La extensión también es un factor determinante, ya que la mayoría de los casos de cáncer se dan en pacientes con pancolitis. En general se acepta que los pacientes con proctitis y proctosigmoiditis tienen un riesgo similar a la población general y los pacientes con colitis izquierda un riesgo intermedio.[104] Varios estudios han señalado que los antecedentes familiares de CCR incrementan el riesgo de 2 a 3 veces.[105, 106] Se han constatado rasgos

endoscópicos en la CU que identifican a los pacientes de alto riesgo: las áreas estenóticas y los pseudopólipos aumentan el riesgo de presentar CCR en 4 y 2 veces respectivamente.[107] Por último, la falta del control de la inflamación es otro agente que interviene en la carcinogénesis.[108]

La implantación de los programas de cribado y/o vigilancia es otro factor que puede haber contribuido al descenso en la incidencia de CCR. Si bien no disponemos de estudios que hayan demostrado que esta estrategia disminuye la mortalidad, sí existe evidencia indirecta procedente de estudios observacionales que sugiere que pueden revertir en un diagnóstico precoz del CCR y una mejora de la supervivencia.[109, 110] La colonoscopia es el patrón oro para el seguimiento de pacientes con EII ya que permite la detección de lesiones precursoras y su resección, previniendo así la progresión a cáncer. Las lesiones precursoras del CCR en EII son aquellas con el diagnóstico histológico de displasia o neoplasia intraepitelial (NIE). Histológicamente las lesiones precursoras se dividen en tres tipos, de menor a mayor riesgo de progresión: "indefinido para displasia" (cuando el patólogo no puede decidir si existe o no displasia), de bajo y de alto grado.[111] Las recomendaciones actuales indican el comienzo del cribado endoscópico en pacientes con EII a partir de 8-10 años del diagnóstico. En el caso de la EC, se considera que son susceptibles de seguimiento si la mucosa colónica está afectada en más de un tercio.[104] Aunque la mayoría de estudios se refieren a la CU y existen datos controvertidos respecto al riesgo de la EC de desarrollar neoplasia,[98] actualmente se acepta que los pacientes con EC se benefician de un programa de seguimiento igual que el de la CU.[104]

Las lesiones precursoras del CCR en pacientes con EII tienen la particularidad de pasar fácilmente desapercibidas en la exploración endoscópica ya que en muchas ocasiones tienen una morfología plana, de coloración similar a la mucosa circundante, con bordes mal definidos o incluso pueden asentar sobre mucosa macroscópicamente normal.[112] Además, pueden ser multifocales. Por este motivo históricamente se ha venido recomendando como método de

cribado la toma aleatoria de biopsias de cuatro cuadrantes cada 10 cm del colon con el objetivo de intentar detectar lesiones con NIE que pudieran pasar invisibles al ojo del endoscopista.[113] Se ha estimado que es necesario realizar al menos 64 biopsias a lo largo del colon para que si existe NIE se pueda detectar con 95% de probabilidad.[114] Sin embargo esta práctica comporta alargar el tiempo de exploración, por lo que no se ha acabado de implantar en la clínica habitual.[115] Aun más importante, aunque algunos pacientes se benefician de este procedimiento no ha dado los resultados esperados. La toma de biopsias aleatorias tiene bajo rendimiento (sólo detectó el 5,7% de todas las NIE en un estudio retrospectivo con 466 colonoscopias de vigilancia),[116] además de una tasa demasiado alta de CCR de intervalo (en un estudio con 600 pacientes en seguimiento durante 30 años el 53% de los CCR se detectaron entre dos pruebas de vigilancia).[117]

Por ello se plantearon nuevos métodos para el diagnóstico de estas lesiones. Hoy en día disponemos de extensa evidencia científica que indica que la cromoendoscopia permite realizar biopsias dirigidas y mejora la detección de NIE en pacientes con CU (figura 5).[118-126] La ventaja de este procedimiento es la detección de mayor número NIE reduciendo la cantidad de biopsias, es decir, mejorando su rendimiento. Kiesslich mostró en 2003 en un estudio controlado y aleatorizado con 165 pacientes que la cromoendoscopia fue capaz de diagnosticar 32 NIE en 84 pacientes frente a 10 NIE en 81 pacientes detectadas por las biopsias aleatorias, con un menor número de muestras (14,2 frente a 38,2 biopsias/paciente).[125] La amplia evidencia en este sentido ha hecho que las últimas recomendaciones sobre las colonoscopias de vigilancia hayan cambiado. En las guías estadounidenses de la Asociación Americana de Gastroenterología aún se recomienda la toma de múltiples biopsias aleatorias, pero se alienta el uso de CE por personal entrenado[104] y en las guías europeas (de la Sociedad Británica de Gastroenterología y de la Organización Europea para el estudio de la Enfermedad de Crohn y la Colitis) se recomienda la CE como método de elección, optando por la toma

aleatoria de biopsias si aquella no está disponible.[127, 128] Sin embargo, a pesar de la utilidad

demostrada de este procedimiento, no se ha implantado en la práctica clínica debido a que es

una técnica laboriosa y que requiere dedicación.
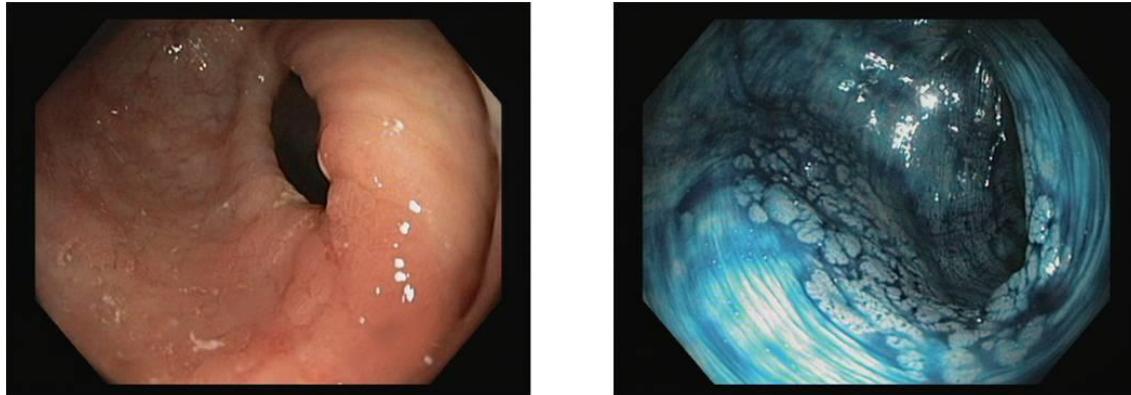


**Figura 5.** Lesión con NIE en un paciente con EII de larga evolución. Apariencia endoscópica con luz blanca (izquierda) y con CE (derecha).

Posteriormente se han desarrollado técnicas avanzadas de imagen como el NBI que

pretenden superar estos inconvenientes. La utilidad del NBI en la vigilancia de pacientes con

CU de larga evolución se descartó en un estudio que comparaba un prototipo frente a la

endoscopia convencional.[129] Al comparar la segunda generación del sistema NBI frente a la

endoscopia de alta definición, ambas técnicas obtuvieron rendimientos comparables.[130, 131] A

pesar de ser el método actualmente recomendado, hasta la fecha no se ha comparado la

utilidad de la CE con el NBI para la vigilancia en estos pacientes.

# Justificación de la tesis

## Justificación general

Las enfermedades con mayor probabilidad de desarrollar cáncer digestivo presentan ciertas características que hacen que las técnicas auxiliares de realce endoscópico tengan potencialmente muchas beneficios que ofrecer. En muchos casos el denominador común de estas patologías es la forma de presentación con lesiones poco obvias que pasan desapercibidas al endoscopio convencional y que podrían identificarse mejor con herramientas auxiliares que mejoren el contraste y calidad de la imagen. Lo que es más, en las enfermedades de alto riesgo la necesidad de detectar todas las lesiones precursoras posibles cobra una especial relevancia, ya que podrían tener una progresión más rápida.

Por otro lado, esta tecnología endoscópica puede orientar sobre el tipo de lesión que se ha detectado mediante la inspección detallada de la estructura de su superficie y su vascularización. Así podría ayudar a elegir las lesiones con mayor riesgo de progresión para aplicar el mejor tratamiento en cada caso o bien descartar aquellas que sin riesgo de degeneración.

Estas personas deberán seguir un programa de control endoscópico de por vida, por lo que se les debe ofrecer una atención con una imagen de la mejor calidad posible que aumente el rendimiento de cada exploración. Eventualmente esto podría revertir en un alargamiento del intervalo entre pruebas de vigilancia, mejorando así la calidad de vida del paciente además de prevenir el desarrollo de cáncer.

## Justificación al estudio 1

*Utilidad del NBI para la evaluación de las neoplasias del tracto digestivo superior en pacientes con poliposis adenomatosa familiar*

Las neoplasias del tracto digestivo superior, y en concreto el cáncer en el contexto de poliposis duodenal, son la primera causa de mortalidad en pacientes con PAF desde que se realiza en ellos colectomía profiláctica.[63] Actualmente la clasificación de Spigelman[64] se utiliza en todo el mundo para estratificar el riesgo de cáncer en pacientes con poliposis duodenal, pero tiene ciertas limitaciones. Por ejemplo, se han descrito casos de cáncer en pacientes en estadios precoces, además de regresiones de estadio en endoscopias posteriores. [58, 67, 68] Por otro lado, no se ha evaluado el impacto de las nuevas tecnologías endoscópicas en esta clasificación. Un aumento teórico de las lesiones detectadas podría resultar en un estadio de Spigelman más avanzado sin que ello significara necesariamente un mayor riesgo de cáncer duodenal. Las nuevas tecnologías endoscópicas podrían además ayudar a identificar en cada lesión los rasgos que indiquen un mayor riesgo de progresión para la toma de biopsias dirigidas que puedan predecir mejor el riesgo de cáncer duodenal y permitan decidir el mejor manejo en cada caso.

El sistema NBI es una herramienta endoscópica que podría mejorar la detección de los pólipos duodenales y ayudar a identificar los rasgos que indiquen mayor riesgo de progresión a cáncer.

Resultados publicados en: **Lopez-Ceron M**, van den Broek FJ, Mathus-Vliegen EM, Boparai KS, van Eeden S, Fockens P, Dekker E. The role of high-resolution endoscopy and narrow-band

imaging in the evaluation of upper GI neoplasia in familial adenomatous polyposis. **Gastrointest Endosc. 2013 Apr;77(4):542-50.**

## Justificación al estudio 2

*Utilidad del NBI para la caracterización de adenomas serrados sésiles en pacientes con síndrome de poliposis serrada*

El SPS es una entidad predisponente para el CCR y se caracteriza por la presencia de múltiples pólipos serrados o con un tamaño significativo a lo largo del colon.[75] El ASS es la lesión precursora fundamental en esta patología, donde también pueden encontrarse PH y adenomas. Actualmente se está profundizando en el conocimiento de los pólipos serrados. Existe evidencia científica que indica que los ASS tienen como mínimo el mismo potencial de progresión a la malignidad que los adenomas,[76] pero el riesgo de los PH parece mucho menor o incluso nulo.[77] A diferencia de los adenomas, que suelen ser lesiones eritematosas, los ASS y los PH son endoscópicamente muy similares.[81] Se trata de lesiones con morfología plana y coloración pálida, en muchas ocasiones cubiertas de moco, que pueden simular un pliegue engrosado, muchas veces difíciles de detectar.

El papel de las nuevas tecnologías endoscópicas en el SPS ha sido poco estudiado. El sistema NBI podría mejorar la caracterización de los ASS identificando los rasgos que los distingan de los PH y adenomas para decidir el mejor tratamiento en cada ocasión.

## Justificación al estudio 3

*Comparación de NBI y cromoendoscopia para la detección de displasia en enfermedad inflamatoria intestinal de larga evolución*

Los pacientes con enfermedad inflamatoria intestinal de larga evolución tienen mayor riesgo de desarrollar CCR.[96, 97] El cáncer se origina en lesiones con displasia o NIE. Estas lesiones precursoras tienen la particularidad de cursar con cambios sutiles de la mucosa o incluso asentar sobre mucosa en apariencia normal, siendo por tanto difíciles de detectar con la endoscopia de luz blanca convencional.[112] Por ello en estos pacientes se ha venido recomendando seguimiento endoscópico con biopsias aleatorias de cada cuadrante del colon cada 10 cm o bien con cromoendoscopia (CE), que resaltaría las irregularidades mucosa dirigiendo así las biopsias.[104, 127, 128] La CE ha demostrado detectar más NIE reduciendo el número de biopsias,[118-126] por lo que actualmente las guías están cambiando sus indicaciones y recomiendan el uso de CE como técnica de habitual o bien alientan su uso en manos expertas. [104, 127, 128]

A pesar de sus ventajas, la CE no se ha implantado en la práctica diaria porque es una técnica laboriosa y que requiere dedicarle tiempo.[115] El sistema NBI es una tecnología que aporta una información similar a la CE ofreciendo una imagen de gran calidad con mayor contraste. Podría

ayudar a la detección de NIE en los pacientes con EII de larga evolución con la ventaja de ser rápida, limpia y reversible.

**<u>Resultados publicados en:</u>** Pellisé M, **López-Cerón M**, Rodríguez de Miguel C, Jimeno M, Zabalza M, Ricart E, Aceituno M, Fernández-Esparrach G, Ginès A, Sendino O, Cuatrecasas M, Llach J, Panés J. Narrow-band imaging as an alternative to chromoendoscopy for the detection of dysplasia in long-standing inflammatory bowel disease: a prospective, randomized, crossover study. **Gastrointest Endosc. 2011 Oct;74(4):840-8.**

# Hipótesis

Las hipótesis de la presente Tesis Doctoral fueron:

1. El sistema NBI puede mejorar la detección de lesiones gástricas y duodenales en los pacientes con PAF. Además puede identificar rasgos de histología avanzada detectables endoscópicamente en adenomas duodenales que permitan la creación de un algoritmo diagnóstico para seleccionar los pacientes de mayor riesgo de desarrollo de cáncer duodenal.

2. La tecnología NBI puede ayudar a describir las características de los ASS que permitan diferenciarlos de los PH. Esto permitiría un mejor manejo por parte del endoscopista, ayudando en la toma de decisiones durante la exploración.

3. El sistema NBI es capaz de detectar NIE en los pacientes con EII de larga evolución al menos con tanta precisión como la cromoendoscopia, con la ventaja de ser una técnica menos laboriosa.

# Objetivos

El objetivo de la presente Tesis Doctoral fue evaluar la utilidad del NBI en el contexto de distintas enfermedades que predisponen al cáncer digestivo:

1. En la detección de neoplasias del tracto digestivo superior en pacientes con poliposis adenomatosa familiar (PAF), en comparación con la endoscopia de luz blanca de alta resolución (EAR)

2. En la caracterización de adenomas duodenales con histología avanzada en pacientes con poliposis duodenal y PAF, junto con la EAR

3. En la identificación de los rasgos diferenciales de los adenomas serrados sésiles en el síndrome de poliposis serrada, junto con la EAR

4. En la detección de lesiones precursoras con NIE en pacientes con EII de larga evolución, en comparación con la CE

# Comunicaciones a congresos

Los resultados de los trabajos que constituyen la base de la presente Tesis Doctoral han sido presentados en los congresos que se relacionan a continuación:

o Lopez-Ceron M, van den Broek FJC, Mathus-Vliegen EM, Boparai KS, van Eeden S, Fockens P, Dekker E. Utilidad de la endoscopia de alta resolución y el Narrow Band Imaging para la evaluación de las neoplasias del tracto gastrointestinal en la poliposis adenomatosa familiar (Comunicación oral). XXXIII Jornada nacional de la Sociedad Española de Endoscopia Digestiva. Madrid, 11-12 de noviembre de 2011. *Endoscopy 2011; 43 (12) A82.*

o Lopez-Ceron M, van den Broek FJC, Mathus-Vliegen EM, Boparai KS, van Eeden S, Fockens P, Dekker E. Utilidad de la endoscopia de alta resolución y el Narrow Band Imaging para la evaluación de las neoplasias del tracto gastrointestinal en la poliposis adenomatosa familiar (Comunicación oral). XV Reunión Nacional anual de la Asociación Española de Gastroenterología. Madrid, 22 de marzo de 2012. *Gastroenterología y Hepatología 2012;35(3):142.*

o Yark Hazewinkel , Maria Lopez-Ceron, Amit Rastogi, James E. East, Maria Pellise, Takeshi Nakajima, Susanne Van Eeden, Paul Fockens, Evelien Dekker.  Validation of Endoscopic Features of Sessile Serrated Adenomas by International Experts Using High Resolution Endoscopy and Narrow Band Imaging (Póster). *Gastrointestinal Endoscopy, Volume 75, Issue 4, Supplement, April 2012, Pages AB323-AB324.*

o M. Pellisé, Josep Llach, Michel Zabalza, Glòria Fernández-Esparrach, Angels, Ginès, Montserrat Aceituno, Miquel Sans, Salvador Navarro, Oriol Sendino, Josep Maria

Bordas, Julia Panés, Antoni Castells. Pancromoendoscopia amb indigo carmin *vs narrow band imaging* per a la deteccio de displasia en pacients amb malaltia inflamatoria intestinal de llarga durada: resultats preliminars d'un estudi prospectiu, aleatoritzat, cas-creuament. (Comunicación oral). XVI Congrés de la Societat Catalana de Digestologia. Girona 1-3 Febrer 2007. *Suplements dels Annals de Medicina 90 (1) Febrer 2007.*

o M. Pellisé, Josep Llach, Michel Zabalza, Glòria Fernández-Esparrach, Ana Petit*, Angels, Ginès, Montserrat Aceituno, Miquel Sans, Salvador Navarro, Oriol Sendino, Josep Maria Bordas, Josep Maria Piqué, Julia Panés, Antoni Castells. Pancromoendoscopia con Indigo Carmin *Vs Narrow Band Imaging* para la deteccion de displasia en pacientes con enfermedad inflamatoria intestinal de larga duración: Resultados preliminares de un estudio prospectivo, Aleatorizado, caso-cruce. (Comunicación oral). X Reunión de la Asociaición Española de Gatsroenterología. Madrid 29-31 Marzo 2007. *Gastroenterologia y Hepatologia 2007; 30(3):148.*

o M. Pellisé, M. Zabalza, C. Rodríguez de Miguel, M. Sans, M. Aceituno, E. Ricart, G. Fernández-Esparrach, A. Ginès, O. Sendino, JM. Bordas, JM. Piqué, J. Panes, J. Llach. High-resolution endoscopy plus chromoendoscopy or narrow-band imaging in the detection of dysplasia and colonic cancer in long standing inflammatory bowel disease: a prospective randomized crossover study. (Comunicación oral). Digestive Disease Week 2008, San Diego, 18-22 de maig de 2008. *Gastroenterology 2008;134:A191-2.*

# Publicaciones originales

Los resultados de los estudios que constituyen la base de la presente Tesis Doctoral han sido recogidos en las siguientes publicaciones:

o **Lopez-Ceron M**, van den Broek F.J.C., Mathus-Vliegen E. M., Boparai K. S., van Eeden S, Fockens P, Dekker E. The role of high-resolution endoscopy and narrow band imagingfor the evaluation of upper gastrointestinal neoplasia in familial adenomatous polyposis patients. **Gastrointest Endosc 2013, Apr;77(4):542-50. (Factor de Impacto = 4,878)**.

o Hazewinkel Y, **López-Cerón M**, East JE, Rastogi A, Pellisé M, Nakajima T, van Eeden S, Tytgat KM, Fockens P, Dekker E. Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white-light endoscopy and narrow-band imaging. **Gastrointest Endosc. 2013. En prensa. (Factor de Impacto = 4,878).**

o Pellisé M, **López-Cerón M**, Rodríguez de Miguel C, Jimeno M, Zabalza M, Ricart E, Aceituno M, Fernández-Esparrach G, Ginès A, Sendino O, Cuatrecasas M, Llach J, Panés J. Narrow-band imaging as an alternative to chromoendoscopy for the detection of dysplasia in long-standing inflammatory bowel disease: a prospective, randomized, crossover study. **Gastrointest Endosc. 2011 Oct;74(4):840-8. (Factor de Impacto = 4,878).**

# Artículo 1

# The role of high-resolution endoscopy and narrow-band imaging in the evaluation of upper GI neoplasia in familial adenomatous polyposis

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**Background:** The Spigelman classification stratifies cancer risk in familial adenomatous polyposis (FAP) patients with duodenal adenomatosis. High-resolution endoscopy (HRE) and narrow-band imaging (NBI) may identify lesions at high risk.

**Objective:** To compare HRE and NBI for the detection of duodenal and gastric polyps and to characterize duodenal adenomas harboring advanced histology with HRE and NBI.

**Design:** Prospective, nonrandomized, comparative study. Retrospective image evaluation study.

**Setting:** Tertiary-care center.

**Patients:** Thirty-seven FAP patients undergoing surveillance upper endoscopies.

**Intervention:** HRE endoscopy was followed by NBI. The number of gastric polyps and Spigelman staging were compared. Duodenal polyp images were systematically reviewed in a learning and validation phase.

**Main Outcome Measurements:** Number of gastric and duodenal polyps detected by HRE and NBI and prevalence of specific endoscopic features in duodenal adenomas with advanced histology.

**Results:** NBI did not identify additional gastric polyps but detected more duodenal adenomas in 16 examinations, resulting in upgrades of the Spigelman stage in 2 cases (4.4%). Pictures of 168 duodenal adenomas (44% advanced histology) were assessed. In the learning phase, 3 endoscopic features were associated with advanced histology: white color, enlarged villi, and size ≥1 cm. Only size ≥1 cm was confirmed in the validation phase (odds ratio 3.0; 95% confidence interval, 1.2-7.4).

**Limitations:** Nonrandomized study, scant number of high-grade dysplasia adenomas.

**Conclusion:** Inspection with NBI did not lead to a clinically relevant upgrade in the Spigelman classification and did not improve the detection of gastric polyps in comparison with HRE. The only endoscopic feature that predicted advanced histology of a duodenal adenoma was size ≥1 cm. (Gastrointest Endosc 2013;77:542-50.)

Familial adenomatous polyposis (FAP) is an inherited autosomal dominant condition caused by a germinal mutation in the adenomatous polyposis coli gene in which more than 100 adenomas are found in the colorectum.

Furthermore, patients with FAP harbor multiple adenomas throughout the upper GI tract, especially in the duodenum.[1] Because preventive colectomy is performed routinely in patients with FAP, survival of these patients has

improved. However, upper GI malignancies and desmoid disease are now the leading causes of death in these patients.[2] Duodenal adenomatosis is a frequent finding in FAP patients, its prevalence varying from 65% to 92%, depending on the age of patients.[3-6] The lifetime cumulative risk for developing duodenal cancer in these patients has been estimated at 4% to 10%.[7,8]

In 1989, Spigelman et al[1] published a study in which duodenal adenomatosis in FAP patients was divided into 5 stages considering number, size, and polyp histology. This grouping allowed an estimation of the risk of developing duodenal carcinoma, which was confirmed in subsequent studies.[9,10] The Spigelman classification has been adopted worldwide as the method of staging duodenal adenomatosis in patients with FAP. Regrettably, this staging system has never been validated, and in prospective studies its predictive value was not as good as desired.[3,7,9] The development of duodenal cancer in patients with initial low Spigelman stages has been described as well as changes to more favorable stages in subsequent endoscopies in patients with initial Spigelman stage IV.[9]

In the last decade, multiple novel endoscopic techniques such as high-resolution endoscopy (HRE) and narrow-band imaging (NBI) have been introduced, allowing more accurate detection and characterization of GI lesions.[11] A recent retrospective analysis demonstrated that the introduction of HRE technology in the endoscopy unit, together with ageing, was the most important reason for higher Spigelman stages over the years.[12] The introduction of new technologies in FAP surveillance may lead to the detection of more duodenal lesions, which could result in higher Spigelman staging but might not necessarily relate to an increased cancer risk. Advanced imaging techniques also could play a role in the characterization of polyps at risk for malignant degeneration, allowing more targeted biopsies, a more representative Spigelman stage, and/or a better prediction of the risk of developing duodenal cancer.

The aim of this prospective study was to identify endoscopic features of duodenal adenomas with advanced histology in FAP patients with HRE and NBI. Secondarily, we aimed to compare HRE and NBI for the assessment of the Spigelman classification of duodenal adenomatosis and to compare the accuracy of both techniques in the detection of gastric polyps.

## PATIENTS AND METHODS

### Patient identification and invitation

Consecutive FAP patients scheduled for duodenal surveillance endoscopy were identified at the outpatient clinic of the Academic Medical Centre in Amsterdam. Eligibility for this study consisted of a proven diagnosis of familial adenomatous polyposis, either by having an APC or MutYH gene mutation on genetic testing or by the presence of more than 100 adenomatous colorectal polyps on colonoscopy. Exclusion criteria were (1) noncorrect-

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**Take-home Message**

- Inspection with narrow-band imaging did not lead to a clinically relevant upgrade in the Spigelman classifications and did not improve the detection of gastric polyps in comparison with high-resolution endoscopy.
- In this study, a duodenal adenoma larger than 1 cm had a 3-fold increased risk of harboring advanced histology. This trait is easily and homogeneously estimated during endoscopy, as shown by the good interrater agreement.

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able coagulopathy, (2) age ≤18 years, and (3) inability to give informed consent. Suitable patients received an invitation and informed consent form. This study was approved by the medical ethical committee of the Academic Medical Centre in Amsterdam.

### Endoscopic equipment

For duodenal surveillance in FAP patients, two endoscopies were performed as recommended in current guidelines: a forward-viewing gastroduodenoscopy to inspect the stomach and duodenum and a side-viewing duodenoscopy to inspect the papilla of Vater and periampullary region.[13] An HRE system equipped with NBI and optical magnification (GIF-Q240Z; Olympus, Tokyo, Japan) was used for forward-viewing examinations. A standard duodenoscope (TJF-160R, Olympus, Hamburg, Germany) was used for side-viewing examinations. Because HRE and NBI were not available in this model, ampullary and periampullary lesions were not included in the analysis.

### Endoscopy protocol

After written informed consent, patients were scheduled for duodenal surveillance endoscopy. Conscious sedation was given with midazolam (2.5-10 mg intravenously) supplemented with fentanyl (50-100 $\mu$g) when necessary. Antispasmodic medication was given at the discretion of the endoscopist. A research assistant was present during all endoscopies to register the findings in a case record form.

First, a forward-viewing endoscopy was performed, starting in the HRE mode. The examined area was divided into 3 segments: second and third part of the duodenum, duodenal bulb, and stomach. After completion of inspection with HRE in one segment, the endoscopist switched the imaging mode to NBI for a second inspection. This process was repeated for each segment of the duodenum and the stomach. Information in both HRE and NBI modes was registered separately in each segment. The total number and size of the detected polyps with both HRE and NBI was assessed. Size was estimated by using an open biopsy forceps (8 mm). If the polyps were too numerous to be counted, the number was estimated, and the largest size was recorded. Biopsy specimens were systematically

**TABLE 1. Modified Spigelman classification.**[1,15,16]*

| Criteria | Score | | |
| --- | --- | --- | --- |
| | **1 point** | **2 points** | **3 points** |
| Polyp no. | 1-4 | 5-20 | >20 |
| Polyp size | 1-4 mm | 5-10 mm | >10 mm |
| Histology | Tubular adenoma | Tubulovillous adenoma | Villous adenoma |
| Dysplasia | Low grade | — | High grade |

*Stage 0, 0 points; stage I, 1-4 points; stage II, 5-6 points; stage III, 7-8 points; stage IV, 9-12 points.

taken as explained below. Lesions that were not initially detected by HRE but were detected by NBI at the second inspection were pictured and biopsied separately.

Histologic samples were processed by using standard procedures and evaluated by a staff pathologist specialized in gastroenterology. Biopsies were classified at histology according to the type of epithelium (inflammatory or hyperplastic polyp, tubular, tubulovillous, or villous adenoma) and degree of dysplasia (none, low grade, high grade, or cancer) according to the updated Vienna criteria for the diagnosis of GI neoplasia, omitting the category moderate dysplasia.[14] A modified Spigelman classification was applied in agreement with this, as previously described (Table 1).[15,16] Advanced histology was defined as the presence of either high-grade dysplasia and/or tubulovillous or villous morphology.

**Duodenum.** Pictures and biopsy specimens were taken from all polyps >10 mm, all suspicious polyps (defined by the presence of a central depression, irregular surface, or irregular vascular pattern), and a random sample of polyps between 1 and 9 mm, up to a total maximum number of 10 polyps biopsied per patient. Two images of each lesion were taken with HRE and NBI: an overview image and a zoomed detailed image. All biopsy specimens were linked to the corresponding pictures, which were subsequently selected for the standardized image evaluation section of this study if they met the following criteria: a minimum of one zoomed and one overview picture per lesion, at least one of them with HRE and the other with NBI, and of sufficient quality (Fig. 1).

**Stomach.** Overview pictures were taken from fundic gland polyps and any other gastric polyps before they were biopsied. Fundic gland polyps were not biopsied unless they looked irregular or remarkable. Antral lesions were always biopsied.

## Image evaluation protocol for duodenal polyps

Selected HRE and NBI images of duodenal polyps were assigned to one of the phases for image evaluation: exploratory phase, learning phase, and validation phase,

according to a methodology described by Kara et al.[17] Image selection was made by one expert in endoscopic imaging (F.v.d.B.) in the exploratory and learning phases and by another expert (M.L.C.) in the validation phase. Images were selected according to the criteria described earlier. Each polyp was evaluated under HRE and NBI with and without zoom, so the final score was made on all of the images available for the polyp. In each phase, the images were evaluated on a computer screen (HP Compaq LA2205wg 22-inch Widescreen LCD Monitor (Hewlett-Packard, California, USA)).

**Exploratory phase.** Polyp images from the first 16 patients and the corresponding histology were reviewed by a specialized GI pathologist (S.v.E.) and two experts in endoscopic imaging (E.M.V., E.D.) in an unblinded manner. Images were selected by another expert (F.v.d.B.). After a thorough review of the HRE and NBI images, a list of specific endoscopic characteristics of duodenal polyps was drawn up to develop a standardized form that was used for image evaluation in the following phases. The images of patients used in this phase were excluded from further data analysis. All subsequent images and the accompanying histology were divided into a learning set and a validation set in a ratio of 1:2, respectively.

**Learning phase.** Images were evaluated by two experts in endoscopic imaging (E.D. and F.v.d.B.), blinded for clinical and histologic data. F.v.d.B. was in charge of both image selection and image evaluation. To avoid bias, he had access to patient data only after the image evaluation took place. The pictures were assessed for each feature on the standardized form. The score was the result of the assessment of the features with both techniques (HRE and NBI). They were first evaluated by each expert individually, and in case of disagreement, a consensus was reached afterward by discussion. The association between each endoscopic feature and the presence of advanced histology in every lesion was investigated.

**Validation phase.** In this stage, the experts (E.D. and F.v.d.B.) scored the images separately. Only the features that remained associated with advanced histology in the learning phase were assessed in the validation phase.
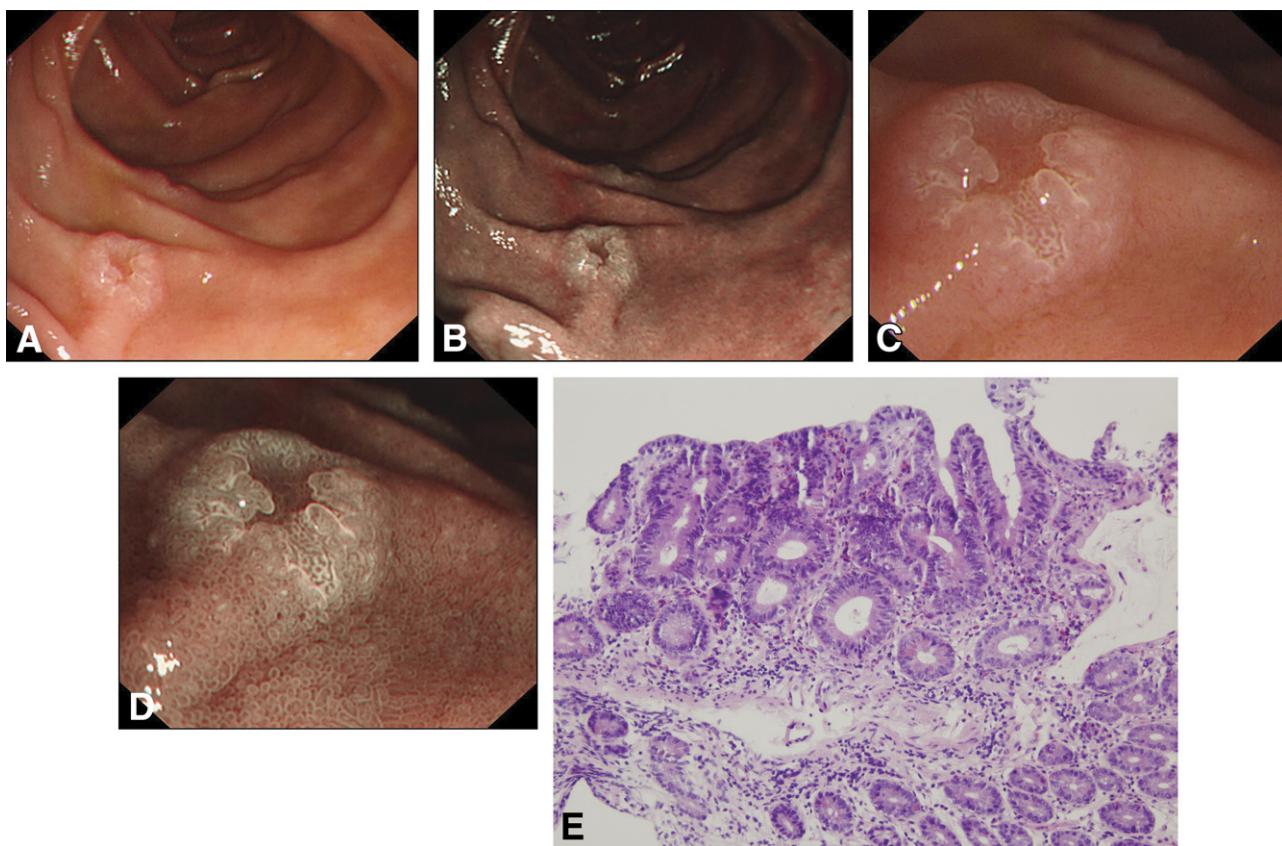
**Figure 1.** Overview and zoomed endoscopic pictures with high-resolution endoscopy and narrow-band imaging as well as a histologic section of a tubular adenoma with low-grade dysplasia in the second duodenal portion. **A,** Overview endoscopic picture with HRE. **B,** Overview endoscopic picture with NBI. **C,** Zoomed endoscopic picture with HRE. **D,** Zoomed endoscopic picture with NBI. **E,** Histologic section (H&E, orig. mag. ×20). *HRE,* high-resolution endoscopy; *NBI,* narrow-band imaging.

They were blinded for histology, for clinical data, and from each other's opinions.

## Statistical analysis

Descriptive statistics were used to characterize the study population. Because continuous variables in this study had a skewed distribution, they were summarized by median and range. The relationship between endoscopic features and histopathologic outcome was investigated with univariate and multivariate logistic regression analysis. The association of advanced histology with each endoscopic feature was analyzed several times, grouping their categories in different ways to conform binary variables. The most discriminative $P$ value was used to choose the definitive binary variable. A $P$ value of .1 was used as the cut-off point for defining an "association" in the learning set, but in the validation set it was lowered to .05. The association was first tested with a univariate analysis. Factors that were found to be significantly associated with advanced histology were again evaluated with multivariate analysis. To test the reproducibility of these findings, interrater agreement was calculated with kappa analysis. A score of <0.20 was considered poor, 0.21 to 0.40 fair, 0.41

to 0.60 moderate, 0.61 to 0.80 good, and 0.81 to 1.00 very good. All statistical analyses were performed by using a statistical software package (Statistical Package for the Social Sciences 12.0.1; SPSS Inc, Chicago, Ill).

## Calculation of sample size

Because NBI has never been used for characterization of duodenal polyps, we could not assess the diagnostic yield of NBI for these means. However, a calculation can be made in terms of detection. In a recent study with high-resolution chromoendoscopy, 66% of patients had a Spigelman stage III or IV.[18] With HRE alone, we assumed a stage III or IV in 45% of our patients. We hypothesized an increase of 21% in adenoma detection with NBI, with a power of 90% ($\beta$ error 0.1) and a significance level of 5% ($\alpha$ error 0.05). A within-subjects design for 1-sided measurement resulted in a sample size of 46 procedures.

## RESULTS

### Patients

From June 8, 2006 to September 9, 2008, 39 FAP patients underwent one or more endoscopies for screening

**TABLE 2.   No. of patients staged according to Spigelman classification with HRE and NBI.***

| | Narrow-band imaging | | | | |
|---|---|---|---|---|---|
| | 0 | I | II | III | IV |
| **HRE** | | | | | |
| **0** | 4 | 0 | 0 | 0 | 0 |
| **I** | 0 | 3 | 0 | 0 | 0 |
| **II** | 0 | 0 | 3 | *1* | 0 |
| **III** | 0 | 0 | 0 | 16 | *1* |
| **IV** | 0 | 0 | 0 | 0 | 17 |

*HRE,* High-resolution endoscopy; *NBI,* narrow-band imaging.
*Coincident cases are highlighted in bold, and discordant ones are highlighted in italics.



**Figure 2.** Tubular adenomas with low-grade dysplasia in the antrum. **A,** Zoomed picture with high-resolution endoscopy. **B,** Zoomed picture with narrow-band imaging.

or surveillance of duodenal adenomatosis. Two cases were excluded for the analysis because of lack of information about NBI (n = 1) and because of biopsy damage (n = 1). Thirty-seven patients (45 procedures) were included (22 female, median age 49 years, range 28-78 years). All of them except one had undergone colectomy, either total (n = 29) or subtotal (n = 7) and received regular duodenal surveillance according to the Spigelman stage. Twelve patients had an ampullary lesion, 8 had periampullary lesions, and 4 presented both ampullary and periampullary lesions. There were no screening examinations in these cohorts. Because some patients underwent surveillance upper endoscopies more than once during the study period, 45 consecutive procedures were performed in total by two endoscopists (E.D. and E.M.V.). The endoscopists had access to clinical data and previous examinations of the patients as well as histopathology results, if applicable.

## Detection of duodenal and gastric polyps

**Detection of duodenal polyps.** The second look with NBI detected additional polyps in 16 procedures (35.6%), leading to an upgrade in the Spigelman score for 5 of them (11.1%). In 4, the score changed from the second group (5-20 polyps) to the third group (>20); and in one case from the first group (<5) to the second (5-20). In two examinations (4.4%), the largest polyp detected with NBI was larger than the largest polyp detected with HRE, but this resulted in a upgrade in the Spigelman score for size in only one procedure (2.2%). None of the polyps diagnosed by NBI had a worse histology or degree of dysplasia.

When total Spigelman scores were compared, the inspection with NBI led to an upstage in two patients (4.4%) (Table 2). In one, the Spigelman stage increased from II to III because of a higher score for polyp number and size. In the other, a rise in the score for polyp number resulted in a change from stage III to IV.
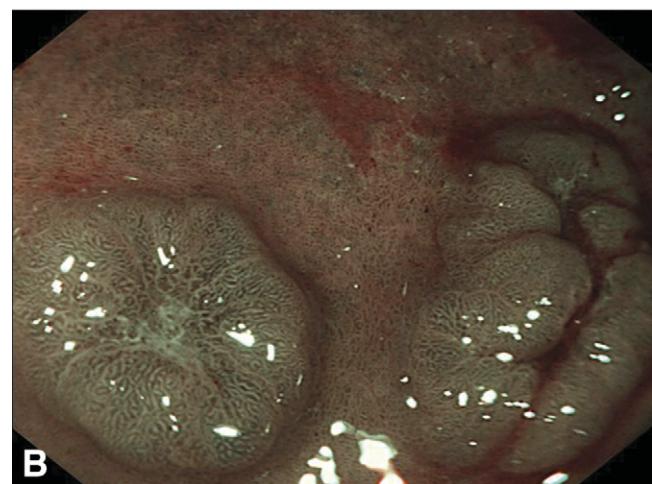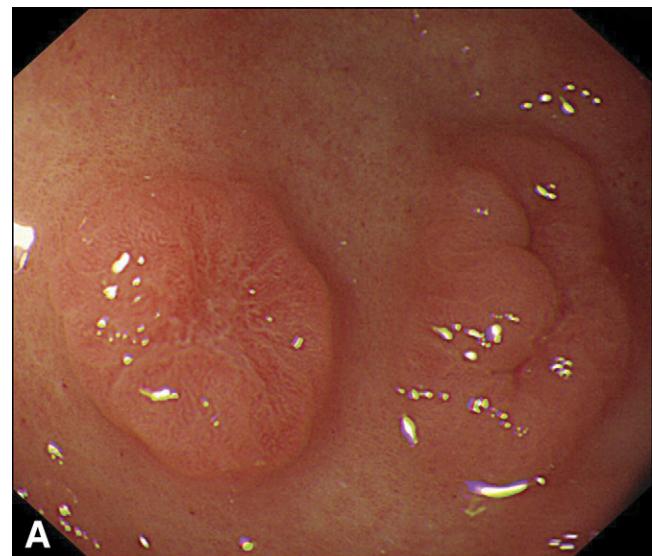
**Detection of gastric polyps.** The presence of fundic gland and antral polyps (Fig. 2) was noted in 30 (81.1%) and 11 (29.7%) patients, respectively. Eight antral polyps were tubular adenomas with low-grade dysplasia, 3 were inflammatory polyps, and in one pathology did not show abnormalities. All antral polyps but one were detected with HRE and then confirmed with NBI. One lesion was detected only with NBI, but histology revealed a healing erosion.

## Standardized image evaluation protocol

In all procedures, pictures of 270 lesions were gathered in total. Of these, 168 fulfilled the criteria for eligibility and quality and were grouped into 3 sets. The content of the phases of the protocol is outlined in Figure 3, and a summary of the findings is shown in Table 3.

**Exploratory phase.** The pictures from the first 16 patients included 24 adenomas (of which 3 showed high-
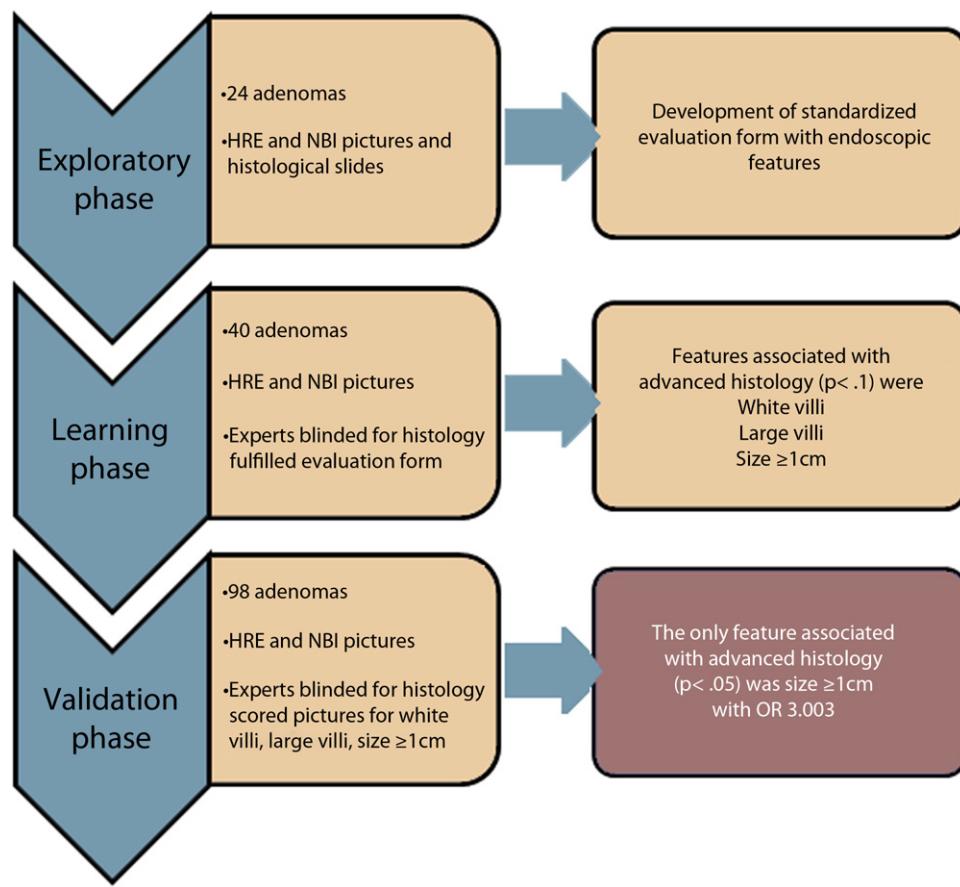
**Figure 3.** Flow chart describing the content and findings in each phase of the image evaluation protocol. *HRE,* high-resolution endoscopy; *NBI,* narrow-band imaging; *OR,* odds ratio.

**TABLE 3.  Summary of the findings in each phase of the image evaluation protocol for duodenal polyps.***

|                                                      | Exploratory phase | Learning phase | Validation phase | Total          |
| ---------------------------------------------------- | ----------------- | -------------- | ---------------- | -------------- |
| No. of patients                                      | 16                | 12             | 19               | 35             |
| No. of endoscopic examinations                       | 16                | 14             | 22               | 52             |
| No. of adenomas assessed                             | 24                | 40             | 98               | 162            |
| No. of adenomas with advanced histology (TV/V/HGD)   | 16 (13/0/3)       | 17 (17/0/0)    | 43 (37/1/7)      | 76 (67/1/10)   |
| No. of adenocarcinomas                               | 0                 | 0              | 0                | 0              |

*TV,* Tubulovillous; *V,* villous; *HGD,* high-grade dysplasia.
*Some patients were included in more than one phase as they could have different polyps included in different phases.

grade dysplasia and 13 villous morphology) and 6 images of normal-appearing mucosa. The list of endoscopic features developed in consensus after reviewing the images is depicted in Table 4. This form was used for image assessment in the following phase of the study.

**Learning phase.** Pictures of 48 duodenal lesions (12 patients) were assessed in this phase. Eight lesions were excluded because of lack of histologic diagnosis (3 lesions) and a diagnosis different from duodenal adenoma (4 normal mucosa, 1 duodenitis). Forty adenomas were finally included. A univariate and multivariate analysis was performed to evaluate a possible relationship between endoscopic features and advanced histology (Table 5). In this set of images, no adenomas with high-grade dysplasia nor pure villous morphology were found. Therefore, the group of adenomas with advanced histology was made up of 17 adenomas with tubulovillous morphology only. After multivariate analysis, several features were significantly

**TABLE 4. Standardized evaluation form developed in consensus for the assessment of duodenal lesions.**

### Endoscopic features

| Image overall quality | Poor | Moderate | Good | Excellent | | |
|---|---|---|---|---|---|---|
| Mucosal pattern | Normal villi | Round/oval | Tubular/long | Branched | Irregular | Villous |
| Overall color | Darker than normal | Equal as normal | Some white villi | All white villi | | |
| Vascular pattern | No vessels | Normal regular vessels | Thick/irregular vessels | | | |
| Surface | Smooth | Bumpy | One or more depressions | Heavily irregular | | |
| Shape (Paris Classification) | 0-Is (sessile) | 0-IIa (flat-elevated) | 0-IIb (flat) | 0-IIc (depressed) | | |
| Villi | No | Normal | Regular large | Irregular large | | |
| Edge | Sharp/clear demarcation | Gradual/unclear demarcation | | | | |
| Estimated size | No lesion | <5 mm | 5-10 mm | 1-2 cm | >2 cm | |

**TABLE 5. Learning phase. Evaluation of the association of endoscopic features of duodenal adenomas with advanced histology.†**

| Endoscopic features | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR | *P* value | OR | *P* value |
| Villous mucosal pattern | 5.727 | *.052 | 0.913 | .946 |
| **White color of all villi** | **3.733** | ***.054** | **20.655** | ***.013** |
| Irregular surface | 4.222 | *.050 | 0.426 | .592 |
| **Large villi (regular and irregular)** | **5.194** | ***.018** | **25.610** | ***.045** |
| No or thin regular vessels | 4.375 | .201 | — | — |
| **Estimated size ≥1 cm** | **3.590** | ***.094** | **6.725** | ***.074** |
| Flat-elevated morphology (0-IIa, Paris classification) | 1.528 | .523 | — | — |
| Gradual demarcation | 1.462 | .554 | — | — |

*OR,* Odds ratio.
*(*P,* <.1).
†Predictive features of advanced histology in this phase are highlighted in bold. Only the features that resulted significantly associated with advanced histology in the univariate analysis were included in the multivariate analysis.

associated with advanced histology: white color of all villi ($P = .013$), enlarged villi (regular and irregular) ($P = .045$), and an estimated lesion size ≥1 cm ($P = .074$).

**Validation phase.** Images of 102 lesions (19 patients) were evaluated in this section. Four lesions were excluded because of a normal histologic diagnosis in 3 and because of biopsy damage in 1. Ninety-eight adenomas were finally analyzed (7 with high-grade dysplasia, 37 with tubulovillous, and 1 with villous histology). Experts scored the pictures individually for white villi and enlarged villi and estimated lesion size >1 cm. Both univariate and multivariate analyses with pooled data from both experts showed that the only endoscopic feature that independently predicted advanced

histology in a duodenal adenoma was an estimated size >1 cm, with an odds ratio (OR) of 3.0 (95% confidence interval [CI], 1.2-7.4; $P = .016$) (Table 6).

Interrater agreement was measured. For lesions >1 cm, a good degree of concordance (kappa value 0.651) was found, and for the rest of the features a moderate concordance was encountered: white villi (kappa 0.459) and enlarged villi (kappa 0.428).

## DISCUSSION

The aim of this study was to evaluate the use of HRE and NBI in the assessment of duodenal adenomatosis and

**TABLE 6. Validation phase. Evaluation of the association of endoscopic features of duodenal adenomas with advanced histology. Pooled analysis of data from both experts.†**

| Endoscopic features | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | P value | 95% CI | OR | P value | 95% CI |
| White villi | 1.440 | .374 | 0.645-3.219 | 1.149 | .752 | 0.485-2.720 |
| Large villi | 1.862 | .132 | 0.829-4.183 | 1.294 | .571 | 0.531-3.150 |
| Estimated size ≥1 cm | 3.304 | *.007 | 1.392-7.840 | 3.003 | *.017 | 1.218-7.406 |

*OR,* Odds ratio; *CI,* confidence interval.
*(P, <.1).
†The only predictive feature of advanced histology in this phase is highlighted in bold.

gastric polyps in FAP patients. The use of NBI for detection of duodenal adenomas resulted in an upgrade in total Spigelman score in only 2 cases (4.4%), and NBI did not detect any additional gastric adenoma. Furthermore, we aimed to detect endoscopic features of duodenal adenomas that would predict advanced histology (either tubulovillous or villous components and/or high-grade dysplasia). After analyzing 8 different traits by both HRE and NBI, the only one that was significantly associated with advanced histology was an estimated polyp size >1 cm, with a 3-fold increased risk (OR 3, 95% CI, 1.2-7.4). This characteristic was appreciated with a good interrater agreement.

With respect to detection of duodenal polyps, this is the first study in which NBI is evaluated. Some studies have investigated the role of new technologies such as high-resolution imaging and chromoendoscopy in FAP patients, specifically addressing the increased adenoma detection rates.[16,18,19] A recent publication by our group showed an increase in high Spigelman stages over a median follow-up of 19.5 years. This phenomenon was explained by both ageing and technical improvements, the change from low-resolution to high-resolution being the most relevant factor.[12]

The use of chromoendoscopy in the assessment of duodenal adenomatosis in FAP has been specifically evaluated in two studies. The first showed a significant increase in number and size of duodenal polyps detected with chromoendoscopy.[19] However, these results were not confirmed by a second study.[18] This difference in findings might be explained by the use of conventional resolution imaging in the first study as opposed to HRE in the second. This suggests that chromoendoscopy might be more helpful in detecting polyps during conventional resolution endoscopy than in HRE because HRE actually improves the detection by itself. Reasoning in the same line, this could be the explanation for the lack of a relevant effect of NBI over HRE in duodenal adenomatosis staging in our study.

Because HRE and NBI both provide highly detailed mucosal images, they could potentially provide information on the histology of a lesion. Endoscopes with HRE

and NBI are widely available, and their use for characterization of lesions throughout the GI tract has been extensively studied. Barrett's esophagus is the only condition for which NBI could differentiate high-grade dysplasia and early cancer from low-grade dysplasia and nonneoplastic tissue with a high sensitivity (71%-100%) but variable specificity (33%-99%).[20] To our knowledge, this is the first study in which both HRE and NBI are evaluated for characterization of duodenal adenomas in FAP patients. Regarding characterization of neoplasia in the duodenum, in a small study in 14 non-FAP patients, pinecone/leaf-shaped and irregular villi as seen with NBI showed 100% accuracy for the identification of ampullary neoplasia (adenoma and adenocarcinoma) versus nonneoplastic lesions.[21] No data on advanced histology were assessed.

Unfortunately, our study did not lead to the identification of endoscopic features that predicted advanced histology in a duodenal adenoma other than its large size, which defines the lesion as advanced[22] and can be easily assessed by HRE (or even low-resolution endoscopy) alone. We have investigated whether the deletion of the characteristic "size," which was so dominantly present, from the multivariate analysis would change the association of the other characteristics with advanced histology, but we could not find any relevant feature (results not shown). The increase in size of the polyps has been previously described as one of the factors that causes an increase in the Spigelman stage,[3] but a higher Spigelman stage does not necessarily imply advanced histology lesions. Because large lesions will contain high-grade dysplasia or villous changes more often,[15] it could be argued that endoscopic polypectomy for all polyps >1 cm should be performed. If this strategy indeed prevents major duodenal surgery and/or duodenal cancer, it should be the subject of a large, prospective trial.

A major limitation of this study is the sequential use of HRE followed by NBI in the detection of polyps, which could have resulted in a biased advantage for NBI. Despite this, NBI did not increase the detection of duodenal and gastric polyps. Hence, we can infer that the role of NBI in this situation is limited. Another drawback was the absence of high-grade dysplasia and pure villous morphol-

ogy in the learning phase of the image evaluation part of the study. However, in the validation phase, enough lesions of every type were present. This represents a limitation because the endoscopic features in the learning phase were assessed only with respect to tubular versus tubulovillous morphology, and a significant association with high-grade dysplasia may have been missed. Moreover, the overall prevalence of high-grade dysplasia and villous morphology in our group of patients is so low (11/76 = 14.5%) that it is difficult to draw a conclusion.

On the other hand, it could be argued that one of the experts (E.D.) fulfilling the image evaluation protocol also performed some of the endoscopies and this could represent a bias because she was not blinded for clinical and histopathologic data during the endoscopy. However, the image evaluation took place months or years after the endoscopies were done (depending on the phase), with no access to clinical or histologic data. Also, the names of the patients were deleted from the images, thus eliminating the risk of bias.

In summary, NBI did not improve the detection of duodenal and gastric polyps, and HRE and NBI have a limited role in the characterization of duodenal adenomas with advanced histology in FAP. Our results indicate that a duodenal adenoma >1 cm has a 3-fold increased risk of harboring advanced histology. This trait is easily and homogeneously estimated during endoscopy, as shown by the good interrater agreement. Our findings may support the resection of adenomas >1 cm in order to delay major surgery. However, endoscopic removal of duodenal lesions is also associated with major complications[23] and therefore should be performed only in patients who will benefit from it.

We believe that the Spigelman classification should be reevaluated and might be simplified by putting more emphasis on size, extension, location (papillary or extrapapillary), villous and tubulovillous architecture, and high-grade dysplasia. This would offer endoscopists a better risk-stratification of these patients and timely endoscopic therapy in an effort to prevent major duodenal surgery and development of duodenal cancer.

## ACKNOWLEDGMENT

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# Artículo 2

ORIGINAL ARTICLE

# Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white-light endoscopy and narrow-band imaging

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**Background:** Sessile serrated adenomas/polyps (SSAs/Ps) are premalignant lesions susceptible to being easily overlooked by endoscopists. A detailed description of the endoscopic appearance of SSAs/Ps might help endoscopists to recognize these lesions to improve the effectiveness of colonoscopy.

**Objective:** To identify various endoscopic features of SSAs/Ps using high-resolution white-light endoscopy (HR-WLE) and narrow-band imaging (NBI).

**Design:** Retrospective image evaluation study.

**Setting:** Single tertiary referral center.

**Patients:** Forty-5 patients with serrated polyposis syndrome undergoing surveillance colonoscopies.

**Intervention:** HR-WLE and NBI images of 150 polyps (50 SSAs/Ps, 50 hyperplastic polyps [HPs], and 50 adenomas) were systematically assessed by 5 experts using various endoscopic descriptors.

**Main Outcome Measurements:** The prevalence of specific endoscopic features observed in SSAs/Ps versus HPs.

**Results:** Multivariate analysis demonstrated that indistinct borders (OR, 3.11; 95% CI, 1.57-6.15) and a cloud-like surface (OR, 2.65; 95% CI, 1.21-5.78) were associated with SSA/P histology on HR-WLE. On NBI, a cloud-like surface (OR, 4.91; 95% CI, 2.42-9.97), indistinct borders (OR, 2.38; 95% CI, 1.14-4.96), irregular shape (OR, 3.17; 95% CI, 1.59-6.29), and dark spots inside the crypts (OR, 2.05; 95% CI, 1.02-4.11) were found to be endoscopic predictors of SSA/P histology. The sensitivity, specificity, and accuracy of NBI for differentiating serrated polyps containing either none or all 4 endoscopic SSA/P features were, respectively, 89%, 96%, and 93%.

**Limitations:** Retrospective, image evaluation analysis.

**Conclusions:** The current study demonstrates that SSAs/Ps possess several specific endoscopic features compared with HPs. Recognition of these characteristics might assist endoscopists in the differentiation of these lesions and could possibly facilitate endoscopic detection of these rather subtle lesions. (Gastrointest Endosc 2013;xx:xxx.)

Over the last decades, much progress has been made in unraveling the development of colorectal cancer (CRC) along the adenoma-carcinoma sequence.[1,2] This has led to colonoscopic screening and surveillance programs aimed at the detection and removal of adenomas to prevent CRC.[3,4] However, population-based and case-controlled studies have shown that screening colonoscopies are less effective in decreasing the incidence and mortality of CRC in the proximal colon compared with the distal part.[5-7] A plausible explanation for this remarkable observation is the proposed alternative pathway of colorectal carcinogenesis, the serrated neoplasia pathway.[8] This pathway describes the progression of a subset of serrated polyps, called sessile serrated adenomas/polyps (SSAs/Ps), to CRC and may be responsible for up to 20% of all sporadic CRCs.[9] This implies that all SSAs/Ps should be accurately recognized and removed during colonoscopy. These lesions, however, are susceptible to being easily overlooked due to their flat morphology and unremarkable color, providing little contrast with surrounding colonic mucosa. Moreover, due to the morphological similarity with hyperplastic polyps (HPs), it seems likely that a proportion of detected SSAs/Ps are left in situ when they are misinterpreted by colonoscopists as clinically irrelevant HPs.

Recognition of specific endoscopic characteristics of SSAs/Ps by colonoscopists may improve SSA/P detection and eventually enhance the effectiveness of colonoscopy. Studies systematically describing the endoscopic appearance of SSAs/Ps are scarce, and the role of advanced imaging techniques, like narrow-band imaging (NBI), in real-time recognition of these lesions is not well studied. The aim of this image evaluation study was to identify specific endoscopic features of SSAs/Ps using high-resolution white-light endoscopy (HR-WLE) and NBI. Secondary aims were to assess the diagnostic accuracy of HR-WLE and NBI for the differentiation of SSAs/Ps from HPs and to assess the interobserver agreement of these features.

## METHODS

### Endoscopic procedure

For this study we retrospectively collected data from colonoscopies that were performed with the Evis Lucera system (CLV-260; Olympus Inc, Tokyo, Japan) or the Evis Exera II system (CLV-180; Olympus Inc) in combination with high-resolution video colonoscopes (CF-H260Z, XCF-H240FZL, or CF-H180AI; Olympus Inc). During all procedures, multiple HR-WLE and NBI images were taken of each polyp. All images were collected in a database and linked to the corresponding data of the polyps, including histopathology, size, location, and the shape (Paris classification[10]). The Paris classification divides lesions into three main categories: I, protruding lesions (Is = sessile or Ip = pedunculated); II, nonprotruding and nonexcavated lesions

> **Take-home Message**
>
> - Sessile serrated adenomas/polyps possess several specific endoscopic characteristics compared with hyperplastic polyps.
> - Recognition of these specific characteristics might assist endoscopists in the differentiation of these lesions and could possibly facilitate endoscopic detection of these rather subtle lesions.

(IIa = flat elevated, IIb = completely flat, and IIc = slightly depressed); and III, excavated lesions.

### Data collection set

In total, 243 polyps with corresponding images were registered in the database. For each histopathologic entity, 50 nonmagnified images were selected based on quality (sharp and well-focused images). This resulted in a dataset of 150 polyps: 50 SSAs/Ps, 50 HPs, and 50 adenomas. Images were taken as part of previous studies as well as during 1 ongoing prospective study comparing polyp miss-rates of HR-WLE with those of NBI in patients with serrated polyposis syndrome.[11-13] All studies were approved by the medical ethical committee of our institution.

For all histopathologic entities, the images were randomly assigned into 2 sets: a learning set, consisting of 60 polyps (20 SSAs/Ps, 20 HPs, and 20 adenomas), and a validation set, consisting of the remaining 90 polyps (30 SSAs/Ps, 30 HPs, and 30 adenomas). Images were incorporated into a slideshow (Microsoft PowerPoint 2003; Microsoft, Redmond, WA, USA) and stored as portable document format (PDF) file without any form of postprocessing.

### Image evolution process

**Exploratory meeting and learning set.** An exploratory meeting with 2 expert endoscopists (E.D. and M.L.) and 1 expert pathologist (SvE) was arranged to discuss and to identify several potential endoscopic features of SSAs/Ps. Subsequently, the learning set was used to determine which of the postulated features were associated with SSA/P histology. This assessment was performed by two observers (E.D. and J.E.) at the same time, both blinded to histopathology and polyp location. HR-WLE and corresponding NBI pictures were displayed simultaneously to both observers at the same time. The observers both stated their assessment of each polyp; in case of disagreement a consensus between the 2 was reached by a joint discussion. Only those features that demonstrated a significant association with SSA/P histology were subsequently scored in the validation set.

**Validation set.** The validation set was used to validate the endoscopic features derived from the learning set and to assess the diagnostic accuracy of each specific feature as

well as to assess the interobserver variability among international experts. The dataset was assessed individually by all 5 observers and consisted of the same observers of the learning set (ED and JE) and 3 additional observers (AR, TN, and MP). In contrast to the learning set, consecutive HR-WLE images and NBI images were scored separately, both in a random order for each technique. Again, the observers were blinded to histopathology and polyp location. In addition to these data, the quality of the images was also scored (poor, moderate, good, or excellent).

**Observers.** The assessment of polyps was done by 5 experienced endoscopists from 5 different hospitals in Europe (E.D., J.E., and M.P.), North America (A.R.), and Asia (T.N.). They had all performed at least 50 colonoscopies with NBI before the start of this study.

**Digital training module.** Before assessment of the images, a short digital training module was provided to the assessors, including descriptions and examples of all endoscopic features. Subsequently, a set of training polyps (3 SSAs/Ps, 1 HP, and 1 adenoma) was displayed to each endoscopist. After scoring these polyps, direct feedback was given to the observer by revealing the correct histopathology. All images used for this training were additional and not included in the final image evaluation process.

## Reference standard

The histopathologic diagnosis served as reference standard. All tissue specimens were evaluated by 1 expert GI pathologist (SvE) according to the revised Vienna criteria.[14] The histopathologic diagnosis was based on the morphologic features on hematoxylin and eosin staining. A SSA/P was defined as a serrated lesion with irregular dilated crypts, including dilatation of the base of the crypts that often have a boot, L, or inverted T shape.[15] The pathologist was blinded to the endoscopic appearance of the lesions.

## Statistical analysis

SPSS for Windows software (version 18.0.2; Chicago, IL, USA) was used for analysis. Descriptive statistics were used to describe the study population. Proportions of endoscopic features and comparison of image quality were tested with the $\chi^2$ test. Features found to be significantly associated ($P < .05$) with SSA/P histology in the learning set were subsequently assessed in the validation set. For multivariate analysis, only features that demonstrated an association ($P < .05$) with SSA/P histology in univariate analysis were used in the model.

In the validation set, pooled data of 5 observers ($5 \times 90$ images) were used. The diagnostic accuracy of the endoscopic features and the predictive models for differentiating SSAs/Ps from HPs were assessed by comparison with histopathology and were reported according the Standards for Reporting of Diagnostic Accuracy statements for diagnostic accuracy studies.[16] Diagnostic accuracy for all fea-

tures was calculated for all 5 observers combined and derived from $2 \times 2$ tables. Outcome parameters were sensitivity, specificity, and overall accuracy. The interobserver agreement was expressed by the percentage of full agreement among the observers as well as by an overall kappa statistic with 95% confidence interval. The interobserver agreement was calculated using the Fleiss kappa measurement (more than 2 observers).[17] Interpretation of kappa values was done according to Landis and Koch.[18]

## RESULTS

### Polyp characteristics

All polyp data were derived from 45 patients (mean age $61 \pm 9$ years [SD], 23 men) with serrated polyposis syndrome, of whom most underwent annual surveillance colonoscopies in one tertiary referral center. The median polyp size was 5 mm (IQR, 3-8 mm); 34 polyps (23%) were at least 10 mm, and 97 polyps (65%) were located proximal to the sigmoid. In total, 76 polyps (51%) were flat (Paris IIa or IIb), 73 polyps were sessile (Paris Is), and 1 polyp had a pedunculated shape.

### Exploratory meeting

During the exploratory meeting, a standard consensus list of 7 potential endoscopic features of SSAs/Ps was developed. Detailed descriptions and endoscopic examples of each individual feature are provided in, respectively, Table 1 and Figure 1.

### Learning set: determining relevant endoscopic features by 2 observers

The combined HR-WLE and NBI images of 48 of 60 polyps (80%) were scored as having excellent or good quality, whereas the image quality of the remaining 12 polyps (20%) was scored as moderate or poor. Univariate analyses showed that 6 features were significantly more often scored as present in SSAs/Ps than in HPs: (1) indistinctive borders (100% vs 60% $P = .003$), (2) cloud-like surface (90% vs 20% $P < .001$), (3) pit pattern IISSA/P (45% vs 10% $P = .031$), (4) dark spots inside the crypts (75% vs 15% $P = .001$), (5) normal vascular pattern intensity (85% vs 40%, $P = .008$), and (6) irregular shape (95% vs 25%, $P < .001$).

### Validation set: validation of endoscopic features by 5 observers

Ninety polyps with both HR-WLE and NBI images were scored by 5 observers, resulting in 450 assessments for each imaging modality. Sixty-six percent of HR-WLE images (299) and 71% of NBI images (319) were scored as having excellent or good quality ($P = .15$). Apart from pit pattern analysis, all features could be assessed on all images by all endoscopists. A pit pattern could not be identified on 26% of HR-WLE images and on 10% of NBI images.

**TABLE 1. Consensus meeting: various potential endoscopic features of SSAs/Ps.**

| Feature | Description | Outcome | Examples of each endoscopic feature as shown on Figure 1 |
|---|---|---|---|
| Indistinctive borders | Vague demarcation of a border of a lesion | Present/not present | A, B, I |
| Cloud-like surface | A bumpy, soft-looking nodular surface resembling a cumulus cloud | Present/not present | C, D, E, F, I |
| Dark spots inside the crypts | Small dark dots inside the open crypts. On HR-WLE they can also appear as red dots | Present/not present | D, F, J |
| Irregular shape | An asymmetric shape, in contrast to the oval, circular shape of small HPs and conventional adenomas | Present/not present | A, B, C, D, G, I |
| Absence of tiny microvessels crossing the surface | Small superficial vessels or telangiectasias occasionally seen on the surface of particular distal HPs | Present/not present | A-J |
| Pit pattern | Kudo pit pattern I-V or pit pattern II SSA/P (defined as a mixture of open crypts and small elongated star-shaped pits) | Kudo type I-V or pit pattern II SSA/P | H (pit pattern II SSA/P) |
| Vascular pattern intensity | Assessment of the darkness of the lines that outline each colonic crypt compared with the normal background mucosa A darker (strong) VPI indicates neoplasia, whereas a same (normal) or lighter (weak) VPI suggests a non-neoplastic lesion[19] | Weak, normal, or strong | B, D, F, H, J (same VPI) |

*SSA/P,* Sessile serrated adenoma/polyp; *HP,* hyperplastic polyp; *VPI,* vascular pattern intensity; *HR-WLE,* high-resolution white-light endoscopy.

Univariate analyses showed that all endoscopic SSA/P features were again significantly more often present in SSAs/Ps compared with HPs (Table 2) (all features P ≤ .002). Subsequent multivariate analysis demonstrated that presence of an indistinctive borders (OR, 3.11; 95% CI, 1.57-6.15) and a cloud-like surface (OR, 2.65; 95% CI, 1.21-5.78) were 2 independent predictive endoscopic characteristics of SSA/P histology on HR-WLE (Table 3). Under NBI a cloud-like surface (OR, 4.91; 95% CI, 2.42-9.97), an irregular shape (OR, 3.17; 95% CI, 1.59-6.29), indistinctive borders (OR, 2.38; 95% CI, 1.14-4.96), and dark spots inside the crypts (OR, 2.05; 95% CI, 1.02-4.11) were found to be independent predictors of SSA/P histology. The sensitivities, specificities, and diagnostic accuracies of the independent predicting feature are listed in Table 4.

## Validation set: differentiation of serrated polyps by combining endoscopic features

By combining the independent endoscopic features derived from the image evolution process, a prediction model per imaging technique was developed to differentiate SSAs/Ps from HPs. A lesion was endoscopically considered as SSA/P if all independent SSA/P features were scored as present, which were 2 features on HR-WLE (indistinctive borders and cloud-like surface) and 4 features on NBI (indistinctive borders, cloud-like surface, irregular shape, and dark spots inside the crypts). An endoscopic diagnosis of an HP was made if none of these features was present. These models were subsequently applied on all eligible lesions in the validation set and compared with histopathology. Of the 300 (5 × 60) serrated polyps, 207 lesions (69%) on HR-WLE and 116 lesions (39%) on NBI were included for differentiation because these lesions were scored as having either none or all SSA/P features. In these subsets of polyps a sensitivity, specificity, and overall accuracy of, respectively, 75%, 79%, and 77% on HR-WLE and 89%, 96%, and 93% on NBI were obtained (Table 5).

## Validation set: interobserver variability

The interobserver agreement regarding the endoscopic features on HR-WLE and NBI among all 5 observers is listed in Table 3. With both modalities, the best agreement was obtained for cloud-like surface, namely moderate
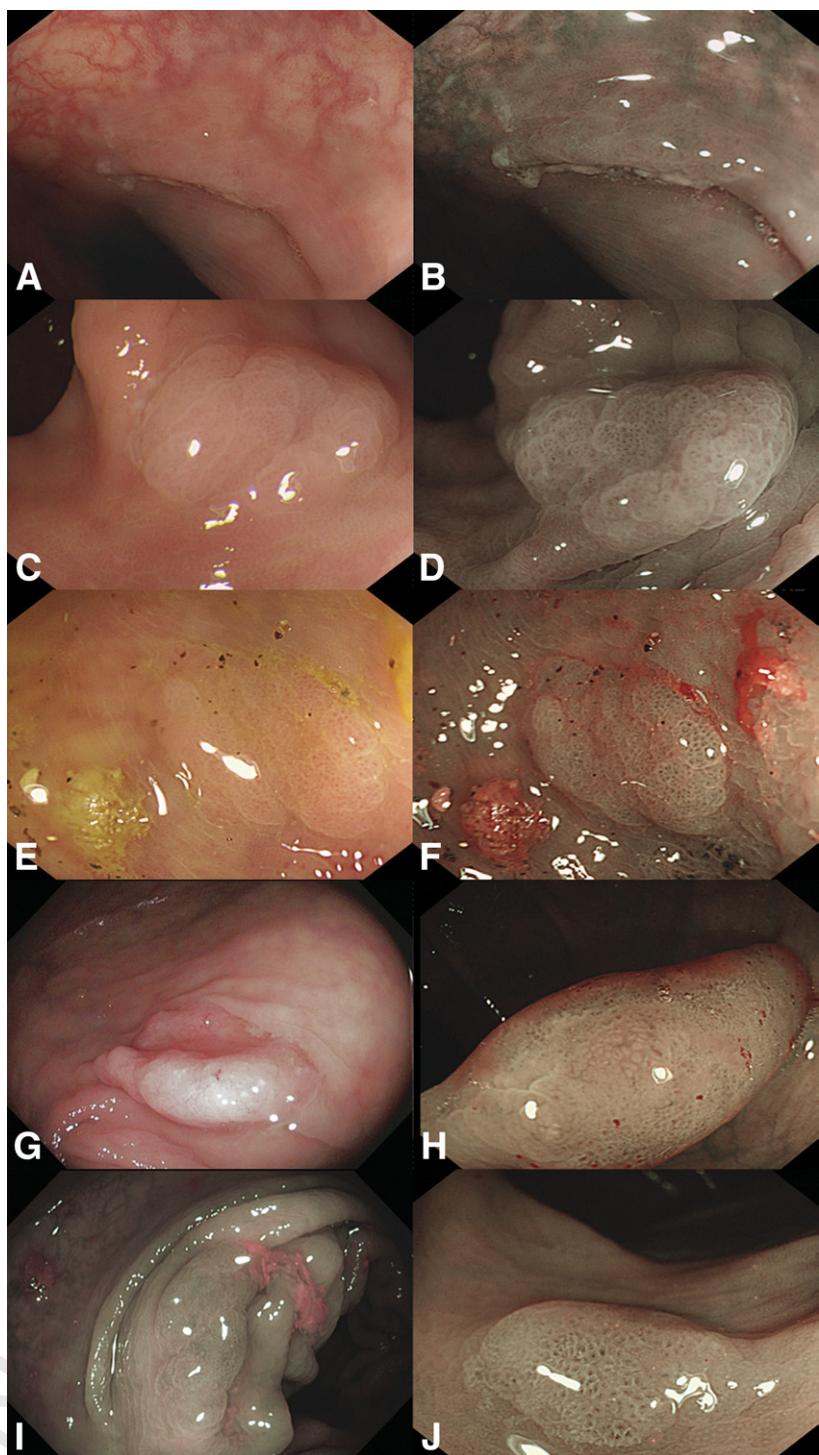
**Figure 1.** HR-WLE and NBI images of sessile serrated adenomas/polyps (SSAs/Ps) illustrating the 7 potential features that were defined during the exploratory meeting. After assessment of the images, 4 features were independently associated with SSA/P histology; a cloud-like surface (**B, C, D, E, F,** and **I**) and indistinctive borders (**A** and **B**) were predictive features on both HR-WLE and NBI, whereas dark spots (**D, F,** and **J**) and an irregular shape (**A, B, C, D, G,** and **I**) were predictive characteristics solely on NBI. **A,** SSA/P demonstrating vague margins seen under HR-WLE. **B,** The same lesion as in **A**, seen under NBI. Again, the borders of the lesion are not well defined. Note the nodular aspect of the surface (cloud-like surface), which was not seen under HR-WLE. **C,** SSA/P expressing a cloud-like surface under HR-WLE. **D,** The same lesion as in **C**, seen under NBI. Again, the cloud-like surface is clearly visible. Note the dark spots inside the crypts. **E,** Flat SSA/P with a cloud-like surface and red dots inside the crypts. **F,** Same lesion as in **E**, seen under NBI, again with a cloud-like surface and dark spots inside the crypts. **G,** Large proximal SSA/P with an irregular shape. **H,** SSA/P expressing a mixture of open crypts and small elongated star-shaped pits (pit pattern IISSA/P). **I,** SSA/P on a fold seen under NBI. The lesion has the same vascular pattern intensity as the background mucosa and an irregular shape. **J,** Flat SSA/P seen under NBI. Note the dark spots inside the crypts in the middle section of the lesion.

**TABLE 2. Validation set: prevalence of endoscopic features in SSAs/Ps, HPs, and adenomas**

| | SSAs/Ps (n = 150 [5 × 30]) | HPs (n = 150 [5 × 30]) | Adenomas (n = 150 [5 × 30]) | P |
|---|---|---|---|---|
| **Indistinctive borders** | | | | |
| HR-WLE | 73 (66-80) | 35 (27-43) | 27 (20-34) | <.001 |
| NBI | 65 (57-73) | 21 (15-28) | 21 (15-28) | <.001 |
| **Cloud-like surface** | | | | |
| HR-WLE | 58 (50-66) | 21 (15-28) | 4 (2-8) | <.001 |
| NBI | 66 (58-73) | 14 (9-20) | 5 (3-10) | <.001 |
| **Pit pattern II SSA/P** | | | | |
| HR-WLE | 36 (28-46) | 12 (7-19) | 6 (3-12) | <.001 |
| NBI | 30 (23-38) | 8 (4-14) | 6 (3-12) | <.001 |
| **Dark spots inside the crypts** | | | | |
| HR-WLE | 37 (30-45) | 21 (16-29) | 9 (6-15) | .002 |
| NBI | 58 (50-66) | 29 (22-36) | 17 (12-24) | <.001 |
| **Normal VPI*** | | | | |
| NBI | 80 (73-86) | 49 (42-57) | 30 (23-38) | <.001 |
| **Irregular shape** | | | | |
| HR-WLE | 71 (63-77) | 42 (34-50) | 27 (20-34) | <.001 |
| NBI | 78 (71-84) | 31 (24-38) | 25 (19-33) | <.001 |

Values are percents, with 95% confidence interval in parentheses. P values result from $\chi^2$ (comparison between SSAs/Ps vs HPs).
SSA/P, Sessile serrated adenoma; HPs, hyperplastic polyps; VPI, vascular pattern intensity; HR-WLE, high-resolution white-light endoscopy; NBI, narrow-band imaging; CI, confidence interval.
*Assessed on NBI imaging only.

**TABLE 3. Validation set: independent endoscopic predictors for SSA/P histology and corresponding interobserver agreement among 5 observers[†]**

| | HR-WLE | | | | NBI | | | |
|---|---|---|---|---|---|---|---|---|
| | Multivariate analysis[†] | | Interobserver agreement | | Multivariate analysis[†] | | Interobserver agreement | |
| | OR (95% CI) | P | Full agreement (%) | Kappa* (95% CI) | OR (95% CI) | P | Full agreement (%) | Kappa* (95% CI) |
| Indistinctive borders | 3.11 (1.57-6.15) | .001 | 39 | 0.38 (0.32-0.45) | 2.38 (1.14-4.96) | .021 | 59 | 0.57 (0.50-0.63) |
| Cloud-like surface | 2.65 (1.21-5.78) | .015 | 62 | 0.52 (0.46-0.59) | 4.91 (2.42-9.97) | <.001 | 71 | 0.67 (0.60-0.73) |
| Pit pattern II SSA/P | 1.89 (0.74-4.85) | .186 | 18 | 0.04 (−0.06-0.15) | 1.04 (0.37-2.94) | .941 | 38 | 0.10 (0.02-0.17) |
| Dark spots inside the crypts | 0.79 (0.35-1.77) | .562 | 48 | 0.29 (0.22-0.36) | 2.05 (1.02-4.11) | .044 | 46 | 0.40 (0.33-0.47) |
| Normal VPI | — | – | – | – | 1.58 (0.79-3.14) | .194 | 34 | 0.34 (0.27-0.41) |
| Irregular shape | 1.57 (0.74-3.31) | .237 | 37 | 0.40 (0.33-0.46) | 3.17 (1.59-6.29) | .001 | 34 | 0.38 (0.31-0.44) |

HR-WLE, High-resolution white-light endoscopy; NBI, narrow-band imaging; SSA/P, sessile serrated adenoma/polyp; HP, hyperplastic polyp; VPI, vascular pattern intensity; OR, odds ratio; CI, confidence interval.
*Fleiss kappa (more than 2 observers).
†Adjusted for polyp size (size group ≥ 10 mm).

**TABLE 4. Validation set: sensitivity, specificity, and diagnostic accuracy of the independent predictive SSAs/Ps features assessed with HR-WLE and NBI**

| | HR-WLE | | NBI | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | Indistinctive borders | Cloud-like surface | Indistinctive borders | Cloud-like surface | Dark spots inside the crypts | Irregular shape |
| Sensitivity | 73 (66-80) | 58 (50-66) | 65 (57-73) | 66 (58-73) | 58 (50-66) | 78 (71-84) |
| Specificity | 65 (57-73) | 79 (71-85) | 79 (72-85) | 86 (80-91) | 71 (64-78) | 69 (62-76) |
| Accuracy | 73 (67-77) | 68 (63-73) | 71 (66-76) | 76 (71-81) | 65 (59-70) | 74 (68-78) |

Values are percents, with 95% confidence interval in parentheses.
SSA/P, Sessile serrated adenoma/polyp; HR-WLE, high-resolution white-light endoscopy; NBI, narrow-band imaging.

**TABLE 5. Validation set: sensitivity, specificity, and accuracy of HR-WLE and NBI for serrated lesions exhibiting either none or all independent SSA/P features***

| | HRE | | NBI | |
| --- | --- | --- | --- | --- |
| | Fraction | % (95% CI) | Fraction | % (95% CI) |
| Sensitivity | 71/95 | 75 (65-82) | 42/47 | 89 (77-95) |
| Specificity | 89/112 | 79 (71-86) | 66/69 | 96 (88-99) |
| Accuracy | 160/207 | 77 (71-82) | 108/116 | 93 (87-96) |

Of the 300 serrated lesions, 207 lesions (95 SSAs/Ps and 112 HPs) on HR-WLE and 116 lesions (47 SSAs/Ps and 69 HPs) on NBI were eligible for differentiation.
HR-WLE, High-resolution white-light endoscopy; NBI, narrow-band imaging; SSA/P, sessile serrated adenoma/polyp; CI, confidence interval.
*All features on HR-WLE include indistinctive borders and cloud-like surface. All features on NBI include indistinctive borders, cloud-like surface, irregular shape, and dark spots inside the crypts.

with HR-WLE (kappa = 0.52; 95% CI, 0.46-0.59) and substantial with NBI (kappa = 0.67; 95% CI, 0.60-0.73).

## DISCUSSION

The introduction of advanced imaging techniques, such as NBI, autofluorescence imaging, and confocal endomicroscopy, has led to many clinical studies focusing on the endoscopic appearance of conventional adenomas.[19-22] In contrast, studies systematically describing and characterizing the endoscopic features of SSAs/Ps are scarce and often lack a systematic approach.[23,24] The current study provides a systematic validation of novel endoscopic features of SSAs/Ps using HR-WLE and NBI assessed by international experts. We demonstrate that SSAs/Ps harbor specific endoscopic features compared with HPs, and we are able to predict the histology of a subset of serrated polyps with NBI with a high diagnostic accuracy.

Strengths of this study include the systematic study approach, the introduction of novel endoscopic features,

and the participation of international experts from various continents with different expertise. Moreover, the introduced features are easy to assess without the necessity of a magnifying endoscope, allowing a widespread implementation in a general practice setting. Our study has several limitations. First, the endoscopic images were assessed post-hoc rather than in real-time, and there was a selection bias because only high-quality images were selected. In a real-time situation, optimal visualization of polyps is not always possible, and these lesions are consequently not evaluated in this study. However, also in the present study almost one third of all images were assessed as having moderate or poor quality by the different observers. A second potential shortcoming is that endoscopic features were postulated and formulated by the relatively small number of 2 endoscopists and 1 pathologist. Although this initial process can be considered as somewhat subjective, some of these features were compatible with features described by other research groups.[24,25] Moreover, we were able to validate these characteristics among various endoscopists from different international hospitals. Finally, it can be discussed whether our results can be extrapolated to the general population because all polyps were derived from patients with serrated polyposis syndrome. We believe, however, that SSAs/Ps in these patients express a similar phenotype compared with SSAs/Ps encountered in nonselected patients.

Four features were independently associated with SSA/P histology: a cloud-like surface and indistinctive borders were predictive features on both HR-WLE and NBI, whereas dark spots and an irregular shape were predictive characteristics solely on NBI. A cloud-like surface, defined as a bumpy, soft-looking nodular surface and indistinctive borders, was present in more than half of all SSAs/Ps. Accordingly, Tadepalli et al[25] observed a focal, subtle irregularity or bumpiness to the mucosal surface in almost one third of all SSAs/Ps. Furthermore, a previous study from Japan reported that SSAs/Ps possess a more granular surface and had vaguer borders compared with HPs.[24] Dark spots or dots inside the crypts were present in two thirds of all SSAs/Ps under NBI. A recent Japanese study

introduced a novel pit pattern as a predictive feature for SSAs/Ps: type II-O.[26] The pits of this type II-O pattern are wider and more rounded in shape, and the authors hypothesized that an overproduction of mucin could be the cause of this phenomenon. Interestingly, the enclosed magnified images of the mentioned study suggest that these wider pits might be the same pits we observe as black dots on nonmagnified NBI images.

The interobserver agreement regarding the assessed features was, except for irregular shape, better for NBI than for HR-WLE. On NBI, a substantial interobserver agreement was obtained for a cloud-like surface ($\kappa$ = 0.67). This is in agreement with Tadepalli et al,[25] that also demonstrated a substantial interobserver agreement for a nodular/cloud-like surface between just 2 observers ($\kappa$ = 0.8). The interobserver agreement of the other endoscopic features ranged from moderate to slight. Although these last figures seem unsatisfactory, one has to bear in mind that the endoscopists received only a minimal training. By gaining knowledge and experience with these specific features, the interobserver agreement will likely increase.

Accurate differentiation of lesions during colonoscopy has the advantage that on-site decisions can be made. Although one could argue that complete resection is needed for all detected lesions, it seems likely that in general practice, endoscopists compromise for time, costs, and risks. Adequate recognition of SSAs/Ps might aid endoscopists in selecting a polypectomy technique that more likely results in a complete resection (eg, endoscopic mucosal resection), whereas HP-appearing lesions can be removed with relatively lower risk techniques. A second potential advantage is that differentiation of polyps could facilitate endoscopists in their decision to leave suspected distal diminutive (<6 mm) HPs in situ because these are generally considered as benign lesions harboring no malignant potential.[27] The advantage of this strategy is that it may reduce pathology costs, the workload for endoscopists, and even the adverse event rate as less unnecessary polypectomies are performed.[20] However, this should not be accompanied by an increased risk of leaving potential neoplastic lesions in situ. Although SSAs/Ps have predilection for the proximal colon, a significant proportion of SSAs/Ps also occur in the rectosigmoid, and these lesions should not be left in place because they are endoscopically misinterpreted as HPs.[28] Therefore, if an endoscopist opts to leave a distal diminutive serrated-appearing lesion in situ, an additional visual technique to differentiate between an HP and an SSA/P could be worthwhile to make a correct decision.

We estimated the diagnostic accuracy of all associated features of SSAs/Ps. The highest diagnostic accuracy was obtained with the feature of indistinctive borders on HR-WLE (73%; 95% CI, 67-77), whereas the presence or absence of a cloud-like surface resulted in the highest accuracy on NBI (76%; 95% CI, 71-81). Because these accuracies of single features are clinically unacceptable for accurate on-site differentiation, the different associated endoscopic features were also used in combination. In this prediction model only serrated polyps that exhibited either none (considered as HP) or all independent significant SSA/P features (considered as SSA/P) were differentiated. Although we still observed a moderate sensitivity and accompanying accuracy for HR-WLE, a remarkable higher sensitivity and accuracy for NBI of, respectively, 89% and 93% was obtained. The drawback of this approach is that only a limited number of serrated polyps, namely 69% on HR-WLE and 39% on NBI, were eligible for differentiation. However, in a real-time setting this figure might be higher because the number of small distal HPs without any SSA/P feature is likely to be higher compared with that in our image evaluation set.[22]

To conclude, the current study demonstrates that SSAs/Ps harbor specific endoscopic features compared with HPs. The presence of a cloud-like surface, indistinctive borders, irregular shape, and dark spots inside the crypts are all features that might aid endoscopists in differentiating premalignant SSAs/Ps from innocuous HPs during colonoscopy. Using a combination of these features, we were able to predict the histology of a subset of serrated polyps with NBI with a high diagnostic accuracy. Prospective studies of consecutive patients in a general setting are warranted to validate the endoscopic SSA/P features during real-time colonoscopy and to determine whether these features are a useful tool in a daily clinical setting.

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# Artículo 3

# Narrow-band imaging as an alternative to chromoendoscopy for the detection of dysplasia in long-standing inflammatory bowel disease: a prospective, randomized, crossover study

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**Background:** Narrow-band imaging (NBI) is a novel technique that may represent an alternative method to chromoendoscopy (CE) for the detection of colitis-associated intraepithelial neoplasia (IN) in patients with long-standing inflammatory bowel disease (IBD).

**Objective:** To compare NBI with CE for the detection of IN.

**Design:** Prospective, randomized, crossover study.

**Setting:** Academic hospital.

**Patients:** Patients with clinically inactive colonic IBD ($\geq$8 years).

**Intervention:** Patients underwent both CE and NBI in randomized order. Targeted biopsy specimens from abnormal areas were obtained. Pathological examination was regarded as the reference standard.

**Main Outcome Measurements:** Number of false-positive and true-positive lesions in patients undergoing CE and NBI were compared as well as the proportion of patients with missed IN lesions.

**Results:** Eighty patients were screened, of whom 20 were excluded. Mean $\pm$ standard deviation withdrawal time for CE was significantly longer than that for NBI (26.87 $\pm$ 9.89 minutes vs 15.74 $\pm$ 5.62 minutes, $P < .01$). Thirteen patients had at least 1 IN lesion on 1 of the examinations. In the per-lesion analysis, NBI resulted in a significantly inferior false-positive biopsy rate ($P = .001$) and a similar true-positive rate. The percentage of missed IN lesions and patients was superior with NBI, albeit without reaching statistical significance.

**Limitations:** Lesions were sampled immediately after detection, which precluded the possibility of paired analysis.

**Conclusions:** NBI appears to be a less time-consuming and equally effective alternative to CE for the detection of IN. However, given the NBI lesion and patient miss rates, it cannot be recommended as the standard technique. (Gastrointest Endosc 2011;74:840-8.)

In recent years, several studies have shown that chromoendoscopy (CE) is more accurate in detecting dysplasia in patients with long-standing inflammatory bowel disease (IBD)[1-9] than is conventional endoscopy. In fact, a recent consensus guideline endorsed the use of CE as the standard detection method in this subset of patients.[10] In addition, recent evidence demonstrates that CE-guided biopsies have a higher diagnostic yield than do random biopsies.[5,7] Furthermore, few endoscopists perform the required 30 to 40 biopsies in their routine practice because this method is both time-consuming and expensive. On the other hand, gastroenterologists have been reluctant to take up CE, possibly out of concerns regarding cost, procedure time, and lack of experience.

Narrow-band imaging (NBI) is a new optical technology that not only improves the visual definition of the epithelial surface, but that also enhances the contrast of mucosal microvessels.[11,12] Because of the density and shape of microvessels in neoplasia, NBI could lead to more accurate identification of colitis-associated dysplasia.[13,14] As reported in recent studies, application of this new technology in GI endoscopy has proven helpful not only for the detection of mucosal lesions, but also for the endoscopic differentiation of neoplastic and non-neoplastic lesions by means of either mucosal pit patterns or vascular detailing.[13-16] This new technology could potentially be as useful as CE and less cumbersome. To date, only 1 randomized study, by Dekker et al,[17] examined the effectiveness of NBI in detecting neoplasia in patients with long-standing ulcerative colitis (UC). In this study, a first prototype NBI system was compared with standard-resolution white-light endoscopy (WLE) and demonstrated that NBI did not improve the ability to detect neoplasia. However, this trial was an underpowered pilot study and used a first-generation NBI system that had some technical inadequacies.

The aim of this study was to compare new-generation NBI systems with high-resolution imaging with CE for the early detection of colitis-associated dysplasia and cancer in patients with long-standing colonic IBD.

## PATIENTS AND METHODS

### Patients

Consecutive patients with clinically inactive, long-standing UC (≥8 years) involving at least the left colon or patients with colonic Crohn's disease (CD) affecting at least one third of the colon (≥8 years) were recruited from the Outpatient Clinic of the Gastroenterology Department at Hospital Clinic, Barcelona, Spain. Patients were excluded if they had previous colorectal cancer, a previous surgical resection of the colon or rectum, coagulopathy, a known allergy to indigo carmine, or if they did not consent. The study protocol was approved by the Medical Ethics Committee of our institution, and written informed consent was obtained from all participating patients.

**Take-home Message**

- NBI is a useful technique for the detection of dysplasia in patients with long-standing IBD that offers several advantages: efficiency, ease of use, and agility.
- However, the relatively high IN lesion and patient missrate encountered with NBI prevents its recommendation as the new standard technique of use.

### Study design

Each patient underwent high-resolution NBI colonoscopy and high-resolution indigo carmine CE with an interval of 3 to 8 weeks between procedures. The order in which the examinations were performed was randomized (1:1) to provide sufficient safeguards against the influence of any potential confounding effects. All colonoscopies were conducted by 1 of 2 experienced endoscopists (M.P., J.L.) who were blinded to the endoscopic and histological findings obtained during the first procedure.

### Endoscopic procedures

Bowel preparation included ingestion of 3 to 4 L of polyethylene glycol electrolyte solution before the examination and a dietary restriction of solid food 2 days before the procedure. Patients who were determined to have poorly or only moderately prepared for either of the 2 examinations were excluded from the study as were those who manifested endoscopically active disease during either of the 2 procedures, all of which were performed with the patients under spontaneous breathing sedation with propofol.

A high-resolution wide-angle video endoscope (Olympus prototype XCF H160AY2L, H180 series; Olympus Europe, Hamburg, Germany) with a high-resolution 1080-line screen was used for the study.

The endoscope was advanced into the terminal ileum or the cecum. No lesions were sustained during introduction of the endoscope. The success of cecal intubation was verified by identification of the usual landmarks. Withdrawal time from the cecum was measured by using a stopwatch. During extubation, each segment was thoroughly washed with a saline solution mixed with N-acetylcysteine and dimethicone. The mucosa was then carefully examined by using the standard procedure.[18]

**CE.** The SURFACE guidelines[2] for CE in UC were followed. The lumen was sprayed in a segmental fashion by using 0.5% indigo carmine delivered via a specially designed dye spray catheter (Olympus PW-5V1; Olympus Europe).

**NBI.** Once the cecal pole was reached under white light, the imaging mode was switched to NBI mode by pressing a button on the instrument control head. NBI was used for the entire withdrawal process. The endoscopic evaluation was focused on the vessel network and on the

differences in hue between the lesion and adjacent mucosa, as previously reported.[15]

The morphology, size, and location of any visible focal lesion were recorded. Any suspicious lesions detected during the examinations were sampled or immediately removed after detection. Suspicious areas were defined as any mucosal irregularity that was not entirely consistent with chronic or active UC, regardless of whether dysplasia was suspected. In patients with several unequivocal postinflammatory polyps, representative biopsy samples were taken only from atypical polyps. The focal lesion morphology was determined in accordance with the Paris classification[19] and pit pattern classification guidelines.[20] Lesion size was estimated by placing fully opened biopsy forceps next to the lesion before resection. Biopsies were performed only on lesions within the colitic area were included. Random biopsies were not performed.

### Histological assessment

Biopsy samples were processed and stained by using standard methods and were subsequently evaluated by an experienced GI pathologist (M.J.). Any specimens exhibiting dysplasia were reviewed by an independent pathologist (M.C.), and in the event of interobserver disagreement, a consensus was reached. For purposes of this study, the pathologists were blinded to the endoscopic technique in question, but were aware of the clinical data of the relevant patient and the type of biopsy.

Neoplastic changes were categorized according to the Vienna Classification system.[21] Low-grade dysplasia, high-grade dysplasia, and carcinoma were grouped into 1 category and designated IN. The histological outcome was classified into 1 of 3 categories: normal or inflammation, hyperplasia, and IN.

### Outcome measures and statistical analysis

Continuous data are given as mean ± standard deviation. Differences were analyzed with either a Student $t$ test or a Wilcoxon rank-sum test, when appropriate. Proportions were compared by using the $\chi^2$ or Fisher exact test.

The combined histological outcome after the 2 procedures was used as the reference standard diagnosis for each patient. Accordingly, the presence of IN in any biopsy sample was used to determine the diagnosis for each patient.

The number of false-positive lesions (a biopsy sample of a lesion negative for IN) and true-positive (a biopsy sample of a lesion positive for IN) recorded by using CE and NBI were compared. Similarly, a per-patient analysis was also performed.

Because most lesions were sampled immediately after detection, only missed lesions and unresected lesions could be detected by using the second technique, which precluded any paired analyses. To determine the effectiveness of CE compared with NBI for IN, we compared the number of IN lesions detected by the second examination and divided it by the total number of IN lesions detected overall (first and second inspections); this figure represented the miss rate of each technique. These proportions, as well as the proportion of patients with missed neoplastic lesions, were then compared.

All statistical analyses were performed by using the SPSS version 16 (SPSS Inc, Chicago, Ill). A type I error ($\alpha$) of 5% was chosen as the cutoff for statistical significance.

## RESULTS

### Patient characteristics

Between April 2006 and November 2007, a total of 80 patients fulfilled inclusion criteria and were enrolled in this study. Twenty patients had to be excluded from further analysis because either 1 or both procedures was incomplete because of poor or fair bowel preparation (n = 6), endoscopic activity (n = 11), or lack of agreement (n = 3) (Fig. 1). Our analysis was therefore restricted to 60 patients for whom paired colonoscopic procedural data were available. CE was the first study performed in 27 of the patients, and NBI was the first study performed in the 33 remaining patients.

Patient baseline characteristics for this study, in accordance with our randomization scheme, are summarized in Table 1. Male patients were predominant in the NBI group compared with the CE group (67% vs 41%, respectively; $P = .04$).

Thirteen patients (21.7%) had at least 1 IN lesion in 1 of the 2 explorations. Baseline characteristics comparing patients with and without IN are shown in Table 2.

### Duration and colonoscopy findings

The mean withdrawal time for CE was significantly higher than that for NBI (26.87 ± 9.89 vs 15.74 ± 5.62 minutes; $P < .01$).

Biopsies were performed on a total of 344 endoscopically suspicious lesions in the colitic colon of the study population in both examinations. Of these, 22 corresponded to IN (6.4%), 84 to hyperplastic polyps (24.4%), and 238 to inflammatory lesions (69.2%). CE detected 208 suspicious lesions that corresponded to low-grade dysplasia (n = 12), hyperplastic polyps (n = 63), and inflammation (n = 133), whereas NBI revealed 136 suspicious lesions that corresponded to low-grade dysplasia (n = 10), hyperplastic polyps (n = 21), and inflammation (n = 105).

### Comparison of paired endoscopic findings

Our comparison of the paired endoscopic findings of CE and NBI in the 60 patients is shown in Table 3. Interestingly, in the per-lesion analysis, NBI colonoscopy resulted in a significantly lower false-positive biopsy rate ($P = .001$).
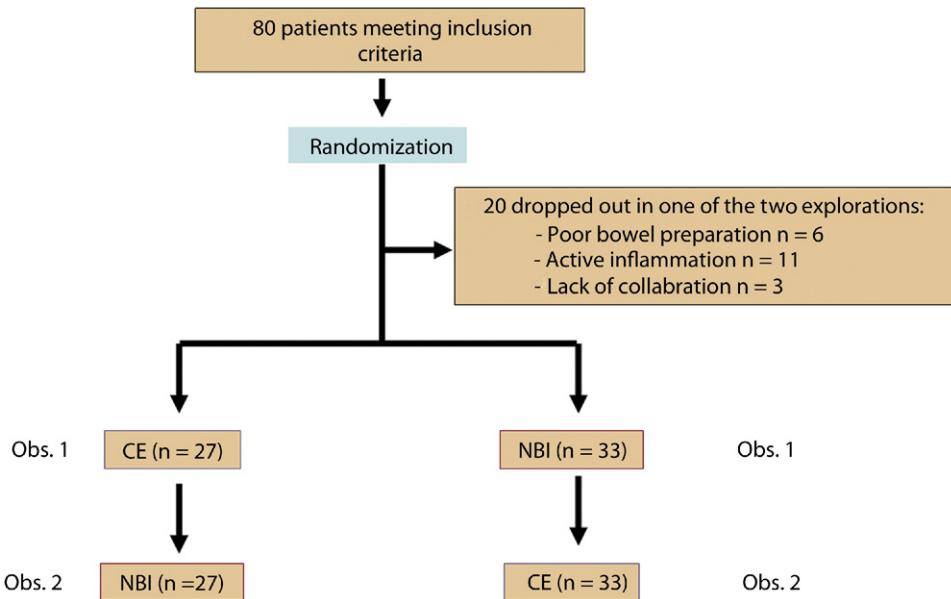
**Figure 1.** Flow chart of the prospective, randomized, crossover study design. CE, high-resolution chromoendoscopy; NBI, high-resolution narrow-band imaging.

| TABLE 1.   Baseline characteristics of those patients randomly assigned to CE and NBI as their first examination | | | |
|---|---|---|---|
| | CE first (n = 27) | NBI first (n = 33) | P Value |
| Male no. (%) | 11 (40.7) | 22 (66.7) | .04 |
| Age, mean ± SD, y | 47.26 ± 13.33 | 49.36 ± 14.55 | .56 |
| UC/CD | 17/10 | 25/9 | .35 |
| Pancolitis, no. (%) | 21 (77.8) | 22 (66.7) | .34 |
| Mean ± SD duration of IBD, y | 15.35 ± 6.75 | 16.52 ± 9.02 | .59 |
| Taking AAS, NSAIDs, ursocholic acid, no. (%) | 20 (74.1) | 27 (81.8) | .47 |
| Treatment with mesalazine, no. (%) | 11 (40.7) | 14 (42.4) | .89 |
| Treatment with immunosuppressants, no. (%) | 14 (51.9) | 11 (33.3) | .15 |
| Family history of colorectal cancer, no. (%) | 4 (14.8) | 4 (12.1) | 1.0 |
| Personal history of colorectal adenoma, no. (%) | 2 (7.4) | 6 (18.2) | .28 |
| Primary sclerosing cholangitis, no. (%) | 2 (7.4) | 3 (9.1) | 1.0 |
| Previous colonoscopy, no. (%) | 18 (66.7) | 28 (84.8) | .13 |
| Time ± SD since previous colonoscopy, y | 4.22 ± 2.80 | 4.59 ± 4.40 | .75 |
| Presence of endoscopic features suggesting predisposition to dysplasia,* no. (%) | 17 (63) | 16 (48.5) | .26 |

*CE*, Chromoendoscopy; *NBI*, narrow-band imaging; *SD*, standard deviation; *UC*, ulcerative colitis; *CD*, Crohn's disease; *IBD*, inflammatory bowel disease; *AAS*: 5-aminosalicylic acid; *NSAIDs*, nonsteroidal anti-inflammatory drugs.
*Shortened, featureless, or tubular colon; presence of pseudopolyps, stenosis, or scarring; or segment with severe inflammation.[32]

## Neoplasia miss rate by using the endoscopic technique

Table 4 shows the characteristics of IN lesions detected with both techniques based on the order in which the examinations were performed.

Among the 27 patients assigned for inspection with CE first, 5 IN lesions were detected in 4 patients. Subsequent examination with NBI detected 3 additional neoplasias as well as 1 additional new patient with IN lesions.

**TABLE 2.  Baseline patient characteristics in relation to the presence or absence of IN**

|  | IN (n = 47) | No IN (n = 13) | P value |
|---|---|---|---|
| Male, no. (%) | 26 (55.3) | 7 (53.8) | 1.0 |
| Mean ± SD age, y | 47.5 ± 13.5 | 51.8 ± 15.4 | .32 |
| UC/CD, no. | 34/13 | 7/6 | .41 |
| Pancolitis, no. (%) | 30 (63.8) | 13 (100) | .01 |
| Mean ± SD duration of IBD, y | 16.7 ± 8.5 | 13.5 ± 5.7 | .21 |
| Intake of AAS, NSAIDs, ursocholic acid, no. (%) | 10 (21.3) | 3 (23.1) | 1.0 |
| Treatment with mesalazine, no. (%) | 23 (48.9) | 2 (15.4) | .05 |
| Treatment with immunosuppressants, no. (%) | 19 (40.4) | 6 (46) | .76 |
| Familial history of colorectal cancer, no. (%) | 5 (10.6) | 3 (23.1) | .35 |
| Personal history of colorectal adenoma, no. (%) | 7 (14.9) | 1 (7.7) | .67 |
| Primary sclerosing cholangitis, no. (%) | 4 (8.5) | 1 (7.7) | 1.0 |
| Previous colonoscopy, no. (%) | 38 (80.1) | 8 (61.5) | .16 |
| Time ± SD since previous colonoscopy, y | 3.8 ± 2.6 | 7.4 ± 6.8 | .19 |
| Presence of endoscopic features suggestion predisposition to dysplasia, no. (%)* | 27 (57.4) | 6 (46.1) | .54 |
| Randomization to CE first, no. (%) | 23 (48.9) | 4 (30.8) | .35 |

IN, Intraepithelial neoplasia; SD, standard deviation; UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease; AAS: 5-aminosalicylic acid; NSAIDs, non-steroidal anti-inflammatory drugs; CE, chromoendoscopy.
*Shortened, featureless, or tubular colon; presence of pseudopolyps, stenosis, or scarring; or segment of severe inflammation.[32]

**TABLE 3.  Comparison of paired endoscopic findings of CE and NBI in the 60 patients**

|  | CE | NBI | P value |
|---|---|---|---|
| Per-patient analysis |  |  |  |
| Patients with suspicious lesions, no. (%) | 52 (87.0) | 47 (78.3) | .17 |
| Patients with true-positive lesions, no. (%) | 11 (18.3) | 12 (20) | .43 |
| Patients with false-positive lesions, no. (%) | 41 (68.3) | 35 (58.3) | .49 |
| Per-lesion analysis |  |  |  |
| Suspicious lesions, no. | 208 | 136 | .001 |
| True-positive lesions, no. (%) | 12 (5.8) | 10 (7.3) | .644 |
| False-positive lesions, no. (%) | 196 (94.2) | 126 (92.6) | .001 |

CE, Chromoendoscopy; NBI, narrow-band imaging.

Among the 33 patients assigned to inspection with NBI first, 7 lesions in 4 patients were detected. Subsequent inspection with CE resulted in the detection of 5 additional neoplasias and 4 additional new patients with IN lesions. Two IN lesions on which biopsies were performed but not removed during the first inspection with NBI were subsequently identified during the second inspection with CE. These 2 lesions were flat and larger than 10 mm. Biopsy samples from the surrounding mucosa were negative for dysplasia, and the lesions were completely removed endo-scopically via a mucosectomy during a third procedure. Hence, the percentage of missed neoplastic lesions was higher with NBI than with CE (31.8% [95% CI, 12.3%-51.3%] vs 13.6% [95% CI, −0.7% to 27.9%]), resulting in a miss rate risk difference of 18.2% (95% CI, −42.4% to 6.0%). Importantly, the percentage of patients with IN lesions who were missed on NBI examination was higher than that the perentage of patients with IN missed on CE examination (46.1% [95% CI, 19.0-73.2] vs 15.4% [95% CI, −4.1 to 35.0]), resulting in a miss rate risk difference of 30.7% (95% CI, −64.2% to

**TABLE 4.   Characteristics of the IN lesions detected in the 13 patients with neoplasia: a comparison of detection techniques**

Randomization

| Patient number | CE No. of IN lesions | Localization | Size, mm | Resection | NBI No. of IN lesions | Localization | Size, mm | Resection |
|---|---|---|---|---|---|---|---|---|
| CE first | | | | | | | | |
| 1 | 1 | TC | 2–4 | Yes | 2 | AC rectum | 2 | Yes |
| | | | | | | | 3 | |
| 7 | 1 | TC | 4 | Yes | 0 | | | |
| 9 | 2 | TC | 4 | Yes | 0 | | | |
| | | TC | 4 | | | | | |
| 26 | 0 | | | | 1 | Rectum | 4 | Yes |
| 31 | 1 | Sigma | 2 | Yes | 0 | | | |
| | NBI | | | | CE | | | |
| NBI first | | | | | | | | |
| 5 | 1 | TC | 15 | No | 1 | TC | 15 | No |
| 17 | 1 | TC | 4 | Yes | 0 | | | |
| 25 | 0 | | | | 1 | TC | 4 | Yes |
| 27 | 0 | | | | 1 | TC | 2 | Yes |
| 28 | 3 | TC | 8 | Yes | 2 | AC | 5 | Yes |
| | | TC | 6 | Yes | | | | |
| | | Rectum | 8 | No | | Rectum | 8 | Yes |
| 46 | 0 | | | | 1 | TC | 6 | Yes |
| 47 | 0 | | | | 1 | TC | 12 | No |
| 53 | 2 | TC | 6 | Yes | 0 | | | |
| | | TC | 12 | Yes | | | | |

*CE*, Chromoendoscopy; *NBI*, narrow-band imaging; IN = intraepitelial neoplasia; TC = trasnverse colon; AC = ascending colon.

**TABLE 5.   Comparison of CE and NBI for the detection of intraepithelial neoplasia (IN) in terms of the miss rate**

| | Miss rate with CE | Miss rate with NBI | Miss rate risk difference | P value |
|---|---|---|---|---|
| Per-lesion analysis | | | | |
| No. of INs in the second inspection/total no. of INs, % (95% CI) | 3/22, 13.6 (−0.7 to 27.9) | 7/22 31.8 (12.3-51.3) | 4/22 −18.2 (−42.4 to 6.0) | .2 |
| Per-patient analysis | | | | |
| No. of INs in the second inspection/total no. of INs, % (95% CI) | 2/13 15.4 (−4.2 to 35.0) | 6/13 46.1(19-73.2) | 4/13 −30.7 (−64.2 to 2.8) | .2 |

*CE*, Chromoendoscopy; *NBI*, narrow-band imaging; *INs*, Intraepithelial neoplasias; *CI*, confidence interval.

2.8%). However, these differences did not reach statistical significance (Table 5). Furthermore, the odds ratio for a missed IN lesion by using NBI was 2.96 (95% CI, 0.65 to 13.41). A per-patient analysis revealed an odds ratio for missed IN patients by using NBI of 4.21 (95% CI, 0.73-30.28), which stemmed from a numerically higher neoplasm miss rate for NBI than for CE, although this difference did not reach statistical significance.

Importantly, considering the difference in the percentages of IN patient miss rates between the CE group (15%) and the NBI group (46%), as well as the number of IN patients included in this series (n = 13), the effectiveness of this study to detect any difference in the miss rate between the 2 techniques was low (39%) (2-sided $\chi^2$ test for 2 independent samples, 5% confidence level).

## DISCUSSION

To our knowledge, this is the first prospective, randomized study to compare the effectiveness of NBI compared with CE for the detection of IN in patients with long-standing colonic IBD. In this study, we provide evidence supporting the use of NBI as a novel method for detecting dysplasia in this patient population.

In this series, we included patients with extensive colonic CD as well as individuals with UC. In both cases, only lesions located in colitic areas were considered. Interestingly, 30% (6/20) of the patients with CD presented with IN lesions. Based on current guidelines, no random biopsies were performed because they not only lengthen examination time, but also increase medical costs without increasing the yield of CE targeted biopsies.[5-10] Thus, we were unable to compare the diagnostic yields of high-resolution endoscopy techniques with those obtained by using previously recommended screening protocols. Additionally, the prevalence of IN lesions was 36.7% (22/60), which was similar to that of previous studies by using CE.[3] To confirm this finding, all patients enrolled in the current study were followed for 2 years; in no cases were cancers or high-grade dysplastic lesions detected during this follow-up period, nor did we find a significant association between IN lesions and primary sclerosing cholangitis. However, the small number of patients with primary sclerosing cholangitis included in this study (n = 5) and the fact that they usually undergo more frequent monitoring might explain this finding. Although we did find a significantly reduced incidence of dysplasia in patients receiving 5-aminosalicylic acid treatment, once again, sample size was too small to permit any definitive conclusions regarding this factor.

Currently NBI is also known as "electronic CE" because it provides an enhanced contrast that can theoretically improve the detection of small and/or subtle mucosal lesions. Four randomized trials and a systematic review failed to demonstrate the superiority of NBI, with respect to white light, for the detection of adenomas in the general population.[16,22-25] In contrast, in a high-risk colorectal cancer population, such as is found in Lynch syndrome patients in whom dysplasia arises within subtle lesions, 2 trials demonstrated that NBI was superior to standard WLE for the detection of adenomas and, in particular, flat adenomas.[26,27] Concerning the detection of dysplasia in patients with long-standing UC, only 1 previous randomized study, that by Dekker et al,[17] reported on the use of NBI. In this study, a prototype NBI system was compared with standard-resolution WLE, and, in this case,

NBI did not demonstrate any increased capability in detecting neoplasia. However, this trial was an underpowered pilot study (only 42 patients were included) and involved a first-generation NBI system with technical inadequacies. More importantly, in this study, the authors did not compare the new technology with the standard protocols then in use. As a consequence, to date, there remains no available valid data supporting the use of this new technology as an alternative method for the detection of dysplasia in the setting of high-risk patients.

This study demonstrates that NBI is able to detect a similar number of patients and lesions with IN as CE. However, it may also offer some advantages: it is a significantly less time-consuming technique and can result in a major reduction in the number of unnecessary biopsies. Based on the endoscopists' experience and previous data, it is important to note that in this study any circumscribed sigmoid or rectal flat lesions with a regular mucosal pit pattern (Kudo types I and II) that exhibited a weak vascular intensity on NBI were considered hyperplastic polyps and often did not undergo biopsy.[16,28] On the contrary, with CE, in which only mucosal pit patterns were attempted, the presence of Kudo pit patterns types I and II did not allow us to completely rule out dysplasia. This resulted in a higher rate of false-positive lesions.[29] In addition to its possible effects on detection, NBI has the potential to identify endoscopic differences between neoplastic and non-neoplastic lesions.[1] In fact, it has been shown that a weak vascular pattern intensity is highly predictive of hyperplastic polyps.[16,28] In the current study, assessment of vascular hue intensity with NBI provided a reliable indicator, allowing the differentiation of these 2 types of lesions and resulting in a more efficient technique. Further studies aimed at confirming these results should be performed.

Despite these positive results, some concerns exist regarding the results of this study. In terms of the miss rate, NBI technology resulted in a numerically higher rate of missed IN lesions and, what is more important, in a higher rate of IN missed patients. In fact, the odds ratio for missed IN patients by using NBI was 4.21, suggesting an increased neoplasm miss rate compared with CE, although statistical significance was not reached. Studies of tandem standard colonoscopy in the general population have shown an overall neoplasm miss rate of 22%.[30] In UC patients, there is scarce information. A retrospective study involving standard colonoscopy showed that 39% of missed lesions were only later detected by additional random biopsies. Van den Broek et al[31] showed that 50% of lesions detected with autofluorescence had been missed in a first examination with high-resolution WLE. Random biopsies did not improve neoplasia identification in any of these cases. In our study, the CE lesion miss rate was only 13.6%, reinforcing the high diagnostic yield of targeted CE biopsies. However, NBI resulted in a nonsignificant higher lesion miss rate (31.8%). In fact, 6 patients with at least 1

low-grade lesion would have been missed if NBI had been used as the screening technique compared with 2 missed lesions if CE had been used as the only screening technique. In some ways, NBI can be regarded as a more specific technique, albeit one with a lower sensitivity than CE. However, in terms of screening, sensitivity must take priority over specificity and efficiency. This lack of sensitivity could be explained by the fact that NBI principally relies on the evaluation of vascular pattern intensity, which may be more subtle than the crypt architecture alterations detected by CE. Moreover, the decreased depth of field and darker light inherent in NBI examination could contribute to the higher NBI lesion miss rate.

One of the strengths of this study stems from the fact that it represents the first clinical trial that compares a commercially available endoscope (Olympus H180; Olympus Europe) offering high-resolution and NBI capabilities with the standard technique currently used to detect dysplasia in a general clinical setting. Additionally, it is a prospective, randomized study with a sizable patient enrollment. On the other hand, the current study has several limitations. First, it is a crossover study in which lesions are sampled immediately after detection, and this precludes any paired analyses. As a result, the accuracy of these 2 techniques could not be directly compared. A comparative study would have been preferable, although the sample size needed would not be achievable at a single center. Moreover, patients had to undergo 2 complete colonoscopies over a short period of time, which resulted in a lower acceptance rate as well as a relatively high dropout rate.

In summary, NBI is a useful technique for the detection of dysplasia in patients with long-standing IBD that offers several advantages: efficiency, ease of use, and agility. However, the relatively high IN lesion and patient miss rate encountered with NBI prevents its recommendation as the new standard technique of use. As a consequence, we believe that CE should still be considered the technique of choice for detecting dysplasia in patients with long-standing IBD.

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# Discusión

Los resultados de la presente Tesis Doctoral demuestran que el sistema NBI puede ser útil para la evaluación de lesiones en las enfermedades con alto riesgo de cáncer digestivo estudiadas, pero presenta ciertas limitaciones.

El **estudio 1** demuestra que la tecnología NBI tiene una utilidad limitada en la detección y caracterización de los pólipos gastroduodenales en la PAF clásica. En primer lugar se comparó el número de pólipos duodenales y gástricos detectados con EAR con los detectados por NBI, observando un aumento no relevante de lesiones visualizadas. Sólo en 2 de 45 casos la inspección con NBI provocó un avance en el estadio de Spigelman. Ello habría supuesto un cambio en el manejo de estos pacientes según las guías actuales[52], al recomendar en el primero un acortamiento del intervalo de vigilancia y en el segundo al considerar la cirugía profiláctica. En cuanto a los pólipos gástricos, el sistema NBI no aportó ninguna ventaja, ya que no detectó ningún adenoma adicional.

En segundo lugar, en un intento de identificar las lesiones con mayor riesgo de progresión, se investigaron los rasgos endoscópicos con EAR y NBI que identificaran la presencia de histología avanzada en los adenomas duodenales. Para ello se utilizó un proceso sistematizado por pasos que evaluó diferentes rasgos, observando la única asociación significativa con el tamaño mayor de 1 cm. Los adenomas duodenales mayores de 1 cm presentaron en nuestro estudio una probabilidad 3 veces mayor de contener histología avanzada. A pesar de que esta característica mostró una buena concordancia interexplorador con la tecnología utilizada, probablemente no es necesario disponer de NBI ni tan siquiera una imagen de alta resolución para estimar el tamaño de un pólipo.

La caracterización de adenomas duodenales no se ha investigado previamente con NBI. Únicamente existe una pequeña serie donde el NBI con magnificación es capaz de

clasificar lesiones la ampolla de Vater como neoplásicas o no neoplásicas con gran precisión, sin datos sobre histología avanzada.[132] Este estudio es el primero que evalúa la utilidad del NBI en el tracto digestivo superior de pacientes con PAF. Anteriormente se ha evaluado la utilidad de la CE en la detección de pólipos duodenales en dos estudios. El primero de ellos, con un diseño cruzado y aleatorizado, comparó con tecnología de resolución estándar la CE frente a la luz blanca observando un aumento significativo en la detección de adenomas por parte de la CE (número medio de pólipos antes y después de la tinción de 1,7 y 5,9 respectivamente).[69] En cambio, el segundo estudio investigó el papel de la CE en un contexto de alta resolución y observó que el uso de CE resultó en un aumento clínicamente no relevante de las lesiones detectadas (sólo en 5 de 43 pacientes provocó un aumento del estadio de Spigelman).[70] Este efecto fue interpretado por los autores como una ausencia de beneficio adicional de la CE frente a la EAR, que por sí sola podría mejorar la detección de lesiones, como ya se ha apuntado.[133] Los resultados de nuestro estudio están en concordancia con este razonamiento, de modo que en el tracto digestivo superior probablemente el sistema NBI tiene pocas ventajas que ofrecer en el contexto de alta resolución a la endoscopia de luz blanca. De manera análoga en el colon el NBI tampoco ha demostrado mejorar la detección de adenomas en comparación con la luz blanca de alta resolución, sin embargo sí la mejora al compararlo con la endoscopia de resolución estándar.[33]

Desconocemos las implicaciones clínicas que tendría el detectar más pólipos duodenales en estos pacientes. Es probable que las nuevas tecnologías nos ayuden a identificar pequeñas lesiones de significado oncológico incierto, mientras que las mayores y más preocupantes ya conseguíamos detectarlas con la tecnología convencional. Esto ha supuesto un incremento de pacientes situados en los estadios más avanzados de la clasificación de Spigelman[133] sin que se haya demostrado un aumento del riesgo de progresión a cáncer. Por otro lado, este sistema de estadificación permite una estimación del riesgo de

cáncer duodenal, pero no se ha demostrado que la vigilancia endoscópica permita disminuir la mortalidad,[62] ya que en la mayoría de casos en grandes series los pacientes fueron diagnosticados a raíz de tener síntomas y no en endoscopias de vigilancia.[61, 67, 134] Tal como apuntan los propios autores, uno de los factores que intervienen en esta falta de éxito es nuestra incapacidad de reconocimiento de lesiones de alto riesgo.[135] Por tanto, pensamos que la clasificación de Spigelman debería ser revisada a la luz de los avances técnicos, donde el tamaño y la histología tengan más peso, incorporando además la región ampular.

El **estudio 2** describe rasgos endoscópicos de los ASS identificables con EAR y con NBI. A pesar de que ciertas características endoscópicas de estas lesiones se habían delineado previamente, el cambio reciente en la clasificación histológica y el progreso en el conocimiento de la vía serrada de la carcinogénesis han hecho que la literatura al respecto sea heterogénea. Este es el primer estudio que realiza un enfoque sistemático según los criterios diagnósticos actuales, combinando la imagen de luz blanca de alta resolución y el sistema NBI, con la colaboración de expertos de diversos países. La presencia de superficie similar a una nube, bordes mal definidos, forma irregular y puntos oscuros dentro de las criptas han demostrado en nuestro estudio predecir de forma independiente el diagnóstico histológico de ASS y se ha puesto de manifiesto que estas cualidades pueden evaluarse sin necesidad de magnificación. Aunque de forma aislada no permiten diferenciar ASS de PH con eficacia, la combinación de todos los rasgos muestra una alta tasa de precisión diagnóstica, especialmente si son identificados con NBI.

Estos hallazgos están en concordancia con estudios previos que han señalado rasgos diferenciales de los ASS. En un estudio retrospectivo que revisó 202 pólipos serrados se observó que los ASS tenían una superficie más granular y de márgenes peor delimitados.[81]

También se ha descrito la presencia de "protuberancia en forma de cúpula" y la "alteración del contorno de un pliegue" como señas características de estas lesiones.[83] Estas peculiaridades pueden considerarse análogas a la superficie en forma de nube y a los bordes mal definidos que describimos en nuestro trabajo. Por otro lado, en nuestro estudio se introduce el concepto de puntos oscuros dentro de las criptas. Este rasgo puede relacionarse con el patrón de criptas II-O descrito por Kimura en referencia a la presencia de criptas dilatadas en los ASS.[84]

Aunque existen pocos datos al respecto, los PH parecen presentar un comportamiento benigno con bajo o nulo riesgo de degeneración maligna.[136] Actualmente se recomienda resecar todos los pólipos que se detecten en el colon con la única salvedad de los PH menores de 5 mm en el recto y sigma, que se consideran inofensivos y por tanto se pueden dejar *in situ*, siempre y cuando el endoscopista esté seguro de su diagnóstico óptico.[78] De acuerdo con este razonamiento se podría discutir la utilidad de diferenciar ASS de HP, ya que casi siempre tendremos que resecarlos. No obstante, el conocimiento de los rasgos diferenciales de los ASS tiene ciertas ventajas. En primer lugar, si bien los ASS son más frecuentes en el colon proximal, también se encuentran en el recto y sigma.[137] [138] Parece razonable por tanto que debamos ser capaces de predecir el diagnóstico de estas lesiones con un alto grado de confianza para estar seguros de no dejar *in situ* pólipos con potencial capacidad de degeneración. En este sentido, la Sociedad Americana de Endoscopia Gastrointestinal ha establecido que las tecnologías utilizadas para evaluar estas lesiones deben demostrar un valor predictivo negativo de al menos el 90% para el diagnóstico de adenoma.[139] El diagnóstico histológico óptico ante un pólipo realizado con un alto grado de confianza permitiría al endoscopista, por un lado, elegir la mejor opción terapéutica valorando en cada caso el balance riesgo-beneficio; y por otro lado, resecar y descartar lesiones de bajo riesgo evitando los costes del estudio histológico.[47] Otra posible ventaja de diferenciar ASS de PH se da en el caso de pacientes con alto riesgo quirúrgico que presenten SPS no controlable endoscópicamente, donde una estrategia

razonable podría ser la resección selectiva de lesiones con mayor probabilidad de progresión.[140] Por último, es conocido que la tasa de detección de pólipos serrados presenta una gran variabilidad entre endoscopistas y se piensa que en general estas lesiones son infradiagnosticadas.[78, 141] Sin embargo, su presencia se ha asociado a lesiones avanzadas colónicas. Los pacientes con un ASS proximal de al menos 10 mm tienen de 2 a 5 veces más probabilidades de presentar una neoplasia avanzada sincrónica.[142-144] Dado que no se reconoce lo que no se conoce, la identificación de las características diferenciales de los ASS puede ayudar a optimizar la detección de estas lesiones, poniendo sobre aviso de la potencial presencia de neoplasias avanzadas.

El **estudio 3** demuestra que el sistema NBI tiene una capacidad similar a la CE para la detección de lesiones precursoras de CCR con displasia o NIE en pacientes con EII de larga evolución. Al comparar el número de lesiones y de pacientes con NIE que detectaron NBI y CE no se encontraron diferencias. Se empleó un diseño cruzado y aleatorizado, de modo que todos los pacientes fueron explorados con ambas técnicas en orden aleatorio. Aunque no era el objetivo primario de este estudio y por tanto el cálculo de la muestra no se hizo en base a este dato, la realización de colonoscopias consecutivas permitió comparar la tasa de lesiones no detectadas por ambas técnicas, observando que el sistema NBI dejaba sin detectar en la primera exploración más lesiones con NIE (46%) que la CE (15%). Aunque la diferencia no fue estadísticamente significativa, la potencia del presente estudio no fue suficiente para determinar este hecho debido al escaso número de pacientes con NIE (n = 13).

Si bien históricamente se ha recomendado la toma de biopsias en los cuatro cuadrantes de la mucosa del colon cada 10 cm como método de cribado o vigilancia de lesiones precursoras de CCR en pacientes con EII de larga evolución, en los últimos años se han

publicado numerosos estudios que demuestran que la CE mejora el rendimiento de estas endoscopias permitiendo la toma dirigida de biopsias,[118-126] y así lo reflejan las últimas recomendaciones oficiales.[104, 127, 128] Este estudio es el primero que investiga la utilidad del NBI frente a la CE, es decir, la técnica que ha demostrado mayor eficacia. Anteriormente se ha explorado la utilidad del NBI en este escenario comparándolo con la endoscopia de luz blanca, con resultados negativos. En primer lugar un prototipo inicial de la tecnología NBI fue confrontado con la endoscopia de luz blanca estándar en un diseño cruzado y aleatorizado, sin encontrar beneficios.[129] Posteriormente el mismo grupo llevó a cabo otro estudio con diseño similar donde se comparaba el sistema NBI con la endoscopia de luz blanca de alta resolución; y de nuevo no se observaron diferencias.[145] La evidencia más reciente proviene de un estudio multicéntrico aleatorizado que compara NBI con luz blanca de alta resolución en dos grupos paralelos, nuevamente sin encontrar diferencias en el número de NIE detectadas por paciente.[130] Los autores sugieren que la imagen de alta resolución puede contribuir a esa falta de beneficio, ya que podría por sí sola aumentar la detección de lesiones. En nuestro estudio el NBI muestra una capacidad similar a la CE para detectar lesiones en un contexto de alta resolución. Curiosamente, en los estudios donde se comparó con luz blanca de alta resolución el NBI presentó una mayor tasa de falsos positivos; una posible justificación podría ser que el NBI resalta también los cambios inflamatorios. Sin embargo, en nuestro estudio la CE presentó una mayor tasa de falsos positivos que el NBI. Este efecto podría explicarse por la capacidad del NBI de valorar la intensidad de la vascularización además del patrón de criptas. Por ejemplo, las lesiones pequeñas en recto o sigma con patrón de criptas regular (clasificación de Kudo I o II[16]) visualizadas con CE se habrían resecado, obteniendo así un falso positivo. Sin embargo la identificación con NBI de un patrón de vascularización débil además de un patrón de criptas regular habría permitido descartar displasia con seguridad, sin necesidad por tanto de resecar o biopsiar.

El NBI mostró en nuestro estudio una capacidad para detectar lesiones con NIE equiparable a la de la CE con la ventaja de ser una técnica sencilla, rápida y limpia. Sin embargo, la alta tasa de lesiones no detectadas por el NBI en el análisis de las exploraciones en tándem no permite recomendarla como técnica de elección, por lo que la CE debe seguir siendo por el momento la técnica de referencia.

# Conclusiones

Los resultados obtenidos en los diferentes estudios que componen esta Tesis Doctoral permiten extraer las siguientes conclusiones:

1. El sistema NBI no mejora la detección de pólipos duodenales ni gástricos en pacientes con poliposis adenomatosa familiar en comparación con la endoscopia de luz blanca de alta resolución

2. El sistema NBI y la luz blanca de alta resolución tienen un papel limitado en la identificación de pólipos duodenales con alto riesgo de degeneración en pacientes con poliposis adenomatosa familiar

3. En un paciente con poliposis adenomatosa familiar un adenoma duodenal con un tamaño mayor de 1 cm presenta un riesgo 3 veces mayor de contener rasgos de histología avanzada que los adenomas más pequeños. La estimación del tamaño tiene una buena concordancia interobservador.

4. Los adenomas serrados sésiles tienen características diferentes de los pólipos hiperplásicos y pueden ser distinguidos endoscópicamente con luz blanca de alta resolución y NBI

5. Los rasgos endoscópicos con luz blanca de alta resolución y NBI que diferencian a los adenomas serrados sésiles de los pólipos hiperplásicos son la superficie similar a una nube, los bordes mal definidos, la forma irregular y la presencia de puntos oscuros dentro de las criptas

6. La combinación de estos rasgos endoscópicos, especialmente evaluados con NBI, discrimina los adenomas serrados sésiles de los pólipos hiperplásicos con gran precisión

7. La concordancia interobservador en la valoración de la mayoría de los rasgos endoscópicos que discriminan adenomas serrados sésiles de pólipos hiperplásicos entre cinco expertos internacionales es moderada o débil.

8. El sistema NBI es capaz de detectar tantas lesiones precursoras con neoplasia intraepitelial como la cromoendoscopia en pacientes con enfermedad inflamatoria intestinal de larga evolución, aportando rapidez, limpieza y reversibilidad

9. Sin embargo, la tecnología NBI tiene una alta tasa de lesiones con neoplasia intraepitelial no detectadas en el análisis con exploraciones consecutivas

10. La alta tasa de lesiones no detectadas del NBI en comparación con la cromoendoscopia no permite recomendarla como técnica de primera elección para las colonoscopias de cribado o vigilancia de estos pacientes

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