

Systematic review with meta-analysis: IBD-associated colonic dysplasia prognosis in the videoendoscopic era (1990 to present)

Misha Kabir^{1,2}  | Rishi Fofaria¹  | Naila Arebi^{1,2}  | Paul Bassett³ |
 Phil J Tozer^{1,2}  | Ailsa L Hart^{1,2}  | Siwan Thomas-Gibson^{1,2}  |
 Adam Humphries^{1,2}  | Noriko Suzuki^{1,2} | Brian Saunders^{1,2} | Janindra Warusavitarne^{1,2}  |
 Omar Faiz^{1,2}  | Ana Wilson^{1,2} 

¹St Mark's Hospital, Harrow, UK

²Imperial College London, London, UK

³Stats Consultancy, Amersham, UK

Correspondence

Dr. Misha Kabir, Clinical Research Fellow,
 Wolfson Unit for Endoscopy, St Mark's
 Hospital, Watford Road, Harrow HA1 3UJ,
 UK.

Email: misha.kabir1@nhs.net

Summary

Background: The prognosis of dysplasia in patients with IBD is largely determined from observational studies from the pre-videoendoscopic era (pre-1990s) that does not reflect recent advances in endoscopic imaging and resection.

Aims: To better understand the risk of synchronous colorectal cancer and metachronous advanced neoplasia (ie high-grade dysplasia or cancer) associated with dysplasia diagnosed in the videoendoscopic era, and to stratify risk according to a lesion's morphology, endoscopic resection status or whether it was incidentally detected on biopsy of macroscopically normal colonic mucosa (ie invisible).

Methods: A systematic search of original articles published between 1990 and February 2020 was performed. Eligible studies reported on incidence of advanced neoplasia at follow-up colectomy or colonoscopy for IBD-dysplasia patients. Quantitative and qualitative analyses were performed.

Results: Thirty-three studies were eligible for qualitative analysis (five for the meta-analysis). Pooled estimated proportions of incidental synchronous cancers found at colectomy performed for a pre-operative diagnosis of visible high-grade dysplasia, invisible high-grade dysplasia, visible low-grade dysplasia and invisible low-grade dysplasia were 13.7% (95% CI 0.0-54.1), 11.4% (95% CI 4.6-20.3), 2.7% (95% CI 0.0-7.1) and 2.4% (95% CI 0.0-8.5) respectively. The lowest incidences of metachronous advanced neoplasia, for dysplasia not managed with immediate colectomy but followed up with surveillance, tended to be reported by the studies where high definition imaging and/or chromoendoscopy was used and endoscopic resection of visible dysplasia was histologically confirmed.

Conclusions: The prognosis of IBD-dysplasia diagnosed in the videoendoscopic era appears to have been improved but the quality of evidence remains low. Larger, prospective studies are needed to guide management.

PROSPERO registration no: CRD42019105736.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Jonathan Rhodes, and it was accepted for publication after full peer-review.

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1 | INTRODUCTION

Patients with ulcerative colitis or Crohn's disease colitis have an increased risk of colorectal cancer. The overall cancer prevalence was reported as 3.7% in the landmark meta-analysis by Eaden et al published in 2001.¹ The cumulative probabilities of developing cancer were reported to be 2% by 10 years, 8% by 20 years and 18% by 30 years of disease duration. However, more recent population-based cohort studies and updated meta-analyses suggest that the risk of cancer is lower than previously thought, although overall this rate is still significantly higher than the non-IBD population.²⁻⁷ Cumulative risks of colorectal cancer in a more recent meta-analysis were 1% by 10 years, 2% by 20 years and 5% after more than 20 years of disease duration.³ It is unclear whether this reduced incidence of IBD cancer is related to optimisation in endoscopic surveillance, medical therapy or timely colectomy in the last decade.^{8,9} A Cochrane systematic review and meta-analysis observed lower incidence rates of cancer in IBD patients on surveillance compared to IBD patients not on surveillance.¹⁰ The ratio of early stage vs late stage cancers detected was also higher in the surveillance group compared to the nonsurveillance group.¹⁰ Taking tumour stage into account, ulcerative colitis patients are still more likely to die of colorectal cancer than patients without ulcerative colitis, but this risk appears to be declining over time.⁷

The purpose of colonoscopic surveillance is to detect dysplasia which is defined as an unequivocal neoplasia of the epithelium confined to the basement membrane, without invasion into the lamina propria.¹¹ The 21st century has witnessed advances in endoscopic surveillance technology such as high definition imaging and chromoendoscopy, which have led to increased detection of dysplasia.^{12,13} Dysplasia incidence rates were reported to have almost doubled from the 1993-2002 to the 2003-2012 time period in the St Mark's surveillance cohort.¹³ Advanced dysplasia resection techniques such as endoscopic submucosal dissection and hybrid techniques have also allowed the resection of flat nonpolypoid lesions, previously destined for surgical management only.^{12,14} However, the impact of these advances on rates of metachronous advanced neoplasia developing during surveillance follow-up remains uncertain. As there are no randomised controlled trials comparing endoscopic surveillance with colectomy, international society guidelines have based their recommendations for the management of higher risk lesions on small numbers of observational studies.^{8,9,15,16} The small patient cohorts, limited follow-up times, contradictory lesion characterisation terminology and inclusion of data from the pre-vid-eoendoscopic era, have limited the interpretation of outcomes from these studies.^{8,9,15,16} The most recent international guidelines are summarised in Table S1.

If dysplasia is able to be completely endoscopically resected, all guidelines recommend continued regular colonoscopic surveillance.^{8,9,15,16} If dysplasia is endoscopically unresectable or invisible (ie the dysplasia is detected on random biopsy of the colonic mucosa without any corresponding visible dysplastic lesion detectable by the endoscopist), guidance on management is less clear due to the wide variation in reported progression rates to advanced neoplasia.^{8,9,15,16}

The management options in these cases are recommended to be 'individualised after discussion of the risks and benefits of surveillance colonoscopy and colectomy' by gastroenterologists and colorectal surgeons with their patients within a multidisciplinary setting.¹⁵ However, acknowledgement of the uncertainty in the prognosis of dysplasia makes these discussions even more challenging. Laypersons can respond to the communication of uncertain individualised cancer risk estimates with heightened cancer-related worry, 'ambiguity aversion' (ie avoidance of engaging in decision making) and 'risk aversion' (ie avoidance of choosing the option associated with more perceived risk, despite its overall advantage).^{17,18}

The wide variation in the reported prognosis of dysplasia may in part be due to the inclusion of older data hailing from the pre-vid-eoendoscopic era (pre-1990s). The high-definition image resolution now achieved with the more sophisticated videoendoscopes available, far exceeds what was possible with the older fibre-optic endoscopes. The endoscopic community now recognises that some dysplasia once characterised as 'invisible' in the pre-videoendoscopic era may actually have represented missed flat lesions. These lesions are now more visible and better characterised with higher definition, blue light imaging and chromoendoscopy.¹⁹ Clarity with regard to the risks of colorectal cancer is needed to help patients decide between endoscopic or surgical management for their IBD-dysplasia. When informing patients of their cancer risk, it may be useful to describe the rate of 'prevalent' (otherwise described as 'synchronous' or 'concurrent') cancers that are found at colectomy performed usually within 6 months of a pre-operative diagnosis of dysplasia. These incidental cancers detected within the colonic specimen may represent cancers that were missed during the last pre-operative colonoscopy. The risk of progressing to a more advanced neoplastic lesion, if an immediate colectomy is not performed after the dysplasia diagnosis, should also be explained to patients. This is often reported in studies as the 'advanced neoplasia progression rate' which is the incidence of new high-grade dysplasia (HGD) or cancer found during surveillance follow-up performed more than 6 months after a low-grade dysplasia (LGD) diagnosis, or the incidence of new cancer found during surveillance follow-up performed more than 6 months after a HGD diagnosis.²⁰⁻²²

1.1 | Aims

1. To gain a better understanding of whether improvements in endoscopic imaging and resection techniques in the videoendoscopic era (1990 to present) have impacted on the prognosis of colitis-associated dysplasia.
2. To obtain the most up-to-date evidence on the risk of incidental cancer ('prevalent cancer rate') found at colectomy performed (usually within 6 months) for a pre-operative diagnosis of visible HGD, invisible HGD, visible LGD, invisible LGD or indefinite for dysplasia.
3. To obtain the most up-to-date evidence on the risks of developing more advanced metachronous neoplasia ('advanced neoplasia

progression rate') during surveillance follow-up of 6 months or more after:

- a. Endoscopic resection of visible LGD and HGD (polypoid vs nonpolypoid)
- b. Detection of invisible LGD and HGD
- c. Detection of indefinite for dysplasia

2 | METHODS

2.1 | Search strategy and study selection

The present systematic review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²³ An a priori protocol was followed and registered at the international prospective register of systematic reviews (PROSPERO registration no. CRD42019105736). An electronic literature search of English language articles was performed using MEDLINE, EMBASE and the Cochrane Library Database, from the dates 1990 to February 2020. The full electronic search strategy can be viewed in Appendix 1 and was designed and conducted with the assistance of an experienced medical librarian. Study eligibility for inclusion was undertaken independently by two researchers (MK and RF) and discrepancies resolved after consensus discussion. Meta-analyses, randomised controlled and observational studies were included if the intervention and outcome met the eligibility criteria. Reference lists of the included full-text articles were also scanned for additional articles. Conference proceedings were also considered.

The inclusion criteria were as follows: (a) studies of ulcerative colitis, Crohn's colitis and indeterminate colitis patients who had a colectomy or at least one follow-up colonoscopy performed after an initial diagnosis of dysplasia was made on colonoscopy; (b) the cohort could be subdivided according to the dysplasia severity grading (ie indefinite, low-grade and high-grade), endoscopic visibility and lesion morphology (polypoid or nonpolypoid as per the SCENIC criteria¹⁵); and (c) reported on the incidence of advanced neoplasia found during surveillance or in the colectomy specimen according to the endoscopic visibility, morphology and grade of the index dysplasia. Articles were excluded if all or most patients included had their dysplasia diagnosed in the pre-videoendoscopic era, which was taken to be before 1990, or it was not possible to extract incidence rates according to visibility, morphology and severity of the index dysplasia from the data provided. Studies reporting on primary sclerosing cholangitis patients were included, except for those cohorts with exclusively these patients as this could skew the data. In the event where a number of publications had been reported by the same group, with duplication of results from the same dataset, the most recent publication was included for analysis of each outcome. Dysplasia detected on random biopsy of the colonic mucosa without any corresponding visible dysplastic lesion detectable by the endoscopist was termed 'invisible'.

2.2 | Data extraction

Data were extracted independently by two investigators (MK and RF). All discrepancies were resolved and consensus achieved after discussion. For each study included, data were retrieved on the country where it was performed, year of publication, enrolment period, study design, subclassification of the IBD, colitis extent, number of patients with dysplasia within the extent of colitis, proportion of endoscopically resected dysplasia, whether the dysplasia histology had been reviewed by a second gastrointestinal expert histopathologist, proportion with multifocal dysplasia or primary sclerosing cholangitis, the mean or median follow-up time, and the number and incidence rate of new histologically proven high-grade dysplasia and colorectal cancer cases found on follow-up or at colectomy.

2.3 | Primary outcomes

2.3.1 | Prevalent cancer rate

Incidental cancers found anywhere in the colectomy specimen when colectomy surgery was performed for a pre-operative diagnosis of dysplasia (usually performed within 6 months of the dysplasia diagnosis).

2.3.2 | Advanced neoplasia progression rate

Incidence of new HGD or colorectal cancer found during surveillance follow-up performed more than 6 months after a LGD diagnosis, or incidence of new cancer found during surveillance follow-up performed more than 6 months after a HGD diagnosis.

2.4 | Quality and risk of bias assessment

Three of the investigators (MK, RF and NA) assessed the methodological quality and risk of bias of every study using a modified Joanna Briggs Institute Critical Appraisal Checklist for studies reporting on prevalence^{24,25} (Table A2). The overall quality of the evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria^{26,27} and are detailed in the summary of findings Tables 1 and 2.

2.5 | Statistical methods

Meta-analysis methods were used to pool together the cancer prevalence rates from different studies. The Stata software package (version 15.1) was used. The DerSimonian-Laird random effects method was used for the analysis, regardless of the degree of heterogeneity between the study results. The Freeman-Tukey double arcsine transformation was performed before analysis, which was used to stabilise

TABLE 1 GRADE summary of findings table—pooled estimates of prevalent cancer rate^a according to dysplasia grading and endoscopic visibility

Patient group	Number of studies	Study design	Total study population	Number of prevalent cancers	Prevalent cancer rate ^a (95% confidence interval)	Between study heterogeneity		GRADE quality of evidence ^d
						P value*	I ² ^c	
Visible HGD	Three	Observational	126	35	13.7% (0.0%-54.1%)	<0.001	91.9%	⊕○○○ VERY LOW Due to risk of bias, inconsistency, imprecision, publication bias
Invisible HGD	Two	Observational	69	9	11.4% (4.6%-20.3%)	^b		⊕○○○ VERY LOW Due to risk of bias, inconsistency, indirectness, publication bias
Visible LGD	Three	Observational	145	5	2.7% (0.2%-7.1%)	0.29	18.9%	⊕⊕○○ LOW Due to risk of bias, publication bias
Invisible LGD	Three	Observational	208	6	2.4% (0.0%-8.5%)	0.12	53.3%	⊕⊕⊕○ VERY LOW Due to indirectness, inconsistency, publication bias
Indefinite for dysplasia	Two	Observational	60	1	1.2% (0.0%-6.6%)	^b		⊕○○○ VERY LOW Due to risk of bias, inconsistency, publication bias

Abbreviations: HGD, high-grade dysplasia; LGD, low-grade dysplasia.

^aPrevalent cancer rate is the proportion of patients who have colectomy surgery performed for a pre-operative diagnosis of dysplasia (usually performed within 6 mo of the dysplasia diagnosis) and a colorectal cancer is found incidentally anywhere in the colectomy specimen.

^bInsufficient studies to evaluate heterogeneity between studies.

^cI² value above 50% assumes substantial between study heterogeneity.

^d**Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working group grades of evidence:** With prognostic outcomes, longitudinal cohort studies are initially rated as high quality and downgraded by one level or more if one or more of the following apply: 1. **High risk of bias** in study design as indicated by modified Joanna Briggs Institute Critical Appraisal Checklist median scores of less than eight out of 10 or failure of most of the studies to adequately measure the proportion of dysplasia which was endoscopically resected pre-operatively, which is an important confounding factor. 2. **Inconsistency** of results between the studies. Where calculated this is reflected by high between-study heterogeneity (I² >50%). 3. **Imprecision** of results if there is a wide 95% confidence interval around the pooled estimate. 4. **Indirectness** of evidence where the studied population does not correspond to patients who have a colectomy for a pre-operative diagnosis of dysplasia now. This is likely to be in the case of patients with invisible dysplasia as most of the data from these studies are taken from a time period before high-definition imaging and chromoendoscopy were adopted into clinical practice. 5. **High risk of publication bias** is suspected for all outcomes due to the very small number of studies published and the suspected exclusion of the smallest population studies.

*Chi-squared heterogeneity test: P value < 0.05 considered statistically significant.

the variances when the proportions were close to 0 and 1, and therefore the normal approximation to the binomial distribution did not hold. The heterogeneity between studies was assessed based on the significance of the between-study heterogeneity, and also on the size of the I² value. Substantial heterogeneity was assumed if the I² value was above 50% or the chi-squared test P value was less than 0.05.

3 | RESULTS

3.1 | Systematic search results

The search strategy is described in detail in the PRISMA flow diagram (Figure 1). The initial search yielded 5095 citations and from

these 33 studies were eligible for inclusion. All of these were observational studies: one was a prospective cohort study; 18 were retrospective cohort studies; and 14 were retrospective case series (see Table A2). All studies were from academic centres which were based in the USA (n = 21), UK (n = 4), Japan (n = 4), the Netherlands (n = 2), Korea (n = 1), Italy (n = 1), Belgium (n = 1) and Portugal (n = 1). Twenty of the eligible studies included only ulcerative colitis patients, one study included only Crohn's colitis patients and 12 studies included patients with ulcerative colitis and Crohn's colitis and/or indeterminate colitis.

Twenty-three (69.7%) of the studies satisfied at least 80% of the 10 criteria in the modified Joanna Briggs Institute Critical Appraisal Checklist for studies reporting on prevalence (detailed in Table A2). Most of the studies adequately described the study

TABLE 2 GRADE summary of findings table—rates of advanced neoplasia progression^a after invisible dysplasia has been diagnosed or visible dysplasia has been endoscopically resected (sub-categorised by dysplasia grade and morphology)

Dysplasia grade, morphology and resection status	No. and design of studies included	Total no. patients included	Advanced neoplasia progression rates ^a	Colorectal cancer progression rates ^b	GRADE quality of evidence ^d
Visible polypoid HGD <i>post-polypectomy</i>	Seven observational studies	At least 26 (from five studies ^c)	0.0%-40.0% at median 4 y	0.0%-40.0% at median 4 y	⊕○○○ VERY LOW Due to risk of bias, inconsistency, publication bias
Visible non-polypoid HGD <i>post-polypectomy</i>	Six observational studies	At least 11 (from four studies ^c)	0.0% at median 2 y 50.0% at median 11 y	0.0% at median 2 y 50.0% at median 11 y	⊕○○○ VERY LOW Due to risk of bias, inconsistency, indirectness, publication bias
Invisible HGD	None	N/A	N/A	N/A	—
Visible polypoid LGD <i>post-polypectomy</i>	Nine observational studies	At least 143 (from six studies ^c)	0.0%-5.0% at median 1 y 0.0%-23.0% at median 5 y	0.0%-4.5% at median 2 y 0.0%-13.6% at median 4 y	⊕⊕○○ LOW Due to inconsistency, publication bias
Visible non-polypoid LGD <i>post-polypectomy</i>	Eight observational studies	At least 29 (from six studies ^c)	0.0%-22.2% at median 2 y 40.0% at median 10 y	0.0%-22.2% at median 2 y 40.0% at median 10 y	⊕○○○ VERY LOW Due to risk of bias, inconsistency, indirectness, publication bias
Invisible LGD	Eight observational studies	186	4.6%-44.0% at median 2 y	0.0%-28.0% at median 2 y	⊕⊕○○ LOW Due to inconsistency, indirectness
Indefinite for dysplasia	Six observational studies	252	2.4%-14.6% at median 2 y 4.8%-36.5% at median 5 y	0.0%-1.2% at median 2 y 5.1%-14.3% at median 4 y	⊕○○○ VERY LOW Due to risk of bias, inconsistency, publication bias

Abbreviations: HGD, high-grade dysplasia; LGD, low-grade dysplasia.

^aThe 'advanced neoplasia progression rate' is the incidence of new high-grade dysplasia or colorectal cancer found during surveillance follow-up performed more than 6 mo after a low-grade dysplasia diagnosis, or incidence of new cancer found during surveillance follow-up performed more than 6 mo after a high-grade dysplasia diagnosis.

^bThe 'colorectal cancer progression rate' is the incidence of new colorectal cancer found during surveillance follow-up performed more than 6 mo after the dysplasia diagnosis.

^cThe other studies did not specify number of patients by dysplasia grading but number of polyps by dysplasia grading so number of patients included could not be extracted from these studies.

^d**Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working group grades of evidence:** With prognostic outcomes, longitudinal cohort studies are initially rated as high quality and downgraded by one level or more if one or more of the following apply: 1. **High risk of bias** in study design as indicated by modified Joanna Briggs Institute Critical Appraisal Checklist median scores of less than eight out of 10; or very small sample size or median follow-up time is less than 36 mo; or failure of most of the studies to adequately measure the proportion of dysplasia which was located within the colitis extent and which was endoscopically resected, which are important confounding factors. 2. **Inconsistency** of results between the studies with wide variations in incidence rates between studies. 3. **Indirectness** of evidence where the studied population does not correspond to patients who are being follow-up after a diagnosis of dysplasia: patients with invisible dysplasia as most of the data from these studies are taken from a time period before high-definition imaging and chromoendoscopy were adopted into clinical practice; where included patients in the study had to meet a specific criteria, for example size greater than 10 mm. 4. **High risk of publication bias** is suspected where there are a small number of studies published or a large proportion of case series selected for a specific intervention like endoscopic submucosal dissection.

subjects in detail (93.9%; n = 31), there was sufficient follow-up of the included study participants (93.9%), appropriate statistical analyses were used (100%), and objective, standard criteria for the confirmation of IBD, dysplasia and their subgroup diagnoses were utilised (97.0%; n = 32). Only 21.2% (n = 7) of the studies had an adequate sample size of 75 patients or more. Forty-two percent (n = 14) of the study populations was not felt to be representative

of the target population in view of the selective inclusion/exclusion criteria used, for example in case series where only large LGD lesions for endoscopic submucosal dissection were recruited. Just over half (51.5%; n = 17) of the studies did not include important confounding factors such as specifying whether the dysplasia was located inside or outside of the extent of colitis or was successfully endoscopically resected before colectomy or follow-up. Fifteen

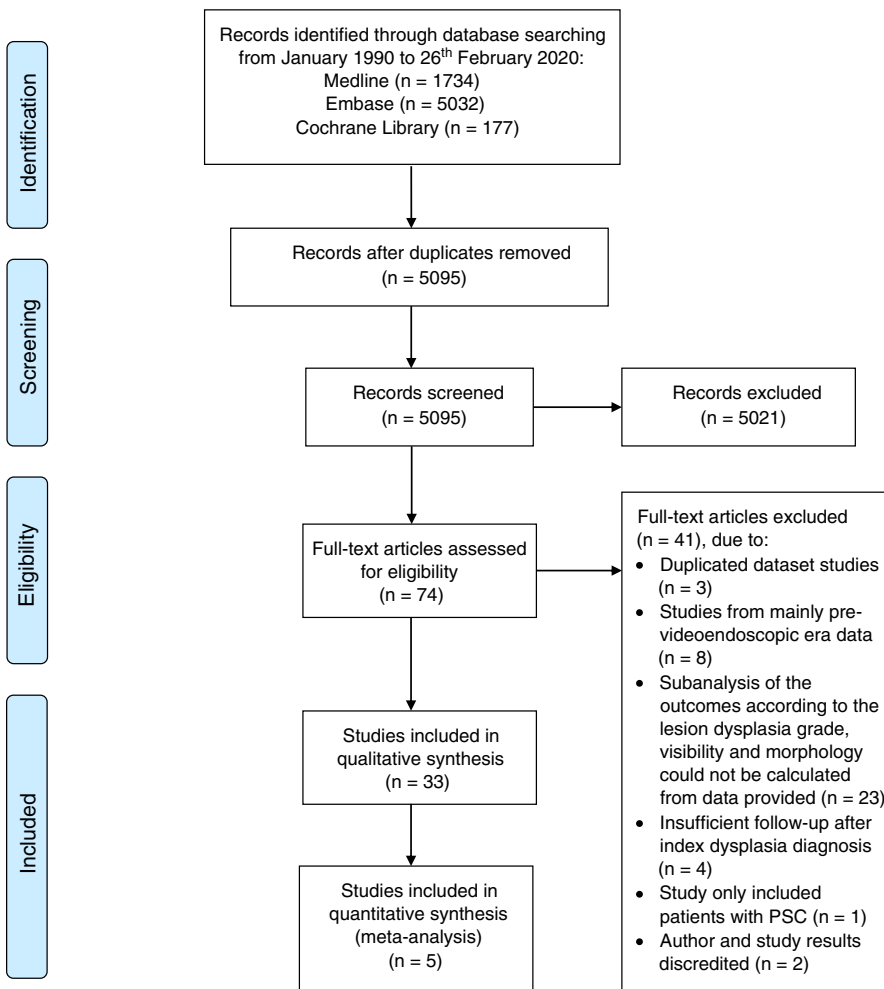


FIGURE 1 PRISMA flow diagram of study selection strategy

percent (n = 5) of the studies did not report whether the dysplasia diagnosis was confirmed by a second expert histopathologist. According to the GRADE criteria, overall the evidence supporting the outcomes produced from these studies was deemed to be of low quality (our confidence in the estimate is limited) or very low quality (we have very little confidence in the estimate and the true prognosis is likely to be substantially different from the estimate). Further explanation of the grading of evidence is provided in the summary of findings Tables 1 and 2.

Five studies met the inclusion criteria to extract the primary outcome: *prevalent cancer rates found at colectomy for a pre-operative diagnosis of dysplasia*. Pooled estimates of this outcome from these five studies were calculated using meta-analysis methods. The results are detailed further in Section 3.2. Twenty-five studies met the inclusion criteria to extract the primary outcome: *Advanced neoplasia progression rates during surveillance follow-up after the index diagnosis of dysplasia*. Due to heterogeneity in the composition of the various study cohorts included, pooled meta-analysis was not deemed appropriate for this outcome. For example, in the post-polypectomy cohorts, the inclusion of mixtures of high-grade and low-grade dysplastic polyps made extraction of accurate incidence data difficult. A median or mean follow-up time was reported by

each included study. However, follow-up times for each individual patient from each study could not be extracted. It was felt that calculating pooled estimates of advanced neoplasia incidence rates based on the pooled median/mean follow-up times reported by each study, rather than individual patient follow-up times, would be inaccurate and potentially misleading. Therefore, qualitative syntheses only have been conducted for the advanced neoplasia progression rates.

3.2 | Prevalent cancer rate

Three of the included cohort studies and two of the case series reported on prevalent cancer rate and are described in more detail in Table A3. Pooled estimates of the prevalent cancer rates were calculated using meta-analysis methods, and the results are summarised in Table 1.

3.2.1 | Visible HGD

Two cohort studies and one case series reported on the rates of prevalent cancer found in the surgical colectomy specimen resected

soon after a pre-operative diagnosis of visible HGD where 94%²⁸ to 100%^{29,30} had not been endoscopically resected pre-operatively. The prevalent cancer rate varied from 0% (n = 0/26),²⁸ 20% (n = 1/5)³⁰ to 35.8% (n = 34/95).²⁹ The studies with the highest prevalent cancer rates only included cases where the dysplasia was located within the extent of inflamed mucosa, rather than proximal to it.^{29,30} The pooled estimated cancer prevalence rate from all these studies was 13.7% (95% CI: 0.0%-54.1%). The results are shown in a forest plot in Figure A4. The significant heterogeneity test ($P < 0.001$) and high I^2 statistic value of 91.9% suggest considerable heterogeneity between studies.

3.2.2 | Invisible HGD

Two cohort studies reported prevalent cancer rates after a pre-operative diagnosis of invisible HGD as 22.2% (n = 8/36) where the dysplasia was specified to be within inflamed mucosa²⁹ and 3.0% where it was not specified (n = 1/33).²⁸ The pooled estimated cancer prevalence rate from all these studies was 11.4% (95% CI: 4.6%-20.3%). The number of studies was too small to be able to assess heterogeneity for this patient group.

3.2.3 | Visible LGD

Two cohort studies and one case series reported prevalent cancer rates with a pre-operative diagnosis of visible LGD of 0.0% (n = 0/24),³⁰ 2.5% (n = 2/79)²⁸ and 7.1% (n = 3/42).²⁹ Here, both the studies with the lowest and highest prevalence rates included cases where only dysplasia found within a colitis-affected segment were included. Krugliak Cleveland et al found a prevalence rate of 0.0%, and included the most recent cohort of patients (2005-2014) who all had surveillance using high-definition colonoscopes.³⁰ However, this was a small case series (n = 24). The pooled estimated cancer prevalence rate from all these studies was 2.7% (95% CI: 0.2%-7.1%). The results are shown in a forest plot in Figure A5. Heterogeneity between studies was low (I^2 calculated statistic = 19%; $P = 0.29$).

3.2.4 | Invisible LGD

Two cohort studies and one case series reported on prevalent cancer rates with a pre-operative diagnosis of invisible LGD. In two studies by Murphy et al (n = 3/141)²⁸ and Kiran et al (n = 1/56),²⁹ the prevalent cancer rate was 2%. The highest reported prevalent cancer rate was 18.2% in the smallest cohort reported by Ullman et al (n = 2/11).³¹ The pooled estimated cancer prevalence rate from all these studies was 2.4% (95% CI: 0.0%-8.5%). The results are shown in a forest plot in Figure A6. All of these studies included data mainly from an era when chromoendoscopy and high-definition imaging were not adopted into widespread practice. There was

substantial between-study heterogeneity. Although the heterogeneity test did not reach statistical significance ($P = 0.12$), the I^2 calculated statistic was still 53% and therefore suggestive of substantial between-study heterogeneity.

3.2.5 | Indefinite for dysplasia

Two cohort studies reported prevalent cancer rates, with a pre-operative diagnosis of indefinite for dysplasia, of 0.0% (n = 0/22)³² and 2.6% (n = 1/38).²⁹ The latter study included a much higher proportion of patients with extensive colitis and primary sclerosing cholangitis.²⁹ The pooled estimated cancer prevalence rate from these studies was 1.2% (95% CI: 0.0%-6.6%). The number of studies was too small to be able to assess heterogeneity for this patient group.

3.3 | Advanced neoplasia progression rate

Table 2 presents the summary of findings for the incidence rate of advanced neoplasia progression categorised by dysplasia grade, morphology and the lesions followed up after endoscopic resection (post-polypectomy).

3.3.1 | Visible HGD

There were 14 observational studies reporting on advanced neoplasia progression rates during surveillance follow-up after an initial diagnosis of visible HGD.³³⁻⁴⁶ The largest study was a Belgian retrospective multicentre cohort study of 27 IBD patients with visible HGD all within the extent of colitis, where 50% of the polyps were polypoid and 50% were nonpolypoid, and 85% of the polyps were endoscopically resected.³⁸ Over the median follow-up time of 6.4 years (IQR 3.8-9.9), 14.8% (n = 4/27) of the patients developed a cancer. All other studies specifically reported on progression to advanced neoplasia after endoscopic resection of the visible HGD and are described in Section 3.3.2 and Table 3 (polypoid HGD followed up after polypectomy) and Section 3.3.3 and Table 4 (nonpolypoid HGD followed up after polypectomy).

3.3.2 | Visible polypoid HGD—post-polypectomy

Seven studies (five cohort studies and two case series) reported on cancer progression rates after endoscopic resection of polypoid HGD (Table 3).^{33-37,39,40} All of the studies reported on very small numbers of polypoid HGD, and based completeness of resection on endoscopist judgement rather than histological assessment. This was due to difficulty in histological assessment of resection margins as a result of diathermy artefact or piecemeal resection. Resection methods included cold snare polypectomy,

TABLE 3 Advanced neoplasia progression rates during surveillance follow-up after endoscopic resection of POLYPOID dysplasia

Study	Enrollment period	No. with polypoid dysplasia	% of polyps WITHIN colitis extent	% resected at endoscopy	Median/mean polyp size (mm)	Dysplasia grading	Mean or median follow-up (years)	No. progressed to AN	No. progressed to CRC	Reported AN progression (incidence) rate	Reported CRC progression (incidence) rate
Odze (2004) ³³	1990-1995	18	100%	100%	8.5 ± 0.7	76% LGD; 24% HGD (of polyps)	6.8 (1.4-13.0)	NS	1	NS	5.6% over mean 7 y (CRC developed in a PSC patient, not being surveilled annually)
Blonski (2008) ³⁹	1997-2004	6	89%	100%	5.4 (2-12)	100% HGD	6.38 (4.3-8.3)	0	0	HGD: 0.0% over mean 6 y	HGD: 0.0% over mean 6 y
Pekow (2010) ⁴⁸	1994-2008	12	100%	100%	NS	100% LGD	6	1	1	LGD: 8.3% over a mean of 6 y (1.5 cases per 100 patient-years)	LGD: 8.3% over a mean of 6 y
Kisiel (2012) ³⁴	1994-2003	44	100%	100%	5 (2-50)	94% LGD; 6% HG (of polyps)	4.5 (range 0.1-11.5)	0	0	0.0% over median 4.5 y	0.0% over median 4.5 y
Quinn (2013) ³⁵	1989-2011	25	100%	100%	NS	96% LGD; 4% HGD (of patients)	2.42 (range 0.04-13)	1	1	4.0% over median 2.4 y	4.0% over median 2.4 y
Patel (2014) ⁴⁰	1998-2011	20	NS	100%	NS	90% LGD; 10% HGD (of patients)	10.4 (for LGD)	0	0	LGD: 0.0% over mean 10.4 y; HGD: 0.0% (follow-up not specified)	LGD: 0.0% over mean 10.4 y; HGD: 0.0% (follow-up not specified)
Subramanian (2016) ³⁶	1991-2011	27	100%	100%	10 (5-35)	81% LGD; 19% HGD (of patients)	4.1 (1.0-9.0)	5	2 from HGD; 3 from LGD	LGD: 13.6% over median 4 y; HGD: 40.0% over median 4 y	LGD: 13.6% over median 4 y; HGD: 40.0% over median 4 y
Branquinho (2016) ⁵³	2010-2014	45	NS	100%	14.4 (6-40)	100% LGD	2.4	0	0	LGD: 0.0% over mean 5 y	LGD: 0.0% over mean 5 y
Krugliak Cleveland (2018) ³⁷	2005-2014	34	100%	100%	5.1 (SD 2.4)	65% LGD; 35% HGD (of patients)	1.7 (range 0.2-15)	6	1 from LGD; 3 from HGD	LGD: 5% at 1 y; 13% at 3 y; 23.0% at 5 y; HGD: 25.0% over median 1.7 y	LGD: 4.5% over median 1.7 y; HGD: 25.0% over median 1.7 y
Yadav (2019) ⁵²	2012-2016	76 polyps (patient no. not extracted)	100%	100%	15 (10-60)	Approx. 71.8% LGD	At most 4 y	0	0	LGD: 0.0% over at most 4 y follow-up	LGD: 0.0% over at most 4 y follow-up

Abbreviations: AN, advanced neoplasia; CRC, colorectal cancer; HGD, high-grade dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; NS, not specified; SD, standard deviation.

and piecemeal or *en bloc* endoscopic mucosal resection. Most of the study cohorts included a mixture of HGD and LGD polyps where the proportion of HGD was in the minority, making pooled analysis inappropriate. Only one study included exclusively HGD polyps ($n = 9$), where two thirds were fully resected endoscopically and the rest surgically, and there was no progression to cancer over a mean follow-up period of 6 years.³⁹ However, polyp recurrence was high at 62.5%. Kisiel et al's study using high-definition chromoendoscopy also showed no progression to cancer over an average follow-up of a median of 4.5 years.³⁴ In two studies where chromoendoscopy was not used, there was progression to cancer at a rate of 25.0% ($n = 3/12$) over a median of 1.7 years³⁷ and 40.0% ($n = 2/5$) over a median of 4 years.³⁶ In the former study high-definition white light colonoscopy and polypectomy were performed by accredited endoscopists.³⁷

3.3.3 | Visible nonpolypoid HGD—post-polypectomy

Six studies (all case series) reported on cancer progression rates after endoscopic resection of nonpolypoid dysplasia, which included a mixture of HGD and LGD polyps making pooled analysis inappropriate (Table 4).⁴¹⁻⁴⁶ The endoscopic resection methods used piecemeal and *en bloc* endoscopic mucosal resection, endoscopic submucosal resection and hybrid techniques. Histological R0 resection (clear resection margins) varied from 67% to 100%. Patients in these studies were followed up intensively using chromoendoscopy and recurrent dysplasia was resected. Most of the studies had short median follow-up times of up to 2 years and did not show progression to advanced neoplasia over that follow-up.^{41-43,45} However, in a study with the longest follow-up time of 10.8 years after endoscopic submucosal dissection of high-risk

TABLE 4 Advanced neoplasia progression rates during surveillance follow-up after endoscopic resection of NON-POLYPOID dysplasia

Study	Enrollment period	No. with non-polypoid dysplasia	% of polyps WITHIN colitis extent	% full endoscopic resection (RO in %)	Median/mean polyp size (mm)	Dysplasia grading	Median/mean Follow-up (years)	No. progressed to AN	No. progressed to CRC	Reported AN progression (incidence) rate	Reported CRC progression (incidence) rate
Iacopini (2015) ⁴¹	2009-2014	7	100%	100% by ESD (RO in 71%)	15 (10-20)	57% LGD; 43% HGD	1.75 (0.5-6)	0	0	0.0% over median 1.75 y	0.0% over median 1.75 y
Kochhar (2017) ⁴²	2014-2017	6	NS	100% by ESD (RO in 85%)	40.7 (25-70)	50% LGD; 50% HGD	0.5	0	0	0.0% over median 0.5 y	0.0% over median 0.5 y
Suzuki (2017) ⁴³	2009-2016	26	100%	100% by ESD (RO in 79%)	33 (12-73)	Approx. 60% LGD; 22% HGD	2.75 (0.5-6.3)	NS	0	NS	0.0% over median 2.75 y
Gulati (2018) ⁵⁴	2011-2016	9	100%	100% by EMR/ESD (RO in 40%)	48.3 (20-90)	100% LGD	2.3 (1-2.9)	2	2	22.2% over median 2.3 y	22.2% over median 2.3 y
Kinoshita (2018) ⁴⁴	2011-2017	20	100%	100% by ESD (RO in 76%)	34.9 ± 17.1	Approx. 50% LGD; 50% HGD	1.75 (0.7-6.7)	1	0	5.0% over median 1.75 y	0.0% over median 1.75 y
Yang (2019) ⁴⁵	2009-2017	11	100%	100% by ESD (RO in 80%)	23 (12-48)	73% LGD; 27% HGD	2.06 (0.4-5.4)	0	0	0.0% over median 2 y	0.0% over median 2 y
Matsumoto (2019) ⁴⁶	1999-2015	7	100%	100% by ESD/hybrid ESD (RO 67%)	All were >10 mm	71% LGD; 29% HGD	LGD: 10.0 (7.1-12.3); HGD: 10.8 (10.5-11.1)	3	3	LGD: 40.0% over median 10 y; HGD: 50.0% over median 10.8 y	LGD: 40.0% over median 10 y; HGD: 50.0% over median 10.8 y
Yadav (2019) ⁵²	2012-2016	48 polyps (patient no. not extracted)	100%	100% by EMR/ESD/hybrid ESD (RO status NS)	1 (10-60)	Approx. 71.8% LGD	At most 4 y	0	0	LGD: 0.0% over at most 4 y follow-up	LGD: 0.0% over at most 4 y follow-up

Note: RO indicates that resection margins were histologically cleared of dysplasia.

Abbreviations: AN, advanced neoplasia; CRC, colorectal cancer; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NS, not specified.

HGD in which only 67% could be resected with histologically clear margins, half progressed to cancer.⁴⁶

3.3.4 | Invisible HGD

No studies reporting on cancer progression rates during surveillance follow-up of invisible HGD in the videoendoscopic era were found.

3.3.5 | Visible LGD

There were 21 observational studies reporting on advanced neoplasia progression rates during surveillance follow-up after an initial diagnosis of visible LGD.^{13,33-37,40-54} Due to the heterogeneity of the study populations involved, advanced neoplasia progression rate outcomes have been subanalysed and extracted according to the morphology of the LGD and whether it was endoscopically resected. These have been described in Section 3.3.6 and Table 3 (polypoid LGD followed up after polypectomy) and Section 3.3.7 and Table 4 (nonpolypoid LGD followed up after polypectomy). In the largest study of visible LGD progression (n = 155) by Choi et al,¹³ polypoid morphology was significantly associated with a better prognosis than nonpolypoid LGD. The cumulative incidence of advanced

neoplasia for *polypoid* LGD was 3.5% at 1 year and 6% at 5 years, and for *nonpolypoid* LGD it was significantly higher at 37% at 1 year and 62.5% at 5 years.¹³ However, this discrepancy is not only secondary to the morphology of the lesion. About 93% of the polypoid LGD in this patient cohort was successfully endoscopically resected, vs 39% of the nonpolypoid LGD. The nonpolypoid lesions were also likely to be multifocal compared with the polypoid lesions. Studies like this that have reported on advanced neoplasia progression rates for visible LGD, where not all of the lesions have been endoscopically resected or endoscopic resection has not been specified, are presented in Table A7.

3.3.6 | Visible polypoid LGD—post-polypectomy

Nine studies (seven cohort studies and two case series) reported on advanced neoplasia progression rates while on surveillance follow-up after endoscopic resection of the index polypoid LGD (Table 3).^{33-37,40,48,52,53} The majority of these studies included a mixture of LGD and HGD polyps, again making pooled analysis inappropriate. Resection techniques included hot and cold biopsy, cold snare, piecemeal and *en bloc* endoscopic mucosal resection. Completeness of resection was based on endoscopist judgement rather than histological assessment. The average polyp diameters were 15 mm or less.

Advanced neoplasia progression rates were reported to be 0.0%–5.0% at 1 year^{33,34,37,40,52,53} and 0%–23.0% at 5 years.^{33,34,36,37,40,48,53} The highest 5-year advanced neoplasia rate of 23.0% was associated with a study which used high-definition white light imaging colonoscopy and not chromoendoscopy.³⁷ Cancer progression rates ranged from 0.0% to 4.5% at 2 years^{34,35,37,53} and 0.0% to 13.6% at 4 years.^{33,34,36,48,53}

3.3.7 | Visible nonpolypoid LGD—post-polypectomy

Eight studies (one cohort study and seven case series) reported on advanced neoplasia progression rates while on surveillance follow-up after endoscopic resection of nonpolypoid LGD (Table 4).^{41–46,52,54} Again, the majority of the studies included a heterogeneous mixture of LGD and HGD polyps in small numbers, with short follow-up times, making pooled analysis inappropriate, but the majority showed no progression to HGD or cancer.^{41–43,45,52} RO resection ranged from 40% to 100%. The only studies to demonstrate progression of nonpolypoid LGD to advanced neoplasia were case series of selected high-risk patients with large lesions which required resection with endoscopic submucosal dissection or hybrid techniques and RO resections rates were the lowest. In Kinoshita et al's⁴⁴ Japanese case series, 20 dysplastic lesions, measuring on average 35 mm in diameter, were resected by endoscopic submucosal dissection and RO resection was only achieved in 76%. During the post-resection follow-up, one case of metachronous HGD (5.0%) developed over a median of 1.75 years. In Gulati et al's⁵⁴ UK case series, nine LGD lesions with a mean diameter of 48 mm were resected using either endoscopic mucosal resection, endoscopic submucosal dissection or hybrid techniques. RO resection was only achieved in 40%. Two patients (22.2%) developed cancer over the 2-year median follow-up time but these cancers arose in different colonic segments to the index dysplastic lesion suggesting that they did not occur due to incomplete resection. Matsumoto et al's⁴⁶ case series importantly described outcomes after the longest follow-up of median 10 years: 40.0% of the LGD progressed to cancer after endoscopic submucosal dissection or hybrid techniques. Again, these lesions were all high risk with size all greater than 10 mm, significant submucosal fibrosis and RO resection only being achieved in 67%.

3.3.8 | Invisible LGD

Eight studies (seven cohort studies and one case series) reported on advanced neoplasia progression rates during surveillance follow-up after an initial diagnosis of invisible LGD (Table 5).^{13,47–51,55,56} All included small numbers with limited follow up, and/or heterogeneous cohorts with widely discrepant proportions of higher risk cases, for example concomitant primary sclerosing cholangitis and multifocal dysplasia. Thus, pooled analysis was deemed to be inappropriate. Advanced neoplasia progression rates were reported at 2.3%–13.0% at 1 year^{13,51,56} and 4.6%–44.0% at 2 years.^{13,47–51,55,56} Reported cancer progression

rates ranged from 0.0% to 28.0% at median 2 years.^{13,48–51,55,56} In Ten Hove et al's multicentre study,⁵¹ which used chromoendoscopy and/or high-definition endoscopes, the advanced neoplasia incidence rate was 2.29 cases per 100 patient-years and only 3.8% developed cancer over a median of 5 years follow-up. They also demonstrated that the incidence of invisible dysplasia has decreased in the most recent decade, with 88% of the invisible LGD lesions being detected before 2010 and 12% being detected after 2010.⁵¹

3.3.9 | Indefinite for dysplasia

Six studies (five cohort studies and one case series) reported on advanced neoplasia progression rates while followed up after an initial diagnosis of indefinite for dysplasia (Table 6).^{32,48,55,57–59} Advanced neoplasia progression rates range from 2.4% to 14.6% at 2 years^{48,59} and 4.8% to 36.5% at 5 years.^{32,48,55,58} Cancer progression rates ranged from 0.0% to 1.2% at 2 years^{57,59} and 5.1% to 14.3% at 4 years.^{32,48,55} The study with the highest progression rates had a very small cohort of seven cases, all of which were invisible.⁴⁸ The three largest cohort studies have found lower advanced neoplasia progression rates.^{32,58,59} Won-Tak Choi et al followed up 84 patients with a diagnosis of indefinite for dysplasia over a mean of 2.3 years.⁵⁹ The advanced neoplasia progression rate was 2.4% and the cancer progression rate was 1.2%. Lai et al followed up a cohort of 59 patients over a longer mean follow-up of 6.8 years and found a 13.6% advanced neoplasia progression rate and a 5.1% cancer progression rate.³² The importance of histological re-review is substantiated in a pooled analysis of 26 patients with invisible indefinite for dysplasia, diagnosed across six Dutch academic centres.⁵⁵ Van Schaik et al initially demonstrated a cumulative incidence of advanced neoplasia as 21% at 5 years, but after histological re-review by an expert gastrointestinal pathologist and reclassification of the indefinite for dysplasia, the cumulative incidence reduced substantially to 5% at 5 years.⁵⁵

4 | DISCUSSION

4.1 | Prevalent cancer rate

This meta-analysis calculated pooled estimates rates of prevalent cancer found at colectomy performed for a pre-operative diagnosis of visible HGD, invisible HGD, visible LGD, invisible LGD and indefinite for dysplasia to be 14%, 11%, 3%, 2% and 1% respectively. In contrast, studies in which the dysplasia has been diagnosed in the pre-videoendoscopic era have shown much higher rates of prevalent cancer on colectomy.^{20,21,60–62} A 1994 systematic review of 10 small prospective surveillance studies by Bernstein et al⁶⁰ demonstrated a prevalent cancer rate of 42% (n = 10/24) with endoscopically unresectable visible HGD. In 1994 Connell et al⁶¹ reported a prevalent cancer rate with invisible HGD as 44%, increasing to 67% (n = 8/12) after histological review and dysplasia reclassification in ulcerative colitis. Prevalent cancer rates with visible LGD in the same

pre-videoendoscopic era studies were reported at 19%-30%.⁶⁰⁻⁶² A meta-analysis by Thomas et al,²¹ where most of the included studies were from the pre-videoendoscopic era, found a prevalent cancer rate with invisible LGD of 22% (n = 18/81). Fumery et al's meta-analysis²⁰ has also suggested that rates of prevalent cancer have reduced over time. Studies published before 2000 were associated with a significantly higher prevalent cancer rate associated with pre-operative LGD (33%; 95% CI, 20-50) compared with studies published after 2000 (11%; 95% CI, 4-29).

It is suspected that standardisation of surveillance intervals, endoscopic technological advancements and routine use of second gastrointestinal histopathologist review have improved dysplasia diagnosis and resection. The consequence of this seems to be a reduction in missed dysplasia or cancers at colonoscopy, hence lower rates of incidental (prevalent) cancers found at colectomy. However, there are important limitations in the interpretation of the results of this meta-analysis: heterogeneity between studies could not be assessed for the outcomes for invisible HGD and indefinite for dysplasia, due to the limited number of studies (n = 2) included; there was substantial heterogeneity between studies reporting on visible HGD and invisible LGD prevalent cancer rates, part of which was

due to the inclusion of small and heterogenous population cohorts; some studies may have included dysplasia located outside the extent of inflamed mucosa,²⁸ whereas certain studies only included dysplasia cases located within the inflamed mucosa^{29,30} and thus displayed higher prevalent cancer rates. There is consensus that colonic dysplasia located outside the extent of colitis has a much better prognosis than true colitis-associated dysplasia, and is similar to that of a sporadic adenoma.^{9,15} The only category to show satisfactorily low between-study heterogeneity was visible LGD. The GRADE quality of evidence supporting the meta-analysis outcomes was determined to be low for visible LGD and very low for visible or invisible HGD, invisible LGD and indefinite for dysplasia due to the risk of bias in the study design, publication bias, indirectness and inconsistency in the results (Table 1).

4.2 | Advanced neoplasia progression rate

In Fumery et al's²⁰ meta-analysis of endoscopically visible LGD, the pooled incidence rate of advanced neoplasia was 1.0 per 100 patient-year follow-up (95% CI, 0-2.1), which did not take into

TABLE 5 Advanced neoplasia progression rates during surveillance follow-up after diagnosis of invisible low-grade dysplasia

Study	Enrollment period	Extensive colitis (%)	Multi-focal dysplasia (%)	PSC (%)	Second histopathologist review	No. with invisible LGD	Median/mean Follow-up (years)	No. progressed to AN	No. progressed to CRC	Reported AN progression (incidence) rate	Reported CRC progression (incidence) rate
Ullman (2002) ⁵⁶	1990-1993	94%	NS	28%	Yes	18	2.6 (0.17-9.75)	4	1	13% at 1 y (95% CI = 0%-29%) 26% at 2 y (95% CI = 4%-48%) 33% at 5 y (95% CI = 9%-56%)	5.6% over median 2.7 y
Pekow (2010) ⁴⁸	1994-2008	NS	NS	14%	Yes	13	4.2 (SD 2.8)	1	0	7.7% over mean 4.2 y; 4.3 cases per 100 person-years	0.0% over mean 4.2 y
Goldstone (2011) ⁴⁹	1994-2006	100%	0%	0%	Yes	32	3.1 (IQR 1.1-6.0)	8	3	25.0% over median 3.1 y	9.3% over median 3.1 y
Van Schaik (2011) ⁵⁵	1990-2006	83%	35%	12%	Yes	25	2.0 (0.2-8.5)	11	7	44.0% over median 2 y	28.0% over median 2 y
Zisman (2012) ⁴⁷	1987-2002	100%	45%	26%	Yes	19	3.9 (1-13)	4	NS	21.1% over mean 3.9 y	NS
Navaneethan (2013) ⁵⁰	1998-2011	100%	NS	0%	Yes	37	3.7 (IQR 2.3-6.2)	3	1	8.1% over median 3.7 y	8.1% over median 3.7 y
Choi (2015) ¹³	1993-2012	100%	21%	6%	Yes	16	4.0 (IQR 1.3-7.3)	6	1	6.7% at 1 y 21.9% at 5 y 56.7% at 10 y	6.2% over median 4 y
Ten Hove (2017) ⁵¹	2000-2014	NS	NS	NS	NS	26	4.7 (0.2-12.6)	3	1	11.5% over median 4.7 y; 2.29 cases per 100 person-years	3.8% over median 4.7 y

Abbreviations: AN, advanced neoplasia; CD, Crohn's disease colitis; CRC, colorectal cancer; IC, indeterminate colitis; IQR, interquartile range; NS, not specified; UC, ulcerative colitis.

TABLE 6 Advanced neoplasia progression rates during surveillance follow-up after a diagnosis of indefinite for dysplasia

Study	Enrolment period	Extensive colitis (%)	PSC (%)	Second histopathologist confirmation of dysplasia	No. with indefinite for dysplasia	Median/mean Follow-up (years)	No. progressed to AN	No. progressed to CRC	Reported AN progression (incidence) rate	Reported CRC progression (incidence) rate
Pekow (2010) ⁴⁸	1994-2008	NS	14%	Yes	7 (all invisible)	3.9 ± 3.2	2	1	28.6% over mean 3.9 y; 7.3 cases per 100 person-years	14.3% over mean 3.9 y
Van Schaik (2011) ⁵⁵	1990-2006	73%	8%	Yes	26	4.5 (range 0-9.25)	5	2	Before histological review: 21% (95% CI, 0.02%-0.4%) at 5 y After histological review: 5% (95% CI, 0.0%-0.2%) at 5 y; 2.4 cases per 100 person-years	7.7% over median 4.5 y (before histological review)
Lai (2015) ³²	1989-2004	49%	14%	83% re-reviewed with no changes in classification	59	6.8 (3.1-9.7)	8	3	13.6% over median 6.8 y; 1.5 cases per 100 person-years	5.1% over median 6.8 y
Won-Tok Choi (2015) ⁵⁹	2003-2013	NS	20%	Yes	84	2.3	2	1	2.4% over mean 2.3 y	1.2% over mean 2.3 y
Murphy (2016) ⁵⁷	1993-2012	NS	20%	Yes	23	1.5 (IQR 0.7-2.5)	NS	0	NS	0.0% over median 1.5 y
Mahmoud (2019) ⁵⁸	2001-2017	74%	32%	Yes	53	4.0 (IQR 3.0-4.8)	7	NS	13.2% over median 4 y	NS

Abbreviations: AN, advanced neoplasia; CD, Crohn's disease colitis; CRC, colorectal cancer; IC, indeterminate colitis; IQR, interquartile range; NS, not specified; UC, ulcerative colitis.

consideration whether the lesion was endoscopically resected. The pooled advanced neoplasia incidence rate for invisible LGD was 6.1 per 100 patient-year follow-up (95% CI, 0.9-11.4) which was sixfold higher, but there was considerable between-study heterogeneity ($I^2 = 82\%$).²⁰ Studies from the pre-videoendoscopic era and a study with exclusively primary sclerosing cholangitis patients⁶³ were included in Fumery et al's meta-analysis.²⁰ In a meta-analysis of 20 mainly pre-videoendoscopic era studies by Thomas et al,²¹ invisible LGD was associated with a 14.6% ($n = 58/396$) progression rate to advanced neoplasia over a mean surveillance period of 12 years. A meta-analysis of 10 studies by Wanders et al,²² comprising 376 ulcerative colitis patients with polypoid dysplasia, demonstrated a pooled incidence of cancer after endoscopic resection of polypoid dysplasia of 0.5 cases per 100 patient-years of follow-up. However, studies where dysplastic lesions were found outside areas of colitis were also included in the meta-analysis, and a subgroup analysis by dysplasia severity was not performed.

The strength of this systematic review of videoendoscopic era studies is that it has attempted to clarify the risk of dysplasia progression to advanced neoplasia and specifically the risk of metachronous advanced neoplasia after endoscopic resection of colitis-associated dysplasia in the videoendoscopic era. In addition, this review has identified a further 20 studies not included in Fumery et al's meta-analysis.^{31,33-38,40-46,51-54,56,57} The wide variation in outcomes demonstrated by our systematic review may be explained by a number of factors. Most of the current data on dysplasia progression risks are based on small retrospective cohort studies and case series with heterogeneous endoscopic surveillance techniques and limited follow-up in some cases. All but one of the case series reporting on metachronous neoplasia after endoscopic resection of nonpolypoid dysplasia have median follow-up durations of 2 years or less. Image quality in the videoendoscopic

era has also gradually improved over the last 30 years. In addition chromoendoscopy has been introduced into endoscopic surveillance practice from 2003 onwards and true high-definition imaging processors have been available from 2012 onwards. Most of the outcomes for invisible LGD in this systematic review were based on data from before the introduction of these endoscopic adjuncts. The most recent study where chromoendoscopy and high-definition imaging were part of routine surveillance practice demonstrated a lower incidence of invisible LGD as well as lower advanced neoplasia progression.⁵¹ Most of the follow-up studies of endoscopically resected dysplasia where these adjuncts were used with surveillance are associated with the lowest advanced neoplasia progression rates.^{13,34,41-43,45,53} The only studies to show significant advanced neoplasia progression despite use of these adjuncts were in one study where high-definition imaging but no chromoendoscopy surveillance was used after resection of LGD and HGD polyps³⁷ and in two studies where high-definition chromoendoscopy surveillance was performed after resection of high-risk large nonpolypoid LGD lesions with significant submucosal fibrosis and where R0 resection rates were less than 70%.^{46,54}

Inconsistency in the outcomes also appears to be associated with variation in the completion of endoscopic resection of dysplasia achieved. Most of the studies reporting on polypoid dysplasia have defined resection completion based on endoscopist judgement rather than histological assessment. The use of diathermy during endoscopic mucosal resection and the potential need for piecemeal resection often makes histological assessment of resections difficult. Differing levels of skill and subjectivity in judging polypectomy completion between the endoscopists have not been accounted for in these studies. This and potential differences in the post-polypectomy surveillance intervals adhered to in independent centres may contribute to the variation in post-polypectomy metachronous advanced neoplasia seen.

The most recent studies in this review describe outcomes after the resection of nonpolypoid dysplasia using advanced techniques such as endoscopic submucosal dissection and hybrid techniques. These are technically difficult procedures performed by a small number of specialist endoscopists for high-risk lesions. Description of histological R0 resection success and intensive post-polypectomy surveillance intervals are strictly adhered to in these more recent studies, which have demonstrated that achieving R0 resection and adhering to close follow-up by expert endoscopists are associated with a lower risk of metachronous advanced neoplasia than previously thought.^{41-46,54} Therefore, although of low quality, the evidence supports the practice of continued close surveillance of patients following successful R0 resection of dysplastic lesions. It should be noted that very small numbers of HGD have been included in the post-polypectomy surveillance studies, making the evidence for choosing continued surveillance over colectomy after visible HGD resection of even lower quality than that for visible LGD. In addition, case series of large high-risk nonpolypoid dysplastic lesions where significant submucosal fibrosis resulted in low R0 resection rates and progression rates to cancer of 22%-40% with LGD^{46,54} and 50% with HGD⁴⁶ highlights the need for caution when deciding to delay a colectomy in these high-risk patients.

Analysis of the largest existing cohort study of LGD outcomes by Choi et al¹³ found that nonpolypoid shape (HR 16.5; 95% CI 6.8-39.8), lesion size greater than 10mm (HR 10.0; 95% CI 4.3-23.4), multifocality (HR 5.0; 95% CI 1.9-7.8), metachronous dysplasia (HR 3.5; 95% CI 1.6-7.5) and presence of a stricture (HR 7.4; 95% CI 2.5-22.1) were all significant risk factors for colorectal cancer development, and presence of two or more of these risk factors cumulatively increased the risk. Fumery et al's meta-analysis²⁰ of LGD outcomes found that concomitant primary sclerosing cholangitis (OR 3.4; 95% CI 1.5-7.8), invisibility (OR 1.87; 95% CI 1.04-3.36) and multifocality (OR 3.5; 95% CI 1.5-8.5) were significant risk factors for cancer development. Therefore, a patient with a combination of one or more of these risk factors should be surveilled more intensively by expert endoscopists. A lower threshold for elective colectomy should also be considered when deciding management with these higher risk patients.

No studies which reported on cancer progression rates after diagnosis of invisible HGD were identified. This is because most of these patients undergo colectomy rather than continue surveillance, based on the high incidences seen from pre-videoendoscopic era studies. Further data on outcomes of patients who have been followed up with surveillance for invisible HGD would need to be published before clinicians would consider recommending surveillance over colectomy. This review has shown that there remains considerable variation in the prognosis with invisible LGD; however, the rate of progression to cancer appears to have reduced in the most recent time period with routine use of high-definition imaging and/or chromoendoscopy.⁵¹ It is therefore not unreasonable for patients with unifocal invisible LGD to be closely monitored with surveillance rather than proceeding to a colectomy. However, the association of other high-risk factors, such as multifocality, concomitant primary sclerosing cholangitis and

family history all need to be borne in mind when decision-making with these patients.

The largest cohorts of patients followed up after a diagnosis of indefinite for dysplasia^{32,58,59} showed lower rates of advanced neoplasia progression compared to invisible LGD. The best prognosis was achieved after confirmation of the diagnosis of indefinite for dysplasia by a second expert gastrointestinal histopathologist.⁵⁵ Due to the interobserver incongruity in histological interpretation of indefinite for dysplasia, particularly on a background of inflammation, it seems entirely appropriate to repeat a surveillance colonoscopy after a period of therapy to reduce the background inflammation.

5 | CONCLUSIONS

As endoscopic techniques in IBD surveillance, such as optical characterisation and resection of dysplasia, advance, clinicians have witnessed changes in the reported natural history of these lesions. Increasing expertise in dysplasia characterisation by histopathologists, as well as optimisation in medical therapy and standardisation of surveillance intervals are also likely to have produced better outcomes. The results of this meta-analysis suggest that dysplasia detected during surveillance in the videoendoscopic era are associated with lower rates of incidental cancers found at colectomy than previously thought. Dysplasia found within an inflamed colonic segment appears to be associated with higher prevalent cancer rates on colectomy than dysplasia detected proximal to the colitis extent. However, due to the very small numbers of heterogeneous studies involved, the quality of the evidence obtained from this meta-analysis remains low.

The findings from this systematic review suggest that the lowest rates of progression to advanced neoplasia, for dysplasia not managed with immediate colectomy but followed up with surveillance, tend to be where high-definition imaging and/or chromoendoscopy surveillance has been used and endoscopic resection of visible dysplasia has been histologically confirmed. When quoting individualised cancer risks to patients, clinicians need to be aware of the cumulative effects of various risk factors such as active inflammation, multifocality, previous history of dysplasia and the presence of primary sclerosing cholangitis. This review highlights the low quality of evidence on the prognosis of dysplasia in the videoendoscopic era. The lowest quality evidence is for nonpolypoid dysplasia that has been successfully resected. Current evidence is based mainly on retrospective cohort studies and case series with small, heterogeneous cohorts and short follow-up times. Interpretation of the data obtained from these studies is therefore limited. Larger, prospective studies are needed in order to make the evidence base used in shared decision-making more robust.

ACKNOWLEDGEMENTS

Jacqueline Kemp, Medical Librarian for Imperial College London, assisted in designing and conducting the full electronic literature search. All the authors approved the final version of the article.

Declaration personal interests: PJT has served as an advisory board member and speaker for Takeda. ALH has served as a consultant, advisory board member or speaker for AbbVie, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Shire and Takeda.

Declaration of funding interests: This systematic review with meta-analysis was not funded by an external funding organisation or grant.

AUTHORSHIP

Guarantor of the article: Dr Misha Kabir.

Author contributions: All the authors contributed to the conception and design of the systematic review and meta-analysis, and critically revised the manuscript drafts until the final version was approved. MK performed the initial electronic literature search. MK and RF performed the study eligibility assessment, data extraction, analysis and interpretation. MK, RF and NA performed the methodological quality and risk of bias assessment of the data. PB is the statistician who performed the meta-analysis and produced the Forrest plots. MK was responsible for the drafting and revisions of the manuscript.

ORCID

Misha Kabir  <https://orcid.org/0000-0003-3991-1015>

Rishi Fofaria  <https://orcid.org/0000-0002-1058-7584>

Naila Arebi  <https://orcid.org/0000-0001-6976-1690>

Phil J Tozer  <https://orcid.org/0000-0002-2532-7267>

Ailsa L Hart  <https://orcid.org/0000-0002-7141-6076>

Siwan Thomas-Gibson  <https://orcid.org/0000-0001-8922-6249>

Adam Humphries  <https://orcid.org/0000-0001-5459-4551>

Janindra Warusavitarn  <https://orcid.org/0000-0002-7950-2833>

Omar Faiz  <https://orcid.org/0000-0003-1117-1588>

Ana Wilson  <https://orcid.org/0000-0001-6046-6281>

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Kabir M, Fofaria R, Arebi N, et al. Systematic review with meta-analysis: IBD-associated colonic dysplasia prognosis in the videoendoscopic era (1990 to present). *Aliment Pharmacol Ther.* 2020;52:5-19. <https://doi.org/10.1111/apt.15778>