Barrett's Esophagus and Adenocarcinoma Risk

The Experience of the North-Eastern Italian Registry (EBRA)

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Objective: To establish the incidence and risk factors for progression to high-grade intraepithelial neoplasia (HG-IEN) or Barrett's esophageal adenocarcinoma (BAc) in a prospective cohort of patients with esophageal intestinal metaplasia [(BE)].

Background: BE is associated with an increased risk of BAc unless cases are detected early by surveillance. No consistent data are available on the prevalence of BE-related cancer, the ideal surveillance schedule, or the risk factors for cancer.

Methods: In 2003, a regional registry of BE patients was created in north-east Italy, establishing the related diagnostic criteria (endoscopic landmarks, biopsy protocol, histological classification) and timing of follow-up (tailored to histology) and recording patient outcomes. Thirteen centers were involved and audited yearly. The probability of progression to HG-IEN/BAc was calculated using the Kaplan-Meier method; the Cox regression model was used to calculate the risk of progression.

Results: HG-IEN (10 cases) and EAc (7 cases) detected at the index endoscopy or in the first year of follow-up were considered to be cases of preexisting disease and excluded; 841 patients with at least 2 endoscopies {median, 3 [interquartile range (IQR): 2–4); median follow-up = 44.6 [IQR: 24.7–60.5] months; total 3083 patient-years} formed the study group [male/female = 646/195; median age, 60 (IQR: 51–68) years]. Twenty-two patients progressed to HG-IEN or BAc (incidence: 0.72 per 100 patient-years) after a median of 40.2 (26.9–50.4) months. At multivariate analysis, endoscopic abnormalities, that is, ulceration or nodularity ($P = 0.0002$; relative risk [RR] = 7.6; 95% confidence interval, 2.63–21.9), LG-IEN ($P = 0.02$, RR = 3.7; 95% confidence interval, 1.22–11.43), and BE length ($P = 0.01$; RR = 1.16; 95% confidence interval, 1.03–1.30) were associated with BE progression. Among the LG-IEN patients, the incidence of HG-IEN/EAc was 3.17 patient-years, that is, 6 times higher than in BE patients without LG-IEN.

Conclusions: These results suggest that in the absence of intraepithelial neoplastic changes, BE carries a low risk of progression to HG-IEN/BAc, and strict surveillance (or ablative therapy) is advisable in cases with endoscopic abnormalities, LG-IEN or long BE segments.

Keywords: Barrett's esophagus, adenocarcinoma, neoplasia, risk factors

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The lining of the distal esophagus with columnar epithelium is known by the eponym of Barrett's esophagus (BE), after the English surgeon who first described this condition in 1950.[1] It has been recognized as a disease acquired because of exposure of the esophageal mucosa to gastrointestinal contents[2] and associated with a 30- to 125-fold increase in the risk of developing primary Barrett's adenocarcinoma (BAc).[3] The BE-related cancer risk has been more specifically linked to a subtype of glandular mucosa comprising intestinalized glands (ie, the presence of goblet cells and so-called "specialized" metaplasia),[4] so the definition of BE has been further restricted to cases showing metaplastic intestinalization of the native squamous esophageal mucosa [ie, "a change in the esophageal epithelium of any length that can be recognized at endoscopy and confirmed to have intestinal metaplasia (IM) at biopsy"].[5,6]

BAc is preceded by a spectrum of morphological alterations previously defined as dysplasia and more recently termed intraepithelial neoplasia (IEN), which is further divided into high-grade intraepithelial neoplasia (HG-IEN) and low-grade intraepithelial neoplasia

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(LG-IEN), depending on its degree of differentiation. BAc is therefore the final step in a cascade of phenotypic and genotypic changes starting with the initial metaplastic transformation and developing into an invasive adenocarcinoma. This biological process provides the rationale for secondary cancer prevention: surveillance of BE patients enables the identification and treatment of early lesions before cancer development and may therefore reduce the high BAc-related mortality rate. Although published guidelines have addressed this issue extensively,[7–9] the effectiveness of BE patient surveillance remains equivocal: the real incidence of BAc in BE patients is still not clear and varies considerably in published cohort studies, from 0.2% to 3.5% annually.[10,11] There are several explanations for this discrepancy, including publication bias in favor of studies with a high incidence of BAc; studies of small numbers of patients in which the incidence of BAc is abnormally high; studies performed at tertiary referral centers where the most severe cases are concentrated; or studies in which patients with incident BAc discovered at the time of accrual (or immediately afterward) were not excluded.

To further our understanding of the natural history of BE, a prospective multicenter registry[12] was established in north-eastern Italy in 2003; the main aims of this BE Registry were to assess:

1. the demographic, endoscopic, and histological characteristics of BE patients;
2. the timing and rate of BE progression to malignancy (ie, its incidence); and
3. the endoscopic and pathological risk factors for progression.

MATERIAL AND METHODS

Patient Selection

Patient registration strictly required: (1) endoscopically visible velvety mucosa (gastric-type epithelium) in the tubular esophagus [ie, 0.5 cm above the gastroesophageal junction (GEJ)] and (2) histologically documented IM in at least one of the biopsies obtained from the velvety epithelium. Only patients with BE or BE-associated IEN (ie, indefinite for IEN, LG-IEN) entered the follow-up study.

After patient enrollment, automatically generated messages were e-mailed to the enrolling centers to notify them (and subsequently remind them) about the timing of endoscopic checkups established by the registry protocol (the timing differed according to the category of histological lesions).[12]

Data Collection

Data were entered in 3 registry sections—demographics, endoscopy, and pathology—as follows:

a. *Demographics* included patients' personal details (name, date of birth, address, Social Security number), together with the main indication for upper gastrointestinal endoscopy.
b. *Endoscopy* included the most relevant endoscopic information: distance from incisors to (i) the squamocolumnar junction, (ii) the diaphragmatic pinchcock, and (iii) the GEJ (defined as the end of the gastric folds). When hiatal hernia (HH) was detected, its length (ie, the distance in centimeters from the diaphragmatic pinchcock to the GEJ) was recorded. Any esophagitis (Los Angeles classification[13]) was also recorded, with a brief description of the size and shape of the BE (in tongues or islands) and any presence of ulcers, nodularity, or other endoscopic abnormalities. BE was further characterized according to its length as (i) short segment BE (SSBE), when it extended less than 3 cm, or (ii) long segment BE (LSBE) when it was 3 or more cm long. After 2006, the Prague C & M classification[14] was incorporated. The Seattle biopsy sampling protocol was applied; that is, when velvety (gastric type) epithelium was endoscopically recognized in the esophagus, 4 targeted biopsies (one for each quadrant) every 2 cm were recommended.[15] Quadrant biopsies were submitted in the same vial. Additional biopsies from the normal esophagus and stomach were recommended, taking 5 samples, that is, 3 from the antral/angularis mucosa and 2 from the oxyntic mucosa. Biopsies were always submitted in separate vials.
c. *Pathology* included all relevant pathological information: score/type of inflammatory infiltrate; grade of noninvasive neoplasia (if any); presence of *Helicobacter pylori* (in gastric specimens). IEN was assessed according to internationally validated criteria and graded as follows: 1, negative for IEN; 2, LG-IEN; and 3, HG-IEN. When a diagnosis of IEN could not be clearly established (usually because of intense inflammation), the term "indefinite for IEN" was adopted. HG-IEN cases were always submitted to a gastrointestinal (GI) pathologist for second opinion and further discussed during audit meetings (as established in the registry rules).

Timing of Follow-Up

Endoscopic check-ups were scheduled according to the histological category: every 2 years for "simple" IM; every 6 months for LG-IEN; and every 3 months for cases indefinite for both IEN and HG-IEN.

Conventional Definition of Pathological Outcome

The following conventional definitions were used to describe the clinicopathological outcome of BE and BE-related lesions[12]:

- *Reversion*: Intestinalized mucosa in the tubular esophagus no longer detectable in 2 consecutive biopsies (the definition applies to the twice-confirmed presence of nonintestinalized glandular mucosa and/or to the finding of native squamous esophageal mucosa during the follow-up).
- *Regression*: Noninvasive neoplasia (or lesions indefinite for IEN) found consistently to a lesser degree (or no longer detected) in at least 2 consecutive biopsies.
- *Persistence*: No change in phenotype category in at least 2 consecutive biopsies.
- *Progression*: High-grade noninvasive neoplasia (after a previous finding of BE or LG-IEN detected at least 12 months after registration).

Noninvasive neoplasia (both LG-IEN and HG-IEN) was considered as "evolving" into BAc when invasive cancer was histologically demonstrated at least 12 months after the initial diagnosis (ie, incident neoplasia). Any invasive or noninvasive neoplasia detected within 12 months of patient enrollment was conventionally considered as "coexisting" (ie, prevalent neoplasia).

Ablative or Resective Therapies

All patients who received ablative or resective therapies were withdrawn from the study. Patients who progressed to HG-IEN were offered endoscopic mucosectomy or endoscopic mucosal resection and thermal ablation with radio frequency, alone or in combination (as of 2007, when radio frequency became available at referral centers). Patients with BAc were offered endoscopic mucosal resections or esophagectomy depending on the tumor stage and the risk to the patient.

Registry-Related Auditing and Monitoring

Meetings (open to all researchers involved in the project) were held every 6 months to check on the status of the registry and discuss any difficulties encountered in managing the online registration of cases. Pathology meetings (also open to all researchers involved) were

held to discuss cases of neoplastic lesions and other cases requiring further consideration. After the second year, all centers submitted to yearly audits and reviews of all enrolled cases.

Statistical Analysis

Data were automatically transferred from the general database to a commercially available spreadsheet (Excel; Microsoft) and analyzed using SAS 9.1 software. Continuous data were expressed as medians and interquartile ranges (IQRs). Categorical data were compared using the Fisher test. The Mann-Whitney test was used for continuous data. Univariate and multivariate analyses of progression to HG-IEN/BAc were performed in patients with 2 or more years of follow-up to reduce the number of right-censored data. The Kaplan-Meier estimator and the log-rank test were used for categorical variables. A Cox model with only explanatory variables was applied to each continuous variable. Risk factors for progression to HG-IEN/BAc were estimated using the Cox regression model.

Ethics

The registry project was approved by the ethics committees of the centers involved, and registration strictly required that patients gave informed consent. All centers had free access to the registry Web site (www.esofagodibarrett.org), using their own passwords, which gave researchers access only to data they had collected themselves. Only the coordinating center had access to all the records to monitor their consistency.

RESULTS

Registry accrual commenced on January 29, 2003, and 13 centers enrolled 1297 BE patients by December 15, 2011; 439 of these patients had only the index endoscopy and were not considered in the present analysis. Eleven patients had a diagnosis of BAc (n = 4) or HG-IEN (n = 7) at their first endoscopy, and 6 patients developed BAc (n = 3) or HG-IEN (n = 3) within the first year after their enrollment. These 17 patients were considered to be cases of preexisting disease and were also excluded, so the study group consisted of 841 patients. The median follow-up was 44.6 (24.7–60.5) months, amounting to an overall 3083 patient-years.

Demographics

The sample included 646 men and 195 women, with a median age of 60 (51–68) years. Table 1 summarizes their demographic details. Women were 2 years older than the men ($P = 0.02$). All patients were treated with standard-dose proton pump inhibitors (esomeprazole 40 mg, lansoprazole 30 mg, or pantoprazole 40 mg), according to patient and general practitioner preferences, and local guidelines), except for 10 patients who underwent antireflux surgery. This small latter group (9 men and 1 woman, median age 67.5 years) was followed up for a median of 54 (28–86) months.

Endoscopy and Biopsies

A total of 2649 upper GI endoscopies were performed during the study period, with a median of 3 (2–4) endoscopies per patient. Endoscopic esophagitis was evident in 17.6% of cases; Los Angeles grade A or B was the most frequently diagnosed (88%). Most patients (58.0%) had a BE segment shorter than 3 cm (SSBE) (Table 1). Patients with LSBE had a higher prevalence of HH larger than 3 cm (33.4% vs 18.1%) than patients with SSBE; $P < 0.0001$). They also had larger hernias than SSBE patients [LSBE 2 cm (IQR: 0–4) vs SSBE 2 cm (IQR: 0–3); $P = 0.003$], whereas the prevalence of endoscopic esophagitis was similar in LSBE and SSBE (19.9% and 16.0%, respectively; $P = 0.19$).

Pathology

IM without IEN was diagnosed in 745 patients (88.6%); 64 patients had a diagnosis of LG-IEN, and a diagnosis of "indefinite for IEN" was recorded for 32 patients. Patients with LSBE had a slightly higher prevalence of granulocytic infiltrate (43.6% vs 37.1%; $P = 0.06$) and lymphomonocytic infiltration (93.6% vs 83.9%; $P = 0.0001$) than patients with SSBE. Together with the higher prevalence of HH and esophagitis at endoscopy, this may indicate that a more active reflux disease coincided with LSBE. The overwhelming majority of patients had no *Helicobacter pylori* infection in their gastric biopsies. Table 2 summarizes the pathological results.

Outcome of BE During the Follow-Up

Reversion

Sixty-two (7.3%) patients showed no evidence of IM in 2 consecutive endoscopic biopsies during the follow-up and were considered as having "reverted," 51 had IM or were indefinite for IEN, and 11 had LG-IEN. Reversions were similarly distributed

TABLE 1. Demographic and Endoscopic Characteristics of 841 Patients Enrolled in the Registry

N	841
Sex, male:female	646:195
Age, median (IQR), y	
All	60 (51–68)
Men	60 (50–68)
Women	62 (54–70)
Length of HH, median (IQR), cm	2 (1–4)
Length of BE segment, median (IQR), cm	2 (0–3)
SSBE	488 (58.0)
LSBE	353 (42.0)
Endoscopic esophagitis*	
No esophagitis	691 (82.4)
Grade A	54 (6.4)
Grade B	76 (9.1
Grade C/D	18 (2.1)
Appearance of lesion†	
Normal	792 (94.5)
Nodularity	28 (3.3)
Ulceration	18 (2.2)

Data expressed as n (%) unless indicated otherwise.
*Data not available for 2 patients.
†Data not available for 3 patients.

TABLE 2. Pathology of Biopsies at Index Endoscopy

N	841
IM without IEN	745 (88.6)
LG-IEN	64 (7.6)
Indefinite for IEN	32 (3.8)
Lymphomonocytic infiltration*	
Absence	99 (11.9)
Presence	732 (88.1)
Granulocytic infiltration†	
Absence	497 (60.2)
Presence	329 (39.8)
Helicobacter pylori infection	
No	733 (87.2)
Yes	108 (12.8)

Data expressed as n (%).
*Data not available for 10 patients.
†Data not available for 15 patients.

between cases of SSBE (37/488, 7.6%) and LSBE (25/353, 7.1%) ($P = 0.89$). The reversion rate was also similar for surgically treated patients (1/10, 10%).

Regression

Biopsies taken at 2 consecutive endoscopies showed regression from LG-IEN to IM without IEN in 43 patients. Six patients regressed to LG-IEN from a previous diagnosis of HG-IEN. The distribution of regressions between SSBE (33/488, 6.7%) and LSBE (16/353, 4.5%) patients did not differ statistically ($P = 0.18$). One patient (10%) in the surgical group regressed from LG-IEN to IM without IEN.

Progression

Progression to LG-IEN. Sixty-four patients progressed from IM to LG-IEN; these patients had a longer BE segment [4 (IQR: 2–6) cm vs 2 (IQR: 1–4) cm, $P = 0.0001$], a larger HH [3 (IQR: 1–5) cm vs 2 (IQR: 0–3) cm, $P = 0.0001$], and granulocytic infiltrate (54.7% vs 38.7% $P = 0.02$) than patients whose disease did not progress. Two (3.1%) of these 64 patients subsequently progressed to HG-IEN, whereas 14 (21.9%) regressed to IM without IEN. None of the patients treated with antireflux surgery progressed to LG-IEN, HG-IEN, or BAc.

Progression to HG-IEN/BAc. Fifteen patients progressed to HG-IEN and 7 to BAc. At the index endoscopy, 68.2% of these patients had IM (or were indefinite for IEN) and 31.8% had LG-IEN. As mentioned earlier, 2 patients progressed from IM to LG-IEN and then to HG-IEN during the study period. To assess the risk of progression, patients enrolled in the registry were divided into groups by endoscopic length of their BE (LSBE vs SSBE) and pathology (IM vs LG-IEN). Table 3 shows the incidence and timing of progression for each of the groups. The overall incidence of HG-IEN/BAc was 0.72% patient-years; patients with LG-IEN at the index endoscopy had a 6 times higher incidence of HG-IEN/BAc than those with IM without IEN; and patients with LG-IEN and LSBE had a 7 times higher incidence of HG-IEN or BAc than for cases with IM without IEN and SSBE. No differences were observed in the timing of disease progression.

Risk Factors for Progression to HG-IEN or BAc

Univariate Analysis

Three continuous variables, age ($P = 0.048$), BE length ($P = 0.0002$), and HH ($P = 0.008$) were associated with progression. Endoscopically visible abnormalities (ie, nodularity or ulceration) ($P = 0.0001$) and LG-IEN ($P = 0.01$) were also associated with progression (Table 4). When patients with LG-IEN at the index endoscopy and those who developed LG-IEN during the follow-up and progressed to HG-IEN/BAc were compared with LG-IEN patients who did not progress (ie, their lesion persisted or regressed), nodularity at endoscopy (40% vs 0.7%, $P = 0.02$) and multifocal LG-IEN, that is, LG-IEN in 2 or more biopsies (50% vs 17.8%, $P = 0.047$), were more common among those who progressed (Table 5).

Multivariate Analysis

All available explanatory variables were included and the final model included lesion appearance (ie nodularity or ulceration, $P = 0.0002$, RR = 7.60), a longer BE length ($P = 0.007$, RR = 1.17), and LG-IEN ($P = 0.03$, RR = 3.41) as independent risk factors of progression to HG-IEN/BAc (Table 6). The probability of progression to HG-IEN/BAc in BE patients with IM without IEN, and in those with LG-IEN, is illustrated in Figure 1.

DISCUSSION

Surveillance in BE remains a controversial issue; evidence from retrospective studies has indicated that patients with a diagnosis

TABLE 4. Univariate Analysis of Progression to HG-IEN/BAc in Patients With 2 or More Years of Follow-Up

	% After 7 y*	*P*
Age,† y	—	0.048
Sex		
Male	96.6	0.98
Female	97.1	—
BE length,† cm	—	0.0002
HH,† cm	—	0.008
Esophagitis		
Yes	97.4	—
No	94.0	0.13
Appearance of lesion		
Normal	97.9	—
Nodularity or ulceration	73.8	<0.0001
IEN		
Absent	97.2	—
LG-IEN	90.8	<0.01
Lymphomonocytic infiltration		
Absent	100	—
Present	96.4	0.20
Granulocytic infiltration		
Absent	96.7	—
Present	96.6	0.80
Helicobacter pylori infection		
No	96.6	—
Yes	97.6	0.82

*Proportions of patients without progression to HG-IEN/BAc.
†As continuous variable.

TABLE 3. Incidence and Timing of Progression to HG-IEN/BAc, Stratified by the Presence of LG-IEN and Length of BE Segment (SSBE vs LSBE)

	N	Follow-Up, patient-year	Progression to EAc/HG-IEN	Incidence EAc/HG-IEN, patient-years	Time to Progression, Median (IQR), mo
All patients	841	3058	22	0.72%	40.2 (26.9–50.4)
IM without IEN	777	2837	15	0.53%	40.5 (23.3–57.3)
IM without IEN - SSBE	454	1628	8	0.49%	42.7 (35.9–46.9)
IM without IEN - LSBE	323	1209	7	0.58%	33.8 (24.7–44.3)
LG-IEN	64	221	7	3.17%	55.1 (20.0–66.0)
LG-IEN - SSBE	34	103	3	2.91%	21.0 (16.9–55.1)
LG-IEN - LSBE	30	118	4	3.39%	62.9 (39.9–69.1)

TABLE 5. Comparison Between Patients With LG-IEN at Any Endoscopy With or without Progression to HG-IEN or EAc

	No Progression to HG-IEN/ACE	Progression to HG-IEN/EAc	*P*
N	118 [92.2%]	10 [08.8%]	—
Age, median (IQR), y	62.5 (56–73)	63.5 (56–71)	0.78
Sex			0.15
Male	88 [74.6%]	10 [100%]	
Female	30 [25.4%]	0 [0%]	
Length of BE, cm	3 (2.0–5.0)	5.5 (3.5–7.7)	0.09
Short segment (<3.0 cm)	55 [46.7%]	2 [20%]	0.19
Long segment (≥3.0 cm)	63 [53.3%]	8 [80%]	—
HH, cm	3 (1–4)	3 (0–6)	0.74
≤3	74 [62.7%]	5 [50%]	0.65
>3	44 [37.3%]	5 [50%]	—
Esophagitis			0.77
Present	35 [29.7%]	2 [20%]	
Absent	83 [70.3%]	8 [80%]	
Appearance of lesion			0.004
Normal	110 [93.2%]	6 [60%]	
Nodularity or ulceration	8 [06.8%]	4 [40%]	
LG-IEN focality			0.047
Monofocal	97 [82.2%]	5 [50%]	
Multifocal	21 [17.8%]	5 [50%]	
Lymphomonocytic infiltration			0.93
Present	97 [84.4%]	8 [80%]	
Absent	18 [15.6%]	2 [20%]	
Granulocytic infiltration			0.51
Present	51 [44.4%]	6 [60%]	
Absent	64 [55.6%]	4 [40%]	
Helicobacter pylori infection			1
No	109 [93%]	9 [90%]	
Yes	9 [07%]	1 [10%]	

TABLE 6. Multivariate Analysis of Progression to HG-IEN or EAc in Patients With at Least 2 Years of Follow-Up

	P	Relative Risk (95% Confidence Interval)
Age	0.12	—
Sex, male:female	0.60	—
BE length, cm	0.01	1.16 (1.03–1.30)
HH, cm	0.25	—
Esophagitis, yes:no	0.43	—
Appearance of lesion (nodularity or ulceration: normal)	0.0002	7.60 (2.63–21.98)
IEN (LG-IEN: absent)	0.02	3.74 (1.22–11.43)
Lymphomonocytic infiltration (present:absent)	0.23	—
Granulocytic infiltration (present:absent)	0.38	—
Helicobacter pylori infection (yes:no)	0.92	—

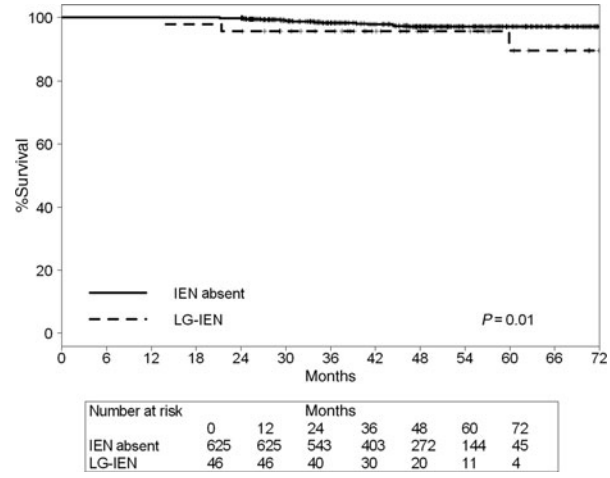

FIGURE 1. Probability of progression to HG-IEN or BAc in patients with and without LG-IEN. Only patients with 2 or more years of follow-up were considered. The number of patients at risk in each interval is indicated in the box below the curve.

of BAc in endoscopic surveillance programs for BE have a better survival than those with a diagnosis after the onset of symptoms, and this has led to recommendations for the endoscopic surveillance of BE patients.[16,17] However, disease incidence plays an important role in determining whether surveillance programs are worthwhile. If the incidence of BAc is high, then a surveillance program is cost-effective; if it is low and does not affect a significant proportion of the patients at risk, then it is not. Although 3 recently published meta-analyses[18–20] identified a lower incidence of BAc than expected, most of the data concerned came from studies with methodological weaknesses, prompting recommendations for the set up of regional registries with clearly reported outcomes and a documented adherence to protocols.[21] Registries could also be helpful in gathering new information for stratifying BE patients with different risks of progression.

The method used in this study avoided most of the sources of bias observed in previous reports, that is, the endoscopic and pathological inclusion criteria and the definition of the outcomes were decided prospectively; the sample size and follow-up were adequate; patients were recruited at both primary endoscopic services and tertiary referral centers; HG-IEN and BAc detected within a year after accrual were considered to be preexisting conditions and were excluded and both HG-IEN and BAc were considered as study outcomes (the inclusion of HG-IEN in the registry outcomes is supported by the recently demonstrated feasibility of eradicating HG-IEN and preventing further progression to BAc with less invasive, highly effective endoscopic therapies.[19,22])

Even considering HG-IEN and BAc together, our prospective study spanning 7 years shows that the risk of progression in BE patients without IEN is relatively small and that lesions (ulceration or nodularity) found at endoscopy or LG-IEN found on pathological examination (be they detected at the index endoscopy or one of the surveillance endoscopies), and the length of a longer BE segment are reasons for concern, because they are strongly associated with progression to HG-IEN/BAc.

The incidence of progression to HG-IEN and BAc seen in our study (0.72% patient-years) is lower than in some of the previously mentioned meta-analyses[18–20] and a cohort study[23] but comparable with a recent report on nondysplastic BE carrying an annual cancer risk of approximately 0.5% patient-years.[24] Our results are also consistent with the cumulative incidence of HG-IEN and BAc reported in a large population-based study in Denmark, in which the incidence of HG-IEN was 0.7% patient-years and for BAc it was 0.12% patient-years (with a cumulative incidence of progression of 0.82% patient-years).[25]

Our study confirms that BE is more common in men (with a male to female ratio of 3.3:1) and that women with BE are a mean of 2 years older than men. This sex-related difference is unlikely to be due to women having more difficulty accessing upper GI endoscopy:

in a previous study,[12] we found that the male to female ratio of patients undergoing this test was close to 1, with no age difference between the 2 sexes. This finding is consistent with a report from Falk et al[24] and gives the impression that women may have some hormonal or lifestyle-associated factor protecting them against the early onset of BE. Unlike the data reported by Yousef et al,[19] no sex differences were found in the incidence of HG-IEN/BAc. This would mean that established BE carries the same risk of progression in males and females, so there should be no sex-related stratification in BE surveillance programs.

The finding that endoscopic abnormalities in BE mucosa (eg, ulceration or nodularity) are strongly associated with a higher risk of progression to Hg-IEN/BAc has previously been reported by MacDonald et al[26] and, more recently, in the meta-analysis conducted by Thomas et al[18] and suggests that more intensive biopsy screening is warranted once ulceration or nodularity has been identified.

The second prognostic factor associated with progression was LG-IEN. Cuivers et al[27] recently demonstrated the association between LG-IEN and BE progression. Previous meta-analyses probably failed to disclose the prognostic impact of LG-IEN because of inconsistencies in LG-IEN assessment methods between different studies. Cuivers et al found that 42% of patients with a consensus diagnosis of LG-IEN progressed to HG-IEN/BAc during a mean follow-up of 37.6 months, with a progression rate of 13.4% per patient-years. This figure is 4 times higher than that in the present study (3.17% patient-years). In our registry, diagnoses of LG-IEN were not reviewed by a second pathologist and this may represent an important limitation. Although pathologists at community hospitals received specific training from expert GI pathologists at the beginning of the study, this strategy might not be a valid alternative to systematically obtaining a second opinion. It is important to bear in mind, however, that a marked variability in the diagnosis of LG-IEN persists even among "expert pathologists" and the diagnostic issues posed by LG-IEN probably cannot be completely overcome even by a formal review process. The need for specific markers to define LG-IEN correctly should therefore be addressed in future research.[28]

One more factor potentially useful for stratifying patients in surveillance programs was the length of the BE segment. The hypothesis that the risk of BAc is higher the longer the BE segment[29,30] was challenged by Rudolph et al,[31] who showed that the segment length did not correlate with cancer risk after adjusting for histology at study entry. This study considered a relatively small number of patients ($n = 300$), however, which also included patients with prevalent HG-IEN. In the present study, we found a significant association between the BE segment absolute length and progression to HG-IEN/BAc, pointing to the need to monitor LSBE patients more closely, especially when they also have LG-IEN.

Finally, when the characteristics of the LG-IEN patients who progressed further were compared with those who did not, 50% of the former patients had multifocal LG-IEN (ie, ≥ 2 biopsies showing LG-IEN), suggesting that a greater extent of "unstable" epithelium correlates with a higher likelihood of progression. According to another hypothesis, LG-IEN might simply be a marker of the presence of synchronous HG-IEN or BAc remaining undetected by random biopsy sampling, or it could represent an underdiagnosis of HG-IEN. Be that as it may, patients with multifocal LG-IEN should be followed up more carefully.

Age and HH size emerged only as factors associated with progression to HG-IEN/BAc at univariate analysis. Hvid-Jensen[25] recently showed that the incidence of both HG-IEN and BAc increased with age and was highest among patients older than 70 years. Both the presence and the size of HH and age were strongly associated with the length of BE segment, however,[32,33] and this may explain why these variables did not emerge from the multivariate statistics.

Despite some recent evidence[34] that antireflux surgery might influence the metaplastic epithelium in BE patients, causing a "reversion" to non-IM (especially in short BE segments), the "reversion" and "regression" rates seen in our sample were similar in medically and surgically treated patients, although the very small number of patients who underwent surgery (1.2%) may explain why there was no difference between the 2 groups.

In conclusion, the findings of this study enable BE patients to be stratified according to their estimated risk of progression. Patients with endoscopic evidence of ulceration/nodularity, LG-IEN (particularly when it is multifocal), and long BE segments should clearly undergo elective surveillance. Radio frequency ablative therapies should be further tested in such higher risk patients (with controlled trials and a long-term follow-up) to thoroughly assess the benefits of this strategy in reducing the risk of progression.

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DISCUSSANTS

T. Demeester (Los Angeles, CA)

Dr Zaninotto reported on the excellent work being performed by the North-Eastern Italian Registry. The study he presented was carefully done and is the culmination of a large effort put forth by this group to measure the incidence of esophageal adenocarcinoma. According to their registry, the incidence of a malignancy in patients with nondysplastic Barrett's esophagus (BE) in north-eastern Italy was 0.7 per 100 years follow-up. This is similar to the 0.63 seen in the United States. After reading the manuscript, I have 3 questions.

First, there were 6 patients who had a normal index endoscopy and went on to develop a malignancy during the first year of follow-up. These 6 patients were excluded and were not added to the 22 patients who subsequently developed a malignancy after 1 year of follow-up. I understand you excluded them on the basis of the fact that you may have missed the lesion at the time of the index biopsy. What evidence do you have that these early cancers were not more aggressive cancers that actually developed within the first year and should be counted in your cancer incidence?

Second, efforts in surveillance require knowing where the esophagus ends and the stomach begins. There are various definitions for this, each supported with various amounts of data. According to your group, the esophagus extended to 0.5 cm above the proximal end of the gastric rugal folds. Assuming this to be the end of the esophagus is debatable. Current evidence suggests that the end of the esophagus is at the level where the gastric oxcyntic mucosa converts to either esophageal squamous or cardiac mucosa. Any pathology that occurs in squamous or cardiac mucosa is within the esophagus. This line of mucosal conversion is much lower than your group's definition for the end of the esophagus. Are you just ignoring the distal part of the esophagus with your definition? The area between your definition and the histological definition is an area where cancers of the cardia develop. On histological bases, there is evidence that these cancers are in reality esophageal cancers. Consequently, correctly defining the end of the esophagus and the beginning of the stomach is critical to the registry. I would like to know how your group would adjust to the new understanding?

Third and the last question, if a physician from your group obtains a biopsy from below the line 0.5 cm above the gastric rugal folds and it shows on histology of intestinal metaplasia (IM), how would you classify the patient in the registry? Would you consider the patient to have BE? Would you consider it not important to survey such a patient? I appreciated the opportunity to review your manuscript. It is the outcome of an enormous amount of organizational work and an excellent study. My questions reflect issues that trouble all of us interested in BE and I am interested to hear your thoughts. Thank you.

Response from G. Zaninotto

Thank you very much for your comments and questions. It is certainly possible that the 6 patients who developed cancer within the first year had a more aggressive disease. It may be, however, that the biopsies missed a small area of already advanced disease [ie, high-grade intraepithelial neoplasia (HG-IEN) or early cancer]. The aim of our registry was to identify BE patients at higher risk of progression, and we excluded all the cases of progression within the first 12 months after enrollment to obtain a homogenous group of patients. An important message emerging from this study is that the first (index) endoscopy needs to be performed with great care, taking an adequate number of biopsies. If we have an adequate map of the disease and no low-grade intraepithelial neoplasia (LG-IEN) or HG-IEN is diagnosed and there are no other risk factors, we can probably extend the timing of surveillance to 4 or 5 years and focus on patients with LG-IEN or other negative prognostic factors, such as a long BE segment, endoscopic abnormalities, or hiatal hernias larger than 3 cm.

The second question concerns the endoscopic definition of the gastroesophageal junction (GEJ). The answer might seem simple enough: the GEJ is the point where the stomach ends and the esophagus starts, but reality is much more complex. A problem with this type of observational study is that it was designed 9 years ago and started 1 year afterward: the definition that we adopted (and retained throughout the study) reflects what we knew 9 years ago. At the time, the endoscopic definition of the GEJ was the "end of the gastric folds": this was a straightforward, practical definition and it showed a good consistency when adopted by different endoscopists. A more recent definition based on the "palisade vessels" may identify the GEJ more precisely, but we decided to keep the former definition. It is also feasible, in histological terms, for the esophagus to end below the gastric folds, but endoscopists can rely only on what they can see, not the information they will have after the endoscopy and biopsy have been completed.

The last question concerns our biopsy protocol, which involves taking biopsies starting from 5 mm above the GEJ. We decided to do so to keep the registry consistent and avoid enrolling patients with IM in the proximal stomach. If a patient was biopsied for a so-called ultra-short BE segment (ie, <5 mm from the GEJ) and histology showed IM in this biopsy, then this patient was kept in the registry, but the number of such patients is very small.

T. Lerut (Leuven, Belguim)

Thank you and congratulations, this is really monumental work that you have done and also of very high quality, which I can confirm because I was privileged to witness some of the preparative work that you have done. I think your data may have consequences for the organization of surveillance, and that is what it is all about for Barrett's metaplasia. I have a couple of practical questions. You have a mean follow-up now of 44 months, and I just wondered whether that is long enough to draw final conclusions, because we all know that it is a process that extends over several years. My second question relates to the 88% of patients in whom there were no microscopic abnormalities and no histological abnormalities. What would you then advise in terms of the follow-up of those patients? Are you going to follow up them up forever? Are you going to make a distinction between the long segment and the short segment, as you showed that the long segment might have a higher risk? The next question is on the low-grade neoplasia; could that be an argument in favor of informing those patients of the latest techniques such as radio frequency ablation? Finally, you have a set of patients in whom BE evolved into adenocarcinoma and I'd just like to know whether they were all T1A and N0 patients? If they were more advanced, that might perhaps alter the way you do the follow-up. Again, congratulations; I think this is fantastic work, it is probably the first really organized database in Europe.

Response from G. Zaninotto

Thank you very much for your comment. Certainly, a longer follow-up would be better, but we have to consider that a median 44 months of follow-up is already in the upper range for this type of study, and 3000 patient-years represents a fairly good observation period. We shall however continue to monitor these patients.

The second question concerned what we should do with these patients, given the findings of the present study. We probably need to revise our surveillance policy: patients with short segment BE with no IEN do not need to follow an intensive surveillance protocol; we could concentrate our surveillance activities—and probably also our therapeutic efforts—on the high-risk group (ie, cases with LG-IEN, long segment BE, and endoscopic abnormalities). The key issue, in my opinion, is how we define LG-IEN, given that pathologists disagree on this diagnosis.

T. Lerut (Leuven, Belguim)

Do you need a second expert pathology opinion?

Response from G. Zaninotto

When we designed the study, we decided to request a second opinion from another pathologist for HG-IEN, not for LG-IEN. The results of the study indicate that LG-IEN is a key marker of progression, and we need to obtain an accurate diagnosis (probably routinely requesting a second opinion). There is a nice study from Holland showing that patients with LG-IEN, confirmed by the second opinion of another pathologist, progress to HG-IEN or invasive adenocarcinoma in about 40% of cases.

The last question was on the stage of patients who progressed to invasive adenocarcinoma; most of them were T1, one was T2, and none had nodal involvement.

J. Van Lanschot (Rotterdam, The Netherlands)

I have a short question, just to extend a bit more on the question of the objectivity of the diagnosis of low-grade and high-grade dysplasia. We surgeons always think pathologists agree upon a certain diagnosis of dysplasia, which is not the case. My question is: Did you use additional p53 and Ki-67 immunohistochemical staining to get better inter- and intraobserver reproducibility?

Response from G. Zaninotto (Venezia, Italy)

No biomolecular investigations were performed in this study, but we now have this huge database of biopsies, and we know the natural story of each patient, so we can use this material to seek biomolecular markers of progression.