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Original Article

Recommendations for endoscopic surveillance after esophageal atresia repair in adults

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SUMMARY. **Background: Endoscopic surveillance of adults with esophageal atresia is advocated, but the optimal surveillance strategy remains uncertain. This study aimed to provide recommendations on appropriate starting age and intervals of endoscopic surveillance in adults with esophageal atresia. Methods: Participants underwent standardized upper endoscopies with biopsies. Surveillance intervals of 3–5 years were applied, depending on age and histopathological results. Patient's age and time to development of (pre)malignant lesions were calculated. Results: A total of 271 patients with esophageal atresia (55% male; median age at baseline endoscopy 26.7 (range 15.6–68.5) years; colon interposition $n = 17$) were included. Barrett's esophagus was found in 19 (7%) patients (median age 32.3 (17.8–56.0) years at diagnosis). Youngest patient with a clinically relevant Barrett's esophagus was 20.9 years. Follow-up endoscopies were performed in 108 patients (40%; median follow-up time 4.6 years). During surveillance, four patients developed Barrett's esophagus but no dysplasia or cancer was found. One 45-year-old woman with a colon interposition developed an adenoma with high-grade dysplasia which was radically removed. Two new cases of esophageal carcinoma were diagnosed in patients (55 and 66 years old) who were not under surveillance. One of them had been curatively treated for esophageal carcinoma 13 years ago. Conclusions: This study shows that endoscopic screening of patients with esophageal atresia, including those with a colon interposition, can be started at 20 years of age. Up to the age of 40 years a surveillance interval of 10 years appeared to be safe. Endoscopic surveillance may also be warranted for patients after curative esophageal cancer treatment.**

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INTRODUCTION

The high prevalence of gastroesophageal reflux (GER) and esophageal stasis of food and saliva in patients born with esophageal atresia (EA) has raised concerns about a possible increased risk of Barrett's esophagus (BE) and esophageal carcinoma.[1] BE is a premalignant lesion in which the squamous epithelium of the distal esophagus is replaced by gastric columnar epithelium containing goblet cells, which can progress into esophageal adenocarcinoma (EAC).[2] Multiple cases of esophageal carcinoma, both EAC and esophageal squamous cell carcinoma (ESCC), have been described in patients with EA at a relatively young age.[1] Given these concerns, endoscopic surveillance has been recommended in the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)—North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guideline.[3] These recommendations are based on expert opinions, since outcomes of standardized endoscopic surveillance programs in patients with EA are lacking.

In 2013, a prospective screening and surveillance program with upper endoscopies for adults with EA was initiated in our hospital. The initial screening of 151 patients revealed a 4-times higher prevalence of BE compared to the general population (6.6% vs. 1.6%) and at a much younger age (median age 34 years vs. 60 years).[4] This is in line with previous literature, in which a prevalence up to 12.5% has been reported.[1]

However, the optimal surveillance strategy remains unknown. The 5-year survival of esophageal carcinoma is known to improve to 90–95% when detected at an early stage.[5] Since no data exists on neoplastic progression times for both EAC and ESCC, relatively short surveillance intervals may be warranted to be on the safe site. On the other hand, endoscopic surveillance may cause an unnecessary burden—both physically and psychologically—for those not at risk, impact on endoscopic resources, and add substantial costs to the health care system. So far, no specific risk factors have been identified in this population, and longitudinal cohort studies on the yield of surveillance in this population are lacking.

The aim of this study was to assess the yield of an endoscopic surveillance program in adult patients with EA, and to assess patients' age and time of development of a (pre)malignant disease. These data may provide guidance in recommendations with regard to starting age and chosen interval of endoscopic surveillance programs for adults with EA.

MATERIALS AND METHODS

Study population

Details about the design of our screening and surveillance program have been described previously.[4] In short, since 2013 all patients with EA who are enrolled in the longitudinal follow-up program for children born with congenital anomalies in our hospital,[6] are being routinely transferred to the Gastroenterology Department for further follow-up after the age of 17 years. From 2019 onwards, we have been expanding our cohort with patients from other Dutch university hospitals. Data were collected until January 2021. Endoscopies were performed both in our center and in general hospitals. Over 95% of the endoscopies were performed under conscious sedation (midazolam and fentanyl). The Institutional Review Board waived the need for formal ethical approval (MEC-2015-093).

Data collection

The following data were retrieved from the electronic patient records: date of birth, gender, type of EA according to Gross,[7] type of primary surgery, and relevant medical history including dilatations and prior diagnosis of gastroesophageal reflux disease (GERD) and/or BE. GERD was defined as the need for fundoplication surgery, pathological reflux established by pH monitoring, or signs of reflux esophagitis at a previous upper endoscopy.[8] Data on the presence of gastrointestinal symptoms, and use of medication, tobacco and alcohol were collected. Dysphagia was graded according to Mellow and Pinkas.[9] GER complaints were defined as chest pain, pyrosis, or regurgitation.

Endoscopies were performed according to a standardized protocol with white light and—in case of suspicion of BE—with narrow-band imaging.[4] Esophagitis and BE were graded according to the Los Angeles and Prague criteria, respectively.[10,11] At every endoscopy, four random biopsies were taken from the esophagus right above the gastroesophageal junction or above the proximal anastomosis (in case of bowel interposition). In case of BE, biopsies were taken according to the Seattle protocol.[12] In patients of 25 years and older, Lugol staining was applied to detect early squamous lesions.[13] All biopsies were reviewed by a gastrointestinal pathologist experienced with BE. Presence of esophagitis (including the number of eosinophils per high-power field), metaplasia and dysplasia were scored. Following the American College of Gastroenterology (ACG) guidelines, BE was defined as columnar metaplasia with the presence

of goblet cells.[2] Short segment BE was defined as <3 cm, and long segment BE as ≥3 cm. Endoscopic and histologic findings were classified according to the most severe abnormality found.

In case of BE, surveillance intervals of the ACG guidelines were followed.[2] In absence of BE, an interval of 5 years was applied for patients up to 30 years old, and of 3 years for patients ≥30 years old.[4]

Statistical analysis

Data are presented as number (%) or median (interquartile range). The yield of surveillance between the baseline endoscopies and follow-up endoscopies was determined by descriptive statistics. Baseline endoscopy was defined as the first endoscopy within the surveillance program. The patient's age at development of a premalignant lesion as well as the time to development of a premalignant lesion were calculated. The number of patient-years was the sum of the follow-up time between the baseline endoscopy and the last surveillance endoscopy of all patients who underwent at least one follow-up endoscopy. Derived from previous research,[14] the progression rate of BE development was calculated by dividing the proportion of progressive cases by the median follow-up time.

Clinical characteristics of patients without metaplasia were compared with patients with columnar metaplasia and with patients with BE (columnar metaplasia with presence of goblet cells), using Mann–Whitney *U* tests. Multivariable logistic mixed regression analysis was used to identify potential predictors of metaplasia. Columnar metaplasia and BE were selected as dependent variables, whereas age, history of GERD, gender, hiatus hernia, (prior) smoking, and (prior) use of alcohol were selected as independent variables. Cases with missing covariate values were excluded. Results were summarized as odds ratios (OR) and 95% confidence intervals (CI). Statistical analyses were performed using SPSS V.25.0 (IBM, Chicago, IL, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), with a two-tailed significance level of $P < 0.05$.

RESULTS

Patient characteristics

A total of 271 patients (55% male) participated in our surveillance program. Baseline characteristics are depicted in Table 1. The median age of these 271 patients was 26.7 (19.1–38.4) years at baseline endoscopy, ranging from 15.6 to 68.5 years. Of them, 96 patients underwent one follow-up endoscopy at a median age of 31.3 (24.1–40.3) years, after a median interval of 4.4 years. Twelve patients underwent a total of two follow-up endoscopies, with the last endoscopy at a median age of 30.9 (24.4–42.3) years, after a median interval of 2.7 years.

Yield of surveillance endoscopy

In total, 391 endoscopies have been performed in 271 patients since the start of the surveillance program. Endoscopic esophagitis was observed in 24 patients (9%). Columnar-lined esophagus was found in 73 patients (27%), with a circumferential extent of 0–5 cm, and a maximum extent of 0–6 cm. A hiatus hernia was present in 183 (68%) patients, with a length ranging from 1 to 10 cm. An inlet patch (ectopic gastric mucosa) was observed in 17 (6%) patients. No dysplastic squamous lesions were found.

Of the 73 patients with columnar-lined esophagus, histopathology revealed columnar metaplasia in 38 patients (14% of total cohort). Nineteen (50%) of them were male, and patients had a median age of 28.3 (22.8–33.6) years. BE was present in 19 patients (7% of total cohort), of whom 14 (74%) were male, and patients had a median age of 36.9 (24.9–51.8) years. No cases of dysplasia were found.

Of the remaining 16 patients with columnar-lined esophagus, histopathology showed either normal mucosa ($n = 1$) or active esophagitis (presence of neutrophil granulocytes, $n = 13$), or no biopsies were taken ($n = 2$). Biopsies were lacking in 22 patients during surveillance endoscopy, due to discomfort of the patient or because of a protocol violation. Endoscopic and histologic findings are shown in Table 2.

Progression of lesions

Out of the 271 patients, 108 (40%) underwent at least one follow-up endoscopy. Table 3 shows progression of findings between the baseline and the last surveillance endoscopy. Of the 71 patients with normal mucosa at baseline, nine (13%) patients developed columnar-lined esophagus during surveillance. In one of them, histopathology confirmed BE. Additionally, BE was diagnosed in 2 out of 17 patients with columnar metaplasia at baseline. No progression to dysplasia or cancer was found in any of these patients. A total of 84 out of 95 patients (88%) did not show any progression between the endoscopies.

Time to premalignant development

Median follow-up time between the baseline endoscopy and the last surveillance endoscopy was 4.6 years, ranging from 2.0 to 7.8 years, resulting in a total of 495 patient-years. Out of the 19 patients with BE (Table 4), two had a history of BE before the start of the surveillance program and 15 were diagnosed at baseline. The median age at first diagnosis of BE was 32.3 (24.4–47.7) years. The youngest age at

Table 1 Patient characteristics of 271 participants of surveillance program

	n (%)
Male/female	150 (55.4)/121 (44.5)
Type of EA[24]	
Type A	26 (9.6)
Type B	1 (0.4)
Type C	213 (78.6)
Type D	5 (1.8)
Type E	5 (1.8)
Unknown	21 (7.7)
Type of surgery	
Primary anastomosis[A]	212 (78.2)
Delayed primary anastomosis[B]	21 (7.7)
Esophageal replacement[C]	23 (8.5)
Resection fistula	5 (1.8)
Unknown	10 (3.7)
History of ≥ 1 dilatation of esophageal stenosis	144 (53.1)
History of fundoplication[D]	54 (19.9)
Age in years, at time of first surveillance endoscopy; median (IQR)	26.7 (19.1–38.4)
Body mass index (kg/m^2); median (IQR)	22.4 (20.1–24.7)
Antireflux medication	
Yes, daily	37 (13.7)
Yes, when needed	7 (2.6)
No	213 (78.6)
Unknown	14 (5.2)
Tobacco smoking	
Yes	42 (15.5)
Former smoker, quit >2 years	39 (14.4)
No	179 (66.1)
Unknown	11 (4.1)
Alcohol consumption	
Yes, ≤7 units/week	156 (57.6)
Yes, >8 units/week	24 (8.9)
No	75 (27.7)
Unknown	16 (5.9)
Dysphagia score[25]	
Grade 0	199 (73.4)
Grade 1	53 (19.6)
Grade 2	2 (0.7)
Grade 3	2 (0.7)
Unknown	15 (5.5)
Gastroesophageal reflux complaints[E]	130 (48.0)

Data are presented as *n* (%) or median (interquartile range, IQR). EA, esophageal atresia.
[A]Livaditis myotomy ($n = 7$).
[B]Livaditis myotomy ($n = 7$), ten Cate procedure ($n = 1$), Rehbein procedure ($n = 1$).
[C]gastric pull up ($n = 2$), colon interposition ($n = 17$), jejunal interposition ($n = 3$), ileocaecal interposition ($n = 1$).
[D]Nissen fundoplication ($n = 49$), Thal fundoplication ($n = 2$), unspecified ($n = 3$).
[E]Defined as chest pain, pyrosis, or regurgitation.

which a clinically relevant BE (≥1 cm or presence of dysplasia, requiring surveillance[2]) was diagnosed was 20.9 years. This was a female without GER or dysphagia complaints.

Progression to BE within the surveillance program occurred in four patients (4% of the patients with ≥1 follow-up endoscopy) at a median age of 39.0 (24.4–54.1) years. Clinical details are depicted in Table 4. These four patients equal one case of progression to BE per 124 patient-years. Given the median follow-up time of 4.6 years, the progression rate of BE development was 0.8% per year.

Predictors of metaplasia

Compared to patients without metaplasia, patients with BE more often had an history of GERD ($P = 0.028$), were older ($P = 0.015$) and more often had a hiatus hernia ($P = 0.028$) at time of diagnosis. Patients with columnar metaplasia more often had a hiatus hernia ($P = 0.035$) compared to patients without metaplasia at time of diagnosis. See Table 5.

Multivariable logistic regression analysis did not show any significant associations between columnar metaplasia and the included variables (age, history of GERD, gender, hiatus hernia, (prior) smoking, and (prior) use of alcohol). Due to the limited number of BE cases, regression analysis was only possible for two variables (age and history of GERD). Both were associated with an increased risk of BE development (OR 1.07, 95% CI 1.01–1.12 and OR 4.16, 95% CI 1.24–13.91, respectively). See Table 6.

Esophageal carcinoma

Since the start of our surveillance program, two new cases of esophageal carcinoma were diagnosed in patients with EA at our hospital. One patient

Table 2 Endoscopic and histologic results from the last surveillance endoscopy in adults born with esophageal atresia ($n = 271$)

		n (%)
Follow-up	Number of FU visits	
	1	163 (60.1)
	2	96 (35.4)
	3	12 (4.4)
	Age in years at last FU visit; median (IQR)	29.4 (22.5–38.9)
	<20 years	44 (16.2)
	20–30 years	93 (34.3)
	30–40 years	70 (25.8)
	40–50 years	40 (14.8)
	>50 years	24 (8.9)
	History of GERD	122 (45.0)
	History of Barrett's esophagus	10 (3.7)
Endoscopic findings	Normal esophagus	174 (64.2)
	Endoscopic esophagitis[A]	
	Grade A	21 (7.7)
	Grade B	2 (0.7)
	Grade unknown[B]	1 (0.4)
	Extension of gastric epithelium above the gastroesophageal junction[C]	
	With esophagitis	19 (7.0)
	Without esophagitis	54 (19.9)
	Secondary findings	
	Hiatus hernia[D]	183 (67.5)
	Inlet patch	17 (6.3)
Histologic findings	Normal mucosa	82 (30.3)
	Esophagitis	
	Mild	86 (31.7)
	Moderate	14 (5.2)
	Erosive	3 (1.1)
	Ulcerative	2 (0.7)
	Eosinophilic	5 (1.8)
	Columnar metaplasia	
	With esophagitis	25 (9.2)
	Without esophagitis	13 (4.8)
	Barrett's esophagus	
	With esophagitis	15 (5.5)
	Without esophagitis	4 (1.5)
	No biopsy taken[E]	22 (8.1)

FU, follow-up; GERD, gastroesophageal reflux disease; IQR, interquartile range.
[A]According to the Los Angeles classification.[10]
[B]Endoscopy performed in general hospital, grade was missing in endoscopy report.
[C]Short segment <3 cm ($n = 63$), long segment ≥3 cm ($n = 10$). Circumferential extent ranges 0–5 cm, maximum extent ranges 0–6 cm.
[D]Median length 2 (range 1–10) cm.
[E]Macroscopic findings: normal mucosa ($n = 18$), esophagitis ($n = 2$) and gastric epithelium above the gastroesophageal junction ($n = 2$).

was a 68-year-old female with ESCC, who was not included in our endoscopic surveillance program. She is currently being treated with chemoradiotherapy. The other case was a tumor-recurrence in one of the previously described ESCC patients.[4] He was treated with curative intent by chemoradiotherapy for an unresectable ESCC at the age of 42 years. After oncological discharge—and start of our surveillance program in 2013—he was invited for endoscopic surveillance, but refused. At the age of 55 years, he returned with complaints of dysphagia, and endoscopy revealed a recurrent ESCC. He is currently scheduled for a laryngopharyngoesophagectomy with esophageal replacement by a jejunal interposition. This is the second patient with EA in our hospital in whom the esophageal cancer has reoccurred more than 10 years after curative oncological treatment.[4]

Besides these two patients with esophageal carcinoma, a tubular adenoma with high-grade dysplasia was detected in a 45-year-old woman with a colon interposition, which was radically removed by endoscopy. She will undergo a surveillance endoscopy in 3 years. This is the second patient who developed a neoplasm of the colon interposition. Earlier, we described a 48-year-old male with an adenocarcinoma in his colon interposition.[4]

DISCUSSION

This is the first prospective cohort study reporting on the yield of standardized endoscopic surveillance in adult patients with EA. We confirmed a 5-fold higher prevalence of BE in these patients compared to the general population (7% vs. 1.3–1.6%).[15] Four (4%) new cases of short segment BE were found during follow-up. Overall, patients had a median age of 32.3 years at first diagnosis of BE, and the youngest

Table 3 Progression in terms of endoscopic (A, upper table) and histologic (B, lower table) results at first surveillance endoscopy (baseline) compared with the last performed surveillance endoscopy (follow-up) ($n = 108$)

	Baseline	No. of patients	Surveillance						
			Normal	Esophagitis		Gastric epithelium above GEJ[A]	Stable	Progression	Unknown
A	Normal	71	57	5		9	57 (80%)	14 (20%)	
	Esophagitis	11	6	1		4	7 (64%)	4 (36%)	
	Gastric epithelium above GEJ [A]	26	–	1		25	24 (100%)	–	
			Normal[B]	Columnar metaplasia	BE[C]	No biopsy			
B	Normal[B]	81	64	7	1	9	64 (79%)	8 (10%)	9 (11%)
	Columnar metaplasia	17	–	11	2	4	11 (65%)	2 (12%)	4 (24%)
	BE	9	–	–	9	–	9 (100%)	–	
	No biopsy	1	–	–	1	–	–	–	1 (100%)

Gray color indicates patens with the same endoscopic or histologic result at both baseline and follow-up. BE, Barrett's esophagus; GEJ, gastroesophageal junction.
[A]This is a macroscopic finding, which means that the histology could show either columnar metaplasia or Barrett's esophagus.
[B]This includes both normal mucosa and esophagitis.
[C]The clinical details of the four patients that developed BE during surveillance are depicted in Table 4.

Table 4 Summary of the patients with BE ($n = 19$)

Case	Age at diagnosis	Gender	BMI	Dysphagia	GER complaints	Alcohol	Antireflux medication	Prague criteria	FU visit	Baseline result	FU interval (years)
1	17.8	Male	20.1	Grade 0	No	Yes, ≤7 units/week	No	C0M0.5	Baseline		
2	20.9	Female	Unknown	Grade 0	No	Yes, ≤7 units/week	No	C0M2	Baseline		
3	22.0	Male	21.6	Grade 0	Yes	No	Daily	C2M0	Baseline		
4	23.4	Male	21.5	Grade 0	No	Yes, ≤7 units/week	No	C2M6	Baseline		
5	24.2	Male	22.6	Grade 0	No	Yes, >8 units/week	No	C0M0.5	FU 1	Normal	5.9
6	24.5	Female	18.2	Grade 0	Yes	No	No	C0M2	FU 2	Columnar metaplasia	6.3 [B]
7	25.3	Female	24.5	Grade 0	No	Yes, ≤7 units/week	No	C1M2	Baseline		
8	30.6	Male	16.2	Grade 0	No	No	Daily	C0M0.5	Baseline		
9	31.8	Male	Unknown	Grade 0	No	Yes, ≤7 units/week	No	C1M1	Baseline		
10	32.3	Male	Unknown	Grade 1	Yes	Yes, ≤7 units/week	No	C2M3	Baseline		
11	38.6	Female	38.8	Grade 1	Yes	Yes, ≤7 units/week	Daily	C0M2	Baseline		
12	39.3	Female	23.4	Grade 1	Yes	Yes, ≤7 units/week	Daily	C5M5	Baseline		
13	44.9	Male	23.4	Grade 0	Yes	Yes, ≤7 units/week	Daily	C0M2	Baseline		
14	50.2	Male	26.6	Grade 0	No	Yes, ≤7 units/week	Daily	C0M0.5	Baseline		
15	52.7 [A]	Male	17.6	Grade 1	Yes	Unknown	Daily	C1M3	Baseline		
16	53.5	Male	23.1	Grade 0	Yes	No	Daily	C1M1	FU 1	No biopsy	3.3
17	54.3	Male	23.6	Grade 0	Yes	No	Daily	C0M1	Baseline		
18	54.6	Male	Unknown	Grade 1	No	No	Daily	C0M0.5	FU 2	Columnar metaplasia	7.2 [B]
19	58.3 [A]	Male	24.7	Unknown	No	Yes, ≤7 units/week	No	C3M3	Baseline		

BMI, body mass index; FU, follow-up; GER, gastroesophageal reflux.
[A] These patients were already diagnosed with BE before the start of the surveillance program, respectively at 45.3 and 56.0 years old.
[B] These patients underwent two follow-up surveillance endoscopies. Interval with previous endoscopy respectively 5.3 and 3.0 years, both showing columnar metaplasia.

patient with a clinically relevant BE was diagnosed at the age of 20.9 years. No dysplasia nor cancer was found in any of the patients who participated in the surveillance program. In 1 of the 17 patients with a colon interposition a tubular adenoma with high-grade dysplasia was found.

Based on the data we recommend endoscopic surveillance of all adults with EA, including those with a colon interposition. It seems safe to start surveillance at the age of 20 years and to extent the interval to 10 years up to the age of 40 years, since the youngest patient with a clinically relevant BE was 20.9 years old and no dysplasia nor malignances were detected in patients younger than 40 years. In addition, in patients who have developed esophageal cancer and have been treated with curative intent

Table 5 Clinical characteristics at time of the last surveillance endoscopy in adults born with esophageal atresia (EA), participating in our screening and surveillance program

	No metaplasia ($n = 192$)	Columnar metaplasia (including BE) ($n = 57$)		Barrett's esophagus ($n = 19$)	
			P-value[A]		*P-value*[B]
Male	109 (56.8)	33 (57.9)	0.502	14 (73.7)	0.222
EA type A[C]	15 (7.8)	4 (7.0)	0.552	2 (10.5)	0.655
Esophageal replacement	14 (7.3)	1 (1.8)	0.103	1 (5.3)	1.000
History of ≥1 dilatation of esophageal stenosis	101 (52.6)	37 (64.9)	0.275	12 (63.2)	0.508
History of fundoplication surgery	35 (18.2)	15 (26.3)	0.191	6 (31.6)	0.219
History of GERD	87 (45.3)	29 (50.9)	0.546	14 (73.7)	0.028*
(Prior) Smoking	58 (30.2)	17 (29.8)	1.000	9 (47.4)	0.197
(Prior) Use of alcohol	138 (71.9)	38 (66.7)	0.240	14 (73.7)	1.000
At time of last diagnosis of no metaplasia, or first diagnosis of columnar metaplasia/BE					
Age in years	29.3 (22.2–39.0)	28.2 (22.9–38.8)	0.694	36.9 (24.5–53.5)	0.015*
BMI (kg/m$^{2)}$	22.7 (20.4–24.8)	22.4 (20.1–24.7)	0.821	22.9 (20.9–24.5)	0.998
Antireflux medication	40 (20.8)	17 (29.8)	0.170	6 (31.6)	0.457
Dysphagia	91 (47.4)	28 (49.1)	0.857	10 (52.6)	0.769
GER complaints	89 (46.4)	27 (47.4)	0.757	9 (47.4)	1.000
Hiatus hernia	129 (67.2)	47 (82.5)	0.035*	17 (89.5)	0.028*

Data are presented as *n* (%) or median (interquartile range). Asterisk indicates significance ($P < 0.05$).

[A]Patients without metaplasia versus patients with columnar metaplasia (including Barrett's esophagus).

[B]Patients without metaplasia versus patients with Barrett's esophagus. In case no biopsies were taken during the last surveillance endoscopy, patients were excluded from this analysis ($n = 22$).

[C]According to the Gross classification.[24] BE, Barrett's esophagus; BMI, body mass index; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease.

Table 6 Results of multivariable logistic regression analysis

	Columnar metaplasia (including BE) ($n = 87$)		Barrett's esophagus ($n = 30$)	
	OR	95% CI	OR	95% CI
Age	1.02	0.99–1.05	1.07	1.01–1.12
History of GERD	1.26	0.72–2.20	4.16	1.24–13.91
Male gender	0.83	0.43–1.58		
Hiatus hernia	1.75	0.88–3.46		
(Prior) Smoking	1.03	0.54–1.99		
(Prior) Use of alcohol	0.85	0.48–1.51		

BE, Barrett's esophagus; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio.

endoscopic surveillance of the remaining esophagus may be warranted.

Endoscopic screening for BE and esophageal carcinoma is not recommended for the general population.[2,16] Screening in the general population can be considered in males with >5 years and/or weekly GER symptoms plus ≥2 predetermined risk factors, such as age >50 years, Caucasian race, presence of central obesity (waist circumference > 102 cm or waist–hip ratio > 0.9), history of smoking, or a family history of BE or EAC.[2] However, given the current literature showing an increased risk of EAC and ESCC in adults with EA and the fact that these patients often do not recognize GER symptoms or complaints of dysphagia, the ESPGHAN-NASPGHAN guideline recommends endoscopic surveillance in adults with EA every 5–10 years, starting at time of transition into adulthood without any other screening criteria.[3]

Over the years, different endoscopic surveillance strategies have been proposed for adults with EA. The optimal age to start endoscopic screening remains a topic of discussion. Rintala *et al.* recommended upper endoscopy at the age of 15, 30, 40, 50, and 60 years.[17] In case of erosive esophagitis, columnar metaplasia, stricture formation, recurrent tracheoesophageal fistula or severe GER symptoms and/or need for chronic GER medication, the surveillance interval should be decreased to 5 years. In case of BE, they advised to repeat endoscopy after 1 year. In a study from the USA, it was suggested to screen all patients at the age of 10 years.[18] In case of erosive esophagitis, endoscopy needed to be repeated after 3–4 months

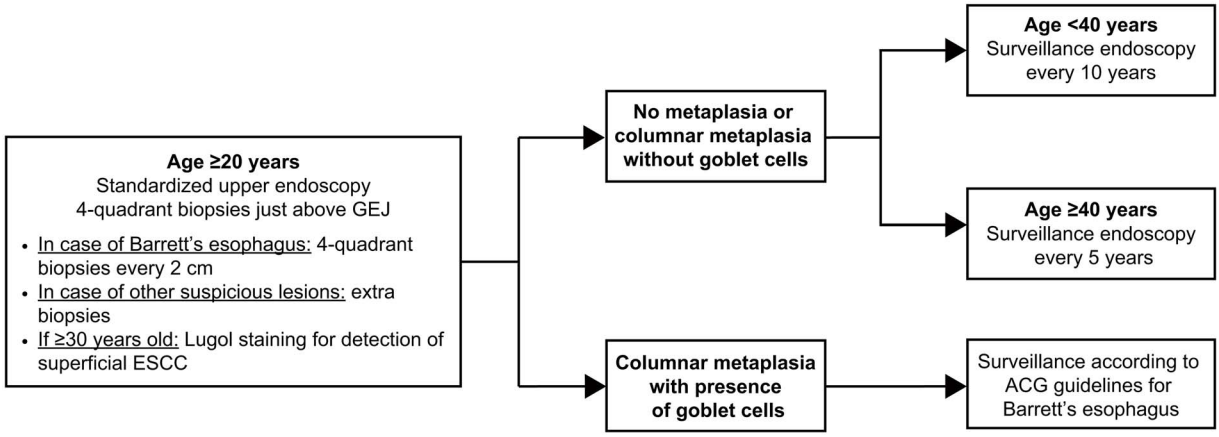

Fig. 1 Flowchart of the updated screening and surveillance program for adults patients with esophageal atresia. GEJ, gastroesophageal junction; ESCC, esophageal squamous cell carcinoma; ACG, American College of Gastroenterology.[2]

of antireflux therapy. In case of columnar metaplasia or BE, endoscopy should be repeated after 3–5 years. No recommendations were made for patients with a negative endoscopy at the age of 10 years. A French research group recommended endoscopic screening before transition to adult health care.[19] In case of columnar metaplasia or BE, surveillance should be performed every 3 years. Otherwise, endoscopy should be repeated every 5–10 years. The above-mentioned recommendations are all expert opinions based on retrospective or small studies in patients with EA at a relatively young age.

Some studies recommend to start endoscopic screening already during childhood,[18] other advices vary between 15 and 30 years as starting age.[17,19–21] In our pediatric follow-up program, children do not undergo surveillance endoscopies in childhood since this would require general anesthesia. Therefore, we scheduled the first surveillance endoscopy at the age of transition to adulthood, namely 17–18 years of age. When evaluating the 391 endoscopies in this study, the youngest patient diagnosed with a clinically relevant premalignant lesion was 20.9 years old. Therefore, we propose to start endoscopic screening adults with EA from the age of 20 years onwards (Fig. 1). However, one can consider to maintain the transition to an adult gastroenterologist at the age of 17–18 years, in order to keep these patients in follow-up and provide them a contact person in case they do develop symptoms.

Currently, the interval in our surveillance program is 3 or 5 years, depending on the patient's age. In the present study, of the 98 patients without BE at baseline (normal mucosa $n = 81$, columnar metaplasia $n = 17$), only three progressed to BE (short segment) during surveillance. A quarter of the patients in our surveillance program are 30–40 years old, and no cases of neoplasm were found in this age category. Based on these findings, combined with the determined progression rate to BE development of 0.8% per year, we consider it justified to extent the surveillance interval to 10 years for patients up to 40 years old in case no BE has been diagnosed. After the age of 40 years, we still suggest intervals of 5 years due to the observed increased incidence of ESCC in adults with EA from the age of 40 years.[4] Over time, it should be evaluated whether surveillance intervals may also be extended for patients ≥40 years old. Furthermore, we recommend to perform chromoendoscopy with Lugol's staining in patients ≥30 years and in patients who have been previously curatively treated for esophageal cancer, to detect dysplasia and early ESCC. Currently, we take biopsies at every endoscopy from all lesions and at random just proximal of the gastroesophageal junction. The latter is done based on the fact that most of the ESCC were located in the distal esophagus. In case of BE, surveillance remains according to the ACG guidelines, regardless of age.

So far, we have found two patients with EA with a (pre)neoplasm in the colon interposition. One case was a moderately differentiated adenocarcinoma (ypT2N1M0) in a 47-year-old male (previously described[22]), who was not under surveillance. The other case was described in this study and concerned a 45-year-old woman with a tubular adenoma with high-grade dysplasia detected during surveillance. Although number of cases are small, based on the prevalence (5%) and young age of onset, we currently would recommend to include patients with EA and a colon interposition in the endoscopic surveillance program as well.

Same matters for endoscopic surveillance after oncological treatment for esophageal cancer in patients with EA. Due to the fact that these patients develop esophageal cancer at a relatively young age, they have potentially more life years to gain. Our findings may underline the importance of endoscopic surveillance after the patient is discharged from oncological check-ups.

In the past, questions have been raised about the effect of screening on survival rates, taking into account the side effects and the cost-effectiveness.[23] The current median follow-up time of 4.6 years over 495 patient-years is too short to draw any conclusions on long-term survival. However, two new ESCCs have developed in patients who did not participate the surveillance program. It is known and confirmed by our results that GER complaints and dysphagia are underreported by patients with EA, due to a different perception of symptoms. Since these complaints have often been present their whole life, they do not recognize them as such. Standardized surveillance of adults with EA therefore may lead to early diagnosis of malignancies in this specific population.

On the other hand, repeated endoscopies may also form a psychological burden for patients, as well as additional costs to the health care system. These two aspects require further research, and would be helpful for future harm-benefit analyses in which potential complications of upper endoscopies should be taken into account as well.

The main strengths of our study are the prospective data collection within the infrastructure of a standardized surveillance program, and the large sample of patients born with this rare congenital anomaly. Yet, some limitations should be addressed. First, our study has a limited median follow-up time of 4.6 years. To be able to draw conclusions on the benefit of screening on survival, longer follow-up is required. Second, in 13 patients no biopsies were taken during follow-up endoscopy. This is explained by the fact that in some general hospital standard biopsies were not taken in case no endoscopic lesions were found. Last, only a few patients developed BE and therefore identification of clinical predictive factors with multivariable analysis was not applicable. This illustrates the importance of expanding the cohort. We pursue collaboration and merge of data within national and international networks, such as the Dutch Consortium of Esophageal Atresia and the European Reference Network for Rare Inherited Congenital Anomalies, in which we both are involved.

CONCLUSION

Our study underlines the importance of standardized endoscopic surveillance for all adults with EA, including those with a bowel interposition. Although the yield of new cases of BE warrants surveillance endoscopies, even if no abnormalities have been found at baseline, our findings justify to start screening at the age of 20 years with a surveillance interval of 10 years up to the age of 40 years (Fig. 1). Patients with EA who have survived esophageal carcinoma may also benefit from endoscopic surveillance of the remnant esophagus.

References

1. Vergouwe F W, IJsselstijn H, Wijnen R M, Bruno M J, Spaander M C. Screening and surveillance in esophageal atresia patients: current knowledge and future perspectives. Eur J Pediatr Surg 2015; 25(4): 345–52PMID: 26302062. 10.1055/s-0035-1559817.
2. Shaheen N J, Falk G W, Iyer P G, Gerson L B, American College of G. ACG clinical guideline: diagnosis and management of Barrett's Esophagus. Am J Gastroenterol 2016; 111(1): 30–50quiz 51. 10.1038/ajg.2015.322 PMID: 26526079.
3. Krishnan U, Mousa H, Dall'Oglio L, Homaira N, Rosen R, Faure C, Gottrand F. ESPGHAN-NASPGHAN guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with esophageal atresia-tracheoesophageal fistula. J Pediatr Gastroenterol Nutr 2016; 63(5): 550–70 [PMID: 27579697].
4. Vergouwe F W T, IJsselstijn H, Biermann K, Erler N S, Wijnen R M H, Bruno M J, Spaander M C W. High prevalence of Barrett's esophagus and esophageal squamous cell carcinoma after repair of esophageal atresia. Clin Gastroenterol Hepatol 2018; 16(4): 513–521 e516PMID: 29133255. 10.1016/j.cgh.2017.11.008.
5. Kastelein F, van Olphen S H, Steyerberg E W, Spaander M C, Bruno M J, ProBar-Study G. Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression. Gut 2016; 65(4): 548–54PMID: 25903690. 10.1136/gutjnl-2014-308802.
6. Gischler S J, Mazer P, Duivenvoorden H J, van Dijk M, Bax N M, Hazebroek F W, Tibboel D. Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. J Pediatr Surg 2009; 44(7): 1382–9PMID: 19573666. 10.1016/j.jpedsurg.2008.12.034.
7. Gross R E. The Surgery of Infancy and Childhood: Its Principles and Techniques. Philadelphia: W.B. Saunders Co, 1953.
8. Katz P O, Gerson L B, Vela M F. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2013; 108(3): 308–28quiz 329. 10.1038/ajg.2012.444 PMID: 23419381.
9. Mellow M H, Pinkas H. Endoscopic laser therapy for malignancies affecting the esophagus and gastroesophageal junction. Analysis of technical and functional efficacy. Arch Intern Med 1985; 145(8): 1443–6 [PMID: 4026476].
10. Lundell L R, Dent J, Bennett J R *et al.* Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45(2): 172–80 PMID: 10403727 PMCID: 1727604.
11. Sharma P, Dent J, Armstrong D *et al.* The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. Gastroenterology 2006; 131(5): 1392–9PMID: 17101315. 10.1053/j.gastro.2006.08.032.
12. Levine D S, Blount P L, Rudolph R E, Reid B J. Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus. Am J Gastroenterol 2000; 95(5): 1152–7PMID: 10811320. 10.1111/j.1572-0241.2000.02002.x.
13. Hashimoto C L, Iriya K, Baba E R *et al.* Lugol's dye spray chromoendoscopy establishes early diagnosis of esophageal cancer in patients with primary head and neck cancer. Am J Gastroenterol 2005; 100(2): 275–82PMID: 15667482. 10.1111/j.1572-0241.2005.30189.x.
14. den Hollander W J, Holster I L, den Hoed C M *et al.* Surveillance of premalignant gastric lesions: a multicentre prospective cohort study from low incidence regions. Gut 2019; 68(4): 585–93PMID: 29875257. 10.1136/gutjnl-2017-314498.
15. Zagari R M, Fuccio L, Wallander M A *et al.* Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. Gut 2008; 57(10): 1354–9PMID: 18424568. 10.1136/gut.2007.145177.
16. Fitzgerald R C, di Pietro M, Ragunath K *et al.* British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014; 63(1): 7–42PMID: 24165758. 10.1136/gutjnl-2013-305372.
17. Rintala R J, Pakarinen M P. Long-term outcome of esophageal anastomosis. Eur J Pediatr Surg 2013; 23(3): 219–25PMID: 23737132. 10.1055/s-0033-1347912.

18. Hassall E. Esophagitis and Barrett esophagus: unifying the definitions and diagnostic approaches, with special reference to esophageal atresia. J Pediatr Gastroenterol Nutr 2011; 52(Suppl 1): S23–6PMID: 21499040. 10.1097/MPG.0b013e3182133143 00005176-201105001-00011 [pii].
19. Schneider A, Michaud L, Gottrand F. Esophageal atresia: metaplasia, Barrett. Dis Esophagus 2013; 26(4): 425–7PMID: 23679037. 10.1111/dote.12057.
20. Sistonen S J, Koivusalo A, Nieminen U *et al.* Esophageal morbidity and function in adults with repaired esophageal atresia with tracheoesophageal fistula: a population-based long-term follow-up. Ann Surg 2010; 251(6): 1167–73PMID: 20485152. 10.1097/SLA.0b013e3181c9b613.
21. Taylor A C, Breen K J, Auldist A *et al.* Gastroesophageal reflux and related pathology in adults who were born with esophageal atresia: a long-term follow-up study. Clin Gastroenterol Hepatol 2007; 5(6): 702–6PMID: 17544997. 10.1016/j.cgh.2007.03.012.
22. Vergouwe F W, Gottrand M, Wijnhoven B P *et al.* Four cancer cases after esophageal atresia repair: time to start screening the upper gastrointestinal tract. World J Gastroenterol 2018; 24(9): 1056–62PMID: 29531469 PMCID: 5840470. 10.3748/wjg.v24.i9.1056.
23. Deurloo J A, Ekkelkamp S, Bartelsman J F, Ten Kate F J, Schoorl M, Heij H A, Aronson D C. Gastroesophageal reflux: prevalence in adults older than 28 years after correction of esophageal atresia. Ann Surg 2003; 238(5): 686–9PMID: 14578730 PMCID: 1356146. 10.1097/01.sla.0000094303.07910.05 00000658-200311000-00008 [pii].
24. Gross R E. Atresia of the esophagus. Am J Dis Child 1947; 74(3): 369 [PMID: 20267729].
25. Knyrim K, Wagner H J, Bethge N, Keymling M, Vakil N. A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. N Engl J Med 1993; 329(18): 1302–7PMID: 7692297. 10.1056/NEJM199310283291803.