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Long-term outcomes in patients newly diagnosed with iron deficiency anaemia in general practice: a retrospective cohort study

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ABSTRACT

Objectives To describe all iron deficiency anaemia (IDA)–related causes during follow-up of patients newly diagnosed with IDA and to assess whether a delayed colorectal cancer (CRC) diagnosis influences survival.

Design and setting Retrospective cohort study of patients from general practices in the Dordrecht area, the Netherlands.

Participants Men and women aged ≥50 years with a new diagnosis of IDA (ie, no anaemia 2 years previously).

Method From February 2007 to February 2018, all relevant data were collected from the files of the referral hospital. Early IDA-related cause was defined as established within 18 weeks after IDA diagnosis. Cox proportional-hazards regression was used to analyse survival of patients with CRC diagnosis.

Results 587 patients with IDA were included with a median follow-up of 4.6 years. Early and late IDA-related causes could be established in 32% and 8% of patients, respectively. Early and late CRC was found in 8% and 2% of patients, respectively, and were located mainly right sided. After adjustment for age, gender and TNM classification, mortality risk was lower in patients with IDA with early CRC diagnosis, but not significantly (HR 0.30, 95% CI 0.09 to 1.02).

Conclusion Even with extended follow-up, the cause of IDA remains elusive in the majority of patients with IDA in general practice. However, patients with IDA are at increased risk for in particular right-sided CRC and a late diagnosis of CRC appears to have a detrimental effect on survival in patients with IDA.

Strengths and limitations of this study

► Large cohort of patients diagnosed with iron deficiency anaemia (IDA) with exclusion of patients known with anaemia 2 years previously.
► Long period of follow-up concerning survival and the most relevant outcome, namely IDA-related hospital diagnoses.
► Limited information concerning IDA-related diagnoses made out-of-hospital.
► Number of events (colorectal cancer) limits the survival analysis of (late) colorectal cancer.

INTRODUCTION

Around 5%–10% of patients with iron deficiency anaemia (IDA) have colorectal cancer (CRC) and, therefore, endoscopic evaluation is advised.[1–5] However, most studies reporting on IDA and CRC only included patients already referred for endoscopic evaluation. Information on general practice patients diagnosed with IDA and *not* referred for endoscopic evaluation is scarce. So far, only two cohort studies have included patients from the moment of IDA diagnosis in general practice.[6 7] These studies reported that a third of patients with IDA diagnosed in general practice receive an endoscopic evaluation within several weeks after IDA diagnosis. Of these patients with IDA, the incidence of CRC was 4.6% and 5.9%, respectively.[6 7] During follow-up of patients with IDA, including those who were not endoscopically evaluated, an additional 3.2% (follow-up of 3 years) and 2.4% (follow-up of 1 year) of patients were diagnosed with CRC.[6 7] Limited data are available for the group of patients who do not receive an endoscopic evaluation and for whom other underlying causes related to IDA might be diagnosed later on. Furthermore, it is unknown whether the 3% of general practice patients with IDA who have a delayed CRC diagnosis have a poorer overall survival.

This study investigated a cohort of general practice patients with a new laboratory diagnosis of IDA. For the entire cohort, all IDA-related diagnoses made in-hospital are described during extended follow-up. Furthermore, we analysed the characteristics of patients with a CRC diagnosis, and the association between a delayed CRC diagnosis and overall survival.

METHOD

Patient and public involvement

This study has been retrospectively conducted in a cohort of patients formed by general practitioners (GPs) participating in a large project on anaemia evaluation improvement.[8] Therefore, the patients' involvement has been limited. Patients were informed about this project by their treating GP. Data about these patients were processed anonymously. The participating GPs were informed about the study results and encouraged to give feedback.

Study population

The laboratory system of the Albert Schweitzer Hospital started a project to improve anaemia evaluation in general practice on 1 February 2007, in which 81 of the invited 150 GPs (in the Dordrecht area, the Netherlands) agreed to participate. Every time the participating GPs requested a blood test for their patients aged ≥50 years and this revealed a low haemoglobin concentration, a comprehensive laboratory assessment was performed. This laboratory protocol consisted of measurement of haemoglobin, mean corpuscular volume (MCV), C reactive protein and/or erythrocyte sedimentation rate, vitamin B_{12}, creatinine, ferritin, folic acid, lactate dehydrogenase, transferrin, reticulocytes, leucocytes, thrombocytes and serum iron.

IDA was defined as haemoglobin <13.7 g/dL for men and <12.1 g/dL for women in combination with ferritin <25 µg/L for men and <20 µg/L for women.[9] The participating GPs were provided with the laboratory results for each patient, including an interpretation of the laboratory diagnosis of IDA, and they were advised to request endoscopic evaluation for their patient. Fast-track endoscopic evaluation places (ie, within 4 weeks) were available for these patients.

Retrospectively, we selected a cohort of patients from the anaemia improvement project who presented with a new laboratory diagnosis of IDA during the period 1 February 2007 until 1 February 2016 and collected additional clinical information. We excluded patients who were already known with anaemia in the previous 2 years.

Data collection

Clinical data were extracted (if available) from the electronic medical files of the Albert Schweitzer Hospital. Collected clinical information consisted of endoscopic evaluations performed within 18 weeks after IDA diagnosis and all IDA-related causes established in-hospital including the date of the IDA-related diagnosis. Other diagnostic investigations to evaluate IDA and/or endoscopic evaluations performed 18 weeks after IDA diagnosis were not collected. CRC and other IDA-related malignancies were checked for registration in the Netherlands Comprehensive Cancer Organization.[10] The location of CRC was verified using pathology and operation reports and divided into either right (ie, colon ascendens, caecum and transversum) or left (ie, sigmoid, colon descendens and rectum). The stage of CRC was registered using the TNM 5 classification.[11] The length of follow-up was variable since patients were selected over a 9-year period (2007–2016). The end of follow-up was defined as the date of death or the last noted hospital record before 1 February 2018 to ensure a follow-up time of at least 2 years.

Definitions

Early endoscopic evaluation was defined as all full endoscopies (ie, gastroscopy and colonoscopy) and colonoscopies performed within 18 weeks after establishment of IDA. Gastroduodenoscopy alone was only counted as early endoscopic evaluation if an IDA-related diagnosis according to the Dutch anaemia guideline was found.[9]

Early IDA-related cause was defined as all in-hospital registered causes within 18 weeks after the establishment of IDA. Late IDA-related cause was defined as all in-hospital registered causes defined 19 weeks or later after the establishment of IDA.

The IDA-related causes were divided into four categories. The first category was defined as all gastrointestinal (GI) malignancies and those with a strong suspicion of GI malignancy but no pathological proof. The second category was defined as other malignancies causing IDA (ie, urothelial or endometria carcinoma) and patients with a GI metastasis of a non-GI primary tumour. The third category was defined as benign GI causes of IDA, which included angiodysplasia, gastritis/erosions, ulcers, haemorrhoids, polyps ≥1 cm, coeliac disease, Crohn's disease and radiation proctitis. Finally, the fourth category was defined as all other non-GI causes of IDA that included in-hospital registration of repetitive blood donation, hypermenorrhoea, low-iron diet and severe epistaxis as cause of IDA.

Statistical analysis

All patients with IDA were divided into either early or no (early) endoscopic evaluation and the data were characterised with standard descriptive statistics. Chi-square tests and Mann-Whitney U tests were used to compare patients receiving endoscopic evaluation and patients without endoscopic evaluation. Univariable and multivariable logistic regression analysis was performed with CRC diagnosis (yes/no) as dependent variable. In these logistic regression analyses, the independent variables were age, haemoglobin, ferritin, gender (male/female) and MCV (microcytic or normocytic/macrocytic anaemia). Interaction effects between gender and haemoglobin and between gender and ferritin were tested, but not included in the final model as they were not statistically significant. The goodness-of-fit of the multivariable logistic regression was assessed using the Hosmer-Lemeshow test. A Cox proportional-hazards regression analysis was performed including only those patients who received a CRC diagnosis during follow-up. In the Cox regression, the time at risk was the time from CRC diagnosis until death, or to the end of follow-up. In the Cox regression, the independent variables were age, gender (male/female), early or late

Table 1 Baseline characteristics of the 587 patients in general practice with iron deficiency anaemia (IDA)

	IDA cohort n=587 (100%)	Early endoscopic evaluation n=211 (36%)	No early endoscopic evaluation n=376 (64%)	P value	Reference value
Age in years	68 (50–101)	69 (50–95)	66 (50–101)	0.207	
Gender				<0.001	
Male	212 (36%)	100 (47%)	112 (30%)		
Female	375 (64%)	111 (53%)	264 (70%)		
Haemoglobin, g/dL					
Male	12.3 (5.3–13.5)	10.6 (5.3–13.5)	12.8 (5.8–13.5)	<0.001	13.7–17.7
Female	10.8 (4.0–11.9)	10.2 (4.5–11.9)	11.1 (4.0–11.9)	<0.001	12.1–16.1
MCV, fL	82 (55–102)	79 (55–96)	83 (58–102)	<0.001	82–98
ESR, mm/h*	20 (2–120)	23 (4–118)	20 (2–120)	0.015	<35
C reactive protein, mg/L†	<5 (<5–144)	<5 (<5–71)	<5 (<5–144)	<0.001	<10
Ferritin, µg/L					
Male	10 (2–24)	9 (2–24)	11 (2–23)	<0.001	25–250
Female	7 (1–19)	7 (1–19)	8 (1–19)	0.055	20–250
Iron saturation, %‡	7 (2–55)	6 (2–22)	7 (2–55)	<0.001	20–60
Serum iron, µmol/L					
Male	6.2 (1.9–22.1)	4.5 (1.9–22.1)	7.4 (2.0–21.0)	<0.001	14–28
Female	5.0 (1.6–42.5)	3.9 (1.9–17.6)	5.3 (1.6–42.5)	0.001	10–25
Transferrin, g/L	3.36 (1.97–4.74)	3.38 (2.38–4.74)	3.34 (1.97–4.74)	0.043	2.00–3.60

*Missing values n=157.
†Missing values n=3.
‡Missing values n=38. Values are median (range). Measured laboratory values are at point of IDA diagnosis. The p value compares the baseline characteristic of patients with and those without an early endoscopic evaluation.
ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume.

CRC diagnosis, and stage of CRC (I, II, III, IV or unknown stage). The proportional-hazards assumption was tested by including interactions of independent variables and follow-up time in a Cox regression with time-dependent covariates. The location of CRC was compared between patients with an early or late diagnosis using a χ^2 test.

Data were analysed using SPSS for Windows, V.24. All statistical tests were two-sided and a p value <0.05 was considered statistically significant.

RESULTS
Cohort description
Between 1 February 2007 and 1 February 2016, a total of 587 patients aged ≥50 years with a new laboratory diagnosis of IDA were included, consisting of 212 (36%) men and 375 (64%) women. The median haemoglobin concentration was 12.3 (range, 5.3–13.5) g/dL and 10.8 (range, 4.0–11.9) g/dL and the median ferritin level was 10 (range, 2–24) µg/L and 7 (range, 1–19) µg/L for men and women, respectively. Basic characteristics (age, gender and laboratory values at point of IDA diagnosis) are presented in table 1.

Early endoscopic evaluation
Of all 587 general practice patients diagnosed with IDA, 211 (36%) had an early endoscopic evaluation, consisting of 45 (21%) colonoscopies, 154 (73%) full endoscopies and 12 (6%) gastroscopies. The median time for early endoscopic evaluation was 5 weeks (IQR 2–7 weeks). Patients receiving endoscopic evaluation versus those who did not receive early endoscopy were significantly different in terms of laboratory values and gender, but not in age (table 1). In 115 (55%) of the 211 patients, who received an early endoscopic evaluation, a GI-related diagnosis could be made.

IDA-related causes
Median time of follow-up for the entire cohort was 4.6 (IQR 2.6–7.0) years, during which an IDA-related cause could be made in 234 (40%) patients, consisting of 190 (32%) early causes and 44 (8%) late causes. However, in 353 patients (60%), no IDA-related cause was found during the entire follow-up period (figure 1). In 18 patients, more than one IDA-related cause was established resulting in 254 in-hospital registered causes of IDA (table 2). Other causes (34%) and benign GI causes (35%) were the most common categories. An early
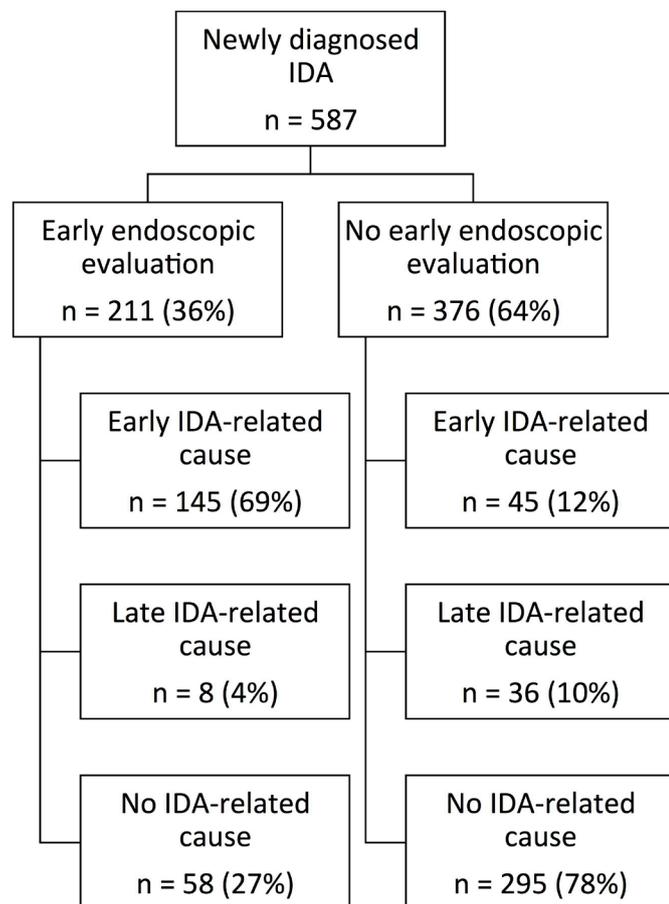
Figure 1 Flowchart of the cohort with iron deficiency anaemia (IDA).

malignant cause for IDA was found in 59 patients (10%), of whom 49 had CRC. An additional 21 patients (4%), of whom four received an early endoscopic evaluation without abnormalities, were diagnosed with a malignant cause for IDA later on, consisting of 12 CRC.

Colorectal cancer
Of the 587 patients with IDA, 61 (10%) received a diagnosis of CRC during the study period (ie, 49 early and 12 late CRC diagnoses). In four patients, two separate tumours were diagnosed in the colon, and one patient presented with three different colon tumour locations. The CRC was right sided in 41 of 49 patients (84%) with an early diagnosis and in 8 of 12 patients (67%) with a late CRC diagnosis (p=0.184). Older age (OR 1.03; 95% CI 1.00 to 1.05), male gender (OR 2.12; 95% CI 1.18 to 3.79), lower haemoglobin concentrations (OR 1.27; 95% CI 1.08 to 2.49) and microcytic anaemia (OR 2.63; 95% CI 1.30 to 5.31) showed a significant association with CRC diagnosis (table 3).

The 61 patients with CRC diagnosis had a median follow-up of 4 years (range, 5 weeks to 10.7 years) from the moment of CRC diagnosis; during this period, 19 patients (31%) died. No significant violations of the proportional-hazards assumption of the Cox regression were detected in patients with CRC diagnosis. After correction for age,

gender and the TNM classification at the moment of CRC diagnosis, mortality risk was lower, but not significant, in the group of patients with an early CRC diagnosis (HR 0.30; 95% CI 0.09 to 1.02) (table 4).

DISCUSSION
Principal findings
In this large retrospective cohort study, an early endoscopic evaluation was done in a third of newly diagnosed patients with IDA, and these patients were more often male gender and had more severe laboratory abnormalities. The most common category if IDA-related causes established in this cohort were benign GI causes (35%). However, in the majority of patients (60%), no in-hospital IDA-related cause could be found during the median follow-up of 4.6 years. In addition, there were 8% early and 2% late CRC diagnoses. A CRC diagnosis was associated with older age, male gender, lower haemoglobin concentrations and microcytic anaemia. In addition, some evidence was found for increased survival in patients with IDA with an early CRC diagnosis adjusted for age, gender and TNM classification, but this association was not statistically significant.

Strengths and limitations of this study
Inclusion of patients in our cohort occurred after an anaemia diagnosis was established in the laboratory. The GPs' reason for laboratory testing was not known. It could have been either specific symptoms in a patient or routine testing for other indications. Still, a diagnostic work-up should start after an IDA is established according to the Dutch GP guideline. This is a well-defined moment in practice.

The participating GPs usually referred their patients to the associated hospital; however, some patients may have preferred referral to a different hospital resulting in an underestimation of the amount of endoscopic evaluations and IDA-related causes. However, since almost all patients in our cohort had an electronic record in the associated hospital, this limits the possibility of missed cases. Furthermore, the two nearest hospitals, both outside the Dordrecht region, had a longer waiting time for endoscopic evaluation compared with the fast-track places we offered the participating GPs. The fast-track places that were offered to the participating GPs during the study period might have led to an increase in early endoscopic evaluations and thereby an increased early IDA-related diagnoses. However, the rate of early endoscopic evaluation was comparable with existing literature and therefore the fast-track places very likely did not affect the study results.[6 7]

Another aspect that we were unable to monitor was the possibility of consciously refraining from endoscopic evaluation by the GP and/or the patient. One study found that endoscopic evaluation in patients aged ≥85 years is safe and enables a high rate of diagnoses and therapeutic modifications.[12] Nevertheless, comorbidities, age

Table 2 Iron deficiency anaemia (IDA)–related causes

| | Early endoscopic evaluation | | No early endoscopic evaluation | | |
	Early cause	Late cause	Early cause	Late cause	Total
GI malignancies					**74 (29%)**
Colon	48	1	1*	11	
Gastric	3			1	
Oesophagus	2				
Small bowel	1				
Strong suspicion of GI malignancy		1	1	4	
Other malignancies					**6 (2%)**
Urothelial		1	1	1	
GI metastasis of a non-GI primary tumour	2	1			
Other causes†	**36**	**3**	**43**	**4**	**86 (34%)**
Benign GI causes					**88 (35%)**
Angiodysplasia	16	2		5	
Gastritis/erosions	19	1		4	
Ulcers‡	10				
Haemorrhoids	4		2		
Polyps >1 cm	13	1		3	
Coeliac/Crohn/ulcerative colitis	4			3	
Radiation proctitis	1				
Total no of IDA-related causes	**159**	**11**	**48**	**36**	**254 (100%)**

*Diagnosis made on the basis of surgery for colon perforation.
†Other causes included repetitive blood donation, hypermenorrhoea, low-iron diet and severe epistaxis.
‡Including gastric ulcers as a result of *Helicobacter pylori* infection.
GI, gastrointestinal.

and limited life expectancy may still be reasons to refrain from endoscopic evaluation. We did not collect data on other diagnostic investigations and/or endoscopic evaluations performed more than 18 weeks after IDA diagnosis. However, we did document all IDA-related diagnoses made in-hospital during follow-up and some diagnoses, especially non-GI related, were made by means of other investigations than endoscopic evaluation.

It is important to realise that, in the present study, all diagnoses made during follow-up were registered in-hospital. A limitation is that the IDA-related causes found by the GP are not registered and, therefore, might be underestimated. However, the most relevant IDA-related causes, mainly GI-tract related, require in-hospital investigations, which makes the incidence of these causes found in our cohort reliable. In addition, the most worrying outcome is IDA-related malignancy; therefore, we registered these diagnoses from the Netherlands Comprehensive Cancer Organization. This organisation covers the entire Dutch population regarding cancer registrations, and therefore this ensures full representation of IDA-related malignancies. Finally, the survival analysis provided some evidence for an association between early CRC diagnosis and decreased mortality; however, lead-time bias may still be present. A more detailed analysis with a larger cohort is required to confirm our hypothesis of increased overall survival in patients with early CRC diagnosis.

Comparison with existing literature
In the present study, a third of newly diagnosed patients with IDA in general practice received early endoscopic evaluation; this is in line with others.[6 7] Patients with IDA receiving early endoscopic evaluation are more often men. In the Netherlands, CRC has a higher incidence among men compared with women.[13] This might have stimulated GPs to perform more endoscopies in men. In addition, if women presented with hypermenorrhea, GPs may not have made an initial endoscopic evaluation or a hospital referral. Furthermore, patients with IDA with early endoscopic evaluation had more severe laboratory abnormalities. Some GPs will have a different policy in case of marginal anaemia, that is, these patients might first be treated with iron supplementation before GPs decide to refer for endoscopic evaluation.

This study shows, for the first time, that a small proportion of the IDA-related causes is made by means of investigations other than endoscopy. These diagnoses were mainly non-GI causes, including blood donation and

Table 3 Logistic regression analysis comparing patients with olorectal cancer (CRC) to those without CRC

	CRC diagnosis n=61	No CRC diagnosis n=526	Univariable analysis		Multivariable analysis	
			OR (95% CI)	P value	OR (95% CI)	P value
Age, median (range)	75 (50–89)	66 (50–101)	1.03 (1.01 to 1.03)	**0.002**	1.03 (1.00 to 1.05)	**0.027**
Gender						
Male	28 (5%)	184 (31%)	Reference group		2.12 (1.18 to 3.79)	**0.012**
Female	33 (6%)	342 (58%)	0.63 (0.37 to 1.08)	0.095	Reference group	
Haemoglobin (g/dL)*, median (range)	9.3 (4.5–12.9)	11.3 (4.0–13.5)	1.41 (1.23 to 1.58)	**<0.001**	1.27 (1.08 to 1.49)	**0.007**
Ferritin (µg/L)*, median (range)	7 (1–22)	9 (1–24)	0.94 (0.89 to 1.00)	0.052	1.01 (0.93 to 1.09)	0.844
MCV category						
Normocytic/ macrocytic† (MCV 80–102 fL)	20 (3%)	349 (60%)	Reference group		Reference group	
Microcytic (MCV <80 fL)	41 (7%)	177 (30%)	4.04 (2.30 to 7.11)	**<0.001**	2.63 (1.30 to 5.31)	**0.007**

*Analysed as continuous variables. ORs should be interpreted as the effect of 1-unit decrease in concentration for haemoglobin and 1-unit increase in concentration of ferritin.
†Three patients had an MCV value >100 fL at the time of IDA diagnosis.
IDA, iron deficiency anaemia; MCV, mean corpuscular volume.

hypermenorrhoea (despite applying a 50-year cut-off to prevent hypermenorrhoea as predominant cause of IDA). Most of these IDA-related diagnoses were made in the subgroup of patients who received early endoscopic evaluation.

The majority of patients who did not receive early endoscopic evaluation did not have an IDA-related cause defined during the extended follow-up. To our knowledge, this has not been described in detail before.

Although the majority of patients with IDA without endoscopic evaluation have no IDA-related diagnosis during follow-up, a third of the patients with a late IDA-related cause were diagnosed with a GI malignancy, and an additional 11% had a strong suspicion of GI malignancy.

Table 4 Cox proportional-hazards survival analysis for patients diagnosed with colorectal cancer

	Deceased n=19 (31%)	Alive n=42 (69%)	Univariable analysis		Multivariable analysis	
			HR (95% CI)	P value	HR (95% CI)	P value
Age, median (range)	78 (50–87)	73 (52–89)	1.06 (1.00 to 1.12)	0.063	1.10 (1.02 to 1.19)	**0.017**
Gender						
Male	8 (13%)	20 (33%)	0.77 (0.31 to 1.93)	0.582	1.58 (0.57 to 4.36)	0.377
Female	11 (18%)	22 (36%)	Reference group		Reference group	
Time to diagnosis						
Early	13 (21%)	36 (59%)	0.32 (0.12 to 0.87)	**0.026**	0.30 (0.09 to 1.02)	0.053
Late	6 (10%)	6 (10%)	Reference group		Reference group	
TNM stage				**0.003**		**<0.001**
I	1 (2%)	11 (18%)	Reference group		Reference group	
II	3 (5%)	13 (21%)	3.23 (0.32 to 32.97)	0.323	3.47 (0.33 to 36.75)	0.302
III	5 (8%)	12 (20%)	4.16 (0.48 to 35.97)	0.195	5.35 (0.57 to 49.94)	0.141
IV	10 (16%)	5 (8%)	24.31 (2.78 to 212.41)	**0.004**	80.15 (7.47 to 859.67)	**<0.001**
Unknown	–	1 (2%)	NA	NA	NA	NA

NA, not applicable.

These diagnoses might represent missed opportunities at the time of IDA diagnosis and should alert GPs in their aim to unravel the underlying cause of IDA. Based on our study results, omitting early endoscopic evaluation in patients with IDA is not safe. As also has been described in several guidelines before, endoscopic evaluation should be performed in all patients aged 50 years and older with a new diagnosis of IDA.[9 11]

We observed 8% of CRC diagnoses within 18 weeks of finding IDA in our cohort, whereas 2% of patients received this diagnosis during follow-up. Comparison of these results with previous data on patients with IDA in general practice revealed a slight increase in early diagnoses and a decrease in delayed diagnoses.[6 7] This might be due to the comment that was added to the laboratory results alerting GPs to an endoscopic evaluation in patients with IDA. Furthermore, we offered participating GPs fast-track places for endoscopic evaluation, which may have led to earlier endoscopic evaluations.

Although the association between early versus late CRC diagnosis and mortality was not statistically significant in our data, the point estimate and its 95% CI were in line with previous studies in which early colonoscopy significantly increased overall survival in patients with CRC diagnosis.[14 15] The estimated association was adjusted for the TNM classification of the tumour at the time of diagnosis. Apparently, early-stage disease is important for better survival rates, and early CRC diagnosis, regardless of TNM classification, is too. This might be due to a better clinical condition at the moment of CRC diagnosis and start of treatment.

Finally, it was observed that in patients with IDA most early CRC diagnoses were right sided (84%) possibly caused by the absence of GI complaints such as rectal bleeding.[16] This lack of complaints may allow tumours to bleed unnoticed for a longer time, resulting in a diagnosis of IDA before the CRC is found. During our study period, 34% of all CRC diagnoses in the whole Dutch population were right sided according to the Netherlands Comprehensive Cancer Organization (data not shown).[10] Our results support the suspicion that right-sided tumours are more frequently encountered in patients with IDA.[9 16]

Implications for clinicians

The majority of patients with IDA in general practice do not have an IDA-related cause defined during extended follow-up. However, endoscopic evaluation for all patients with IDA is justified since these patients are at increased risk for, in particular, right-sided CRC. Importantly, patients with IDA in general practice with a delayed diagnosis of CRC might risk decreased overall survival.

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