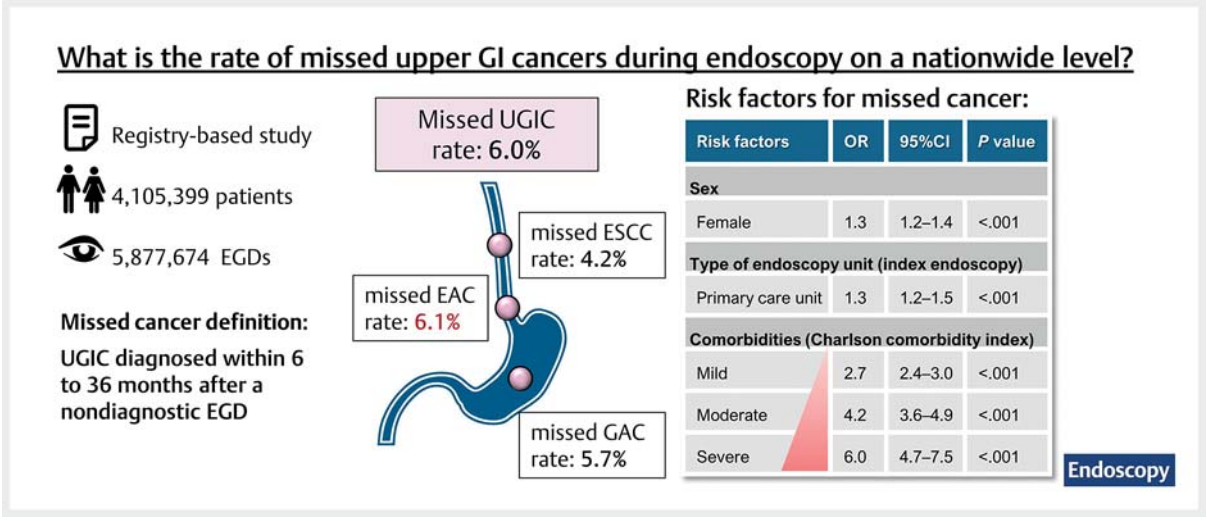
Prevalence and risk factors of upper gastrointestinal cancers missed during endoscopy: a nationwide registry-based study

GRAPHICAL ABSTRACT



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Tables 1 s–5 s, Fig. 1 s
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ABSTRACT

Background A significant proportion of upper gastrointestinal cancers (UGICs) remain undetected during esophagogastroduodenoscopy (EGD). We investigated the characteristics and risk factors of UGICs missed during endoscopy.
Methods In this nationwide registry-based study, we analyzed two large Polish datasets (National Health Fund and National Cancer Registry) to identify individuals who underwent EGD and were subsequently diagnosed with UGIC. Cancers diagnosed < 6 months after EGD were defined as "prevalent" and those within ≥ 6– < 36 months as "missed." We compared the characteristics of missed and prevalent cancers, and analyzed the risk factors for missed UGICs in a multivariable regression model.

Results We included 4 105 399 patients (mean age 56.0 years [SD 17.4]; 57.5 % female) who underwent 5 877 674 EGDs in 2012–2018. Within this cohort, 33 241 UGICs were diagnosed, of which 1993 (6.0 %) were missed. Within esophageal neoplasms, adenocarcinomas were more frequently missed than squamous cell cancers (6.1 % vs. 4.2 %), with a relative risk of 1.4 (95 % confidence interval [CI] 1.1–1.8, $P = 0.01$). Most gastric cancers were adenocarcinomas, of which 5.7 % were classified as missed. Overall, a higher proportion of missed UGICs than prevalent cancers presented at an advanced stage (42.2 % vs. 36.2 %, $P < 0.001$). Risk factors for missed UGICs included initial EGD performed within primary (vs. secondary) care (odds ratio [OR] 1.3, 95 %CI 1.2–1.5), female sex (OR 1.3, 95 %CI 1.2–1.4), and higher comorbidity (Charlson comorbidity index ≥ 5 vs. 0; OR 6.0, 95 %CI 4.7–7.5).

Conclusions Among UGICs, esophageal adenocarcinomas were missed most frequently. Missed cancers occur more frequently within the primary care sector and are found more often in women and individuals with multiple comorbidities.

Introduction

Upper gastrointestinal cancer (UGIC) constitutes a significant burden globally, as evidenced by a combined incidence of over 1.5 million cases of esophageal and gastric cancers worldwide in 2018 [1]. Moreover, these neoplasms are among the most lethal, with a 5-year survival rate ranging between 20 % and 30 % in the Western world [2–4]. This dismal prognosis may be chiefly attributed to the late presentation of UGIC, at which point treatment options are extremely limited. Esophagogastroduodenoscopy (EGD) is the key diagnostic test for detecting UGIC; however, it remains a highly operator-dependent procedure, with a significant rate of missed lesions.

The issue of UGIC being overlooked during endoscopy has been increasingly recognized in recent years. However, most of the available studies on the topic are limited by single-institutional settings and small cohorts of patients, usually with insufficient data to identify risk factors for missed cancers [5–14] (see **Table 1 s** in the online-only supplementary material). Moreover, different study methodologies result in high variability of the reported cancer miss rates, making them challenging to compare; a previous meta-analysis of these studies showed significant heterogeneity [15].

Taken together, the current data on missed UGIC remain limited and poorly understood. To address this gap in our knowledge, we conducted a nationwide registry-based study using two large databases to characterize the prevalence, clinical characteristics, and risk factors of UGICs missed during an upper endoscopy.

Methods

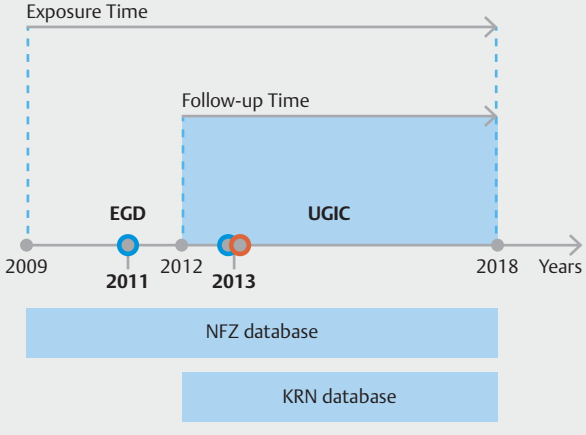
Study design and databases

We performed a nationwide, registry-based cohort study in cross-disciplinary collaboration between clinicians and data analysts from Poland's Ministry of Health. We analyzed the data from two general registries, the National Health Fund Registry (Narodowy Fundusz Zdrowia – NFZ) and the National Cancer Registry (Krajowy Rejestr Nowotworów – KRN), to identify consecutive adult patients (≥ 18 years) who underwent at least one EGD procedure (ICD-9 codes 42.33–45.16; **Table 2 s**) between 1 January 2009 and 31 December 2018 (exposure time) and subsequently received a diagnosis of UGIC (ICD-10 codes C15.0-C17.0; **Table 3 s**) between 1 January 2012 and 31 December 2018 (follow-up time) (▶ **Fig. 1**). We included only the first cancer diagnosis in patients with more than one UGIC.

NFZ is a public state institution financing all health care services for insured citizens (~90 % of the population [16]) and was the primary source of demographic and procedural data for the study. The database includes:

- patient data: age, sex, place of residence (based on the Territorial Division of the Country [TERYT] coding), type of residence (urban/rural);
- endoscopy data: date and type of endoscopy (diagnostic/therapeutic), place of endoscopy unit (urban/rural based on TERYT coding), endoscopy unit type (primary care [outpatient unit]/secondary care [hospital]);
- cancer data: diagnosis date and cancer location (based on ICD-10 coding).

For each endoscopy unit (both primary and secondary care), we calculated the annual endoscopy volume (mean annual number of EGDs per unit) as a potential quality metric.



▶ **Fig. 1** Example timeline of an upper gastrointestinal cancer missed during endoscopy. KRN, National Cancer Registry; NFZ, National Health Fund Registry; EGD, esophagogastroduodenoscopy; UGIC, upper gastrointestinal cancer.

The comorbidity scores were computed using the Charlson Comorbidity Index (CCI) up to 2 years before initial EGD or a cancer diagnosis, and divided into four categories: no comorbidity (CCI 0), mild (CCI 1–2), moderate (CCI 3–4), and severe (CCI ≥ 5) comorbidity.

We used another independent nationwide database, KRN, as the primary source of cancer data. To obtain the most reliable cancer data, we included only those cases primarily identified from KRN and confirmed within NFZ (double reporting). The link between NFZ and KRN databases was established using patients' anonymized personal identification numbers.

KRN is a centralized institution processing data in accordance with the standards of the International Association of Cancer Registries (IACR) [17]. The registry provides high completeness of data with >90 % of cancer cases confirmed by corresponding histology reports [18]. Using this registry, we obtained data on the type and anatomical site of each cancer (ICD-10), its stage at presentation (simplified TNM score), and histological subtype (ICD-O-3) [19]. The simplified TNM score included three stages: I) localized: cancer without nodal involvement or distant metastases; II) regional: locally advanced cancer with regional lymph node involvement but without distant metastases; III) advanced: cancer with distant metastases with or without nodal involvement. Histologically, we grouped esophageal cancers into three groups: 1) esophageal squamous cell carcinoma (ESCC); 2) esophageal adenocarcinoma (EAC); and 3) "others" (e. g. neuroendocrine tumor, lymphoma). Similarly, gastric cancers were divided into: 1) nondiffuse adenocarcinoma; 2) poorly differentiated adenocarcinoma (diffuse-type by Lauren classification [20] and signet ring-cell cancer [SRCC]); and 3) "others" (e. g. gastrointestinal stromal tumor, neuroendocrine carcinoma). Anatomically, using ICD-10 codes, gastric cancers were additionally subdivided into proximal (cardia [C16.0], fundus [C16.1]) and distal (body [C16.2], pyloric antrum [C16.3], pylorus [C16.4]).

Cancer definitions

The type of UGIC was determined by the time that elapsed between EGD and cancer diagnosis. As per previous studies [5–14], malignancies diagnosed within 6 months of the initial endoscopy were defined as "prevalent," those diagnosed between 6 and 36 months after the EGD as "missed," and those diagnosed after > 36 months as "latent" cancers.

Data access and cleaning methods

We used slightly different timeframes for the two databases used in the study: NFZ (2009–2018) and KRN (2012–2018). The timeframe for the NFZ database preceded that of KRN by up to 3 years to ensure full exposure time for each cancer included in the analysis (endoscopy exposure time up to 36 months for each cancer). We applied a multiple imputation procedure for missing data on cancer stages (TNM scores) and histology (ICD-O-3 codes) using a polytomous logistic regression method.

Statistics

Continuous variables were described as mean (SD) and median with interquartile range (IQR), as appropriate. Discrete variables were expressed as counts and percentages. The clinical characteristics of missed and prevalent cancers were compared using Welch's two-sample t test for continuous variables or Pearson's chi-squared test for discrete variables, with Holm–Bonferroni correction for multiple comparisons. The miss rate for each UGIC was calculated as a proportion of cases fulfilling criteria for missed cancer to all cancers diagnosed within the study period (prevalent, missed, and latent cases together; detailed data for latent cancers are not shown).

To identify the risk factors for missed UGICs, we used a multivariable logistic regression model. Factors for the model were chosen by the clinicians according to the best available clinical knowledge and based on the results of previous studies [9, 21–23]. The risk factors included were: patient sex, type of residence (urban/rural), type of endoscopy unit of the initial endoscopy (primary/secondary care), and CCI. The model was adjusted for patient age as a confounding factor for CCI. We reported the odds ratios (ORs), relative risk ratios, and 95 % confidence intervals (95 %CIs). For all analyses, a *P* value of 0.01 was considered statistically significant.

We performed all analyses using R software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org).

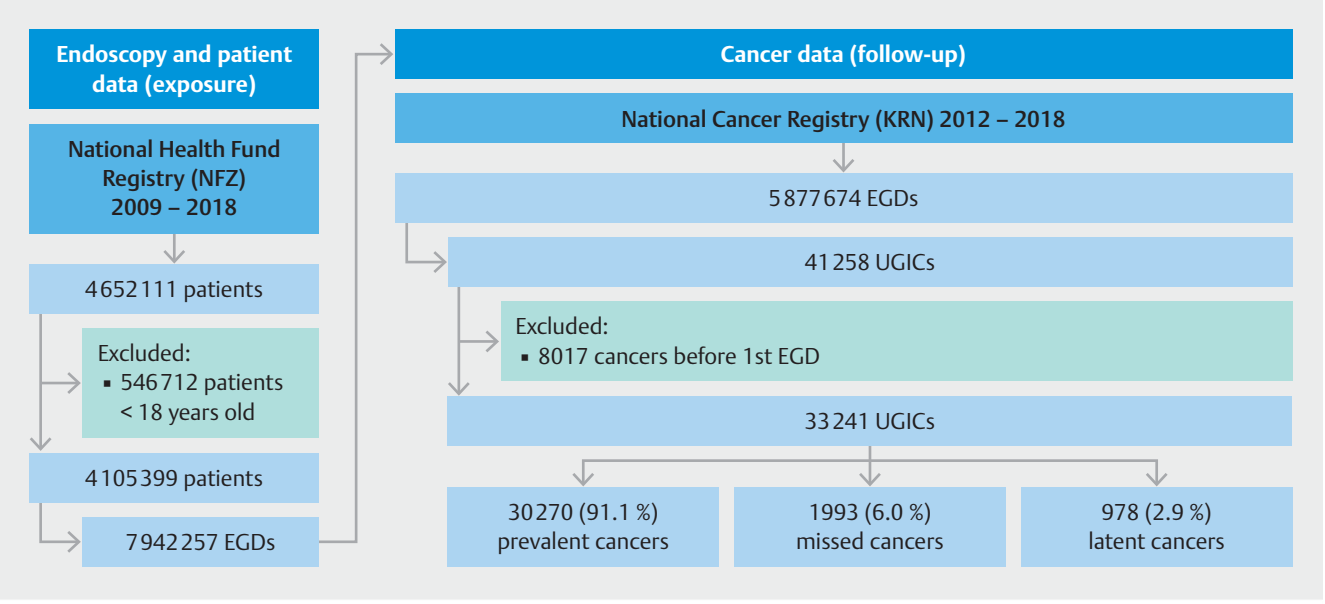
Results

Patient characteristics

Initially, 4 652 111 individuals who underwent at least one EGD within the study period (exposure time 2009–2018) were screened for eligibility. Of these, 546 712 patients aged < 18 years were excluded, and the remaining 4 105 399 patients who underwent 5 877 674 EGDs were included in the final analysis (mean age 56.0 years [SD 17.4]; 2 362 184 female [57.5 %]). The study flow chart is presented in ▶ **Fig. 2**. Most of the individuals (n = 2 751 379 [67.0 %]) were urban residents. The proportion of eligible individuals in each province was fairly evenly distributed throughout the country, varying from 8.7 % to 13.0 % (**Fig. 1 s**).

Endoscopy data

We analyzed 5 877 674 EGDs performed within the study period (follow-up time; 2012–2018), of which 2 911 806 took place within a primary care setting (49.5 %) and 2 965 868 (50.5 %) within secondary care units. Most patients (2 232 401 [68.2 %]) underwent only a single EGD, whereas 608 766 (18.6 %) patients had two EGDs, 211 413 (6.5 %) had three EGDs, and 221 225 (6.8 %) had ≥ 4 EGDs during the timespan of the study. Among all procedures, 5 681 662 (96.7 %) were diagnostic and 196 012 (3.3 %) were therapeutic (e. g. hemostatic procedures, endoscopic resections). Also, of all the procedures, 1 772 410 EGDs involved at least one biopsy for histology (30.2 %). Combined patient characteristics and endoscopy data are presented in ▶ **Table 1**. Nationwide, the number of EGDs performed per



▶ **Fig. 2** Study flow chart. UGI, upper gastrointestinal tract; EGD, esophagogastroduodenoscopy.

year increased significantly from 556752 in 2009 to 1068237 in 2018 (▶ **Fig. 3a**). The annual endoscopy volume was higher in secondary care than in primary care units (mean 682.3 vs. 572.0 EGDs per year).

Cancer characteristics

After excluding cancer cases diagnosed before the first registered endoscopy (n = 8017), we identified 33241 UGICs that were double reported in KRN and NFZ, of which 6948 (20.9 %) were esophageal, 25928 (78.0 %) were gastric, and 365 (1.1 %) were duodenal in origin. The mean age of patients with a UGIC was 67.6 years (SD 11.6), with a male to female ratio of 2:1. We performed data imputation for missing TNM scores (n = 8068, 24.3 %) and ICD-O-3 scores (n = 2238, 6.7 %). Over a third of UGICs presented at an advanced stage (12208 [36.7 %]), 10136 (30.5 %) had regional involvement, and 10897 (32.8 %) were diagnosed at a localized stage. Of all UGICs, 30270 (91.1 %) were classified as prevalent, 1993 (6.0 %) as missed, and 978 (2.9 %) as latent (▶ **Fig. 2**). The fraction of missed UGICs remained relatively stable throughout the study period (2012–2018; minimum 5.6 %, maximum 6.5 %) (▶ **Fig. 3b**).

Missed vs. prevalent cancers

The mean time between EGD and a diagnosis of prevalent and missed UGIC was 17.9 days (SD 29.4) and 507.7 days (SD 260.2), respectively (▶ **Table 2**). Missed UGICs were primarily gastric (81.4 %), followed by esophageal (16.6 %) and duodenal (2.0 %) cancers. Demographically, a higher proportion of female patients with UGIC had missed cancers than prevalent cancers (39.6 % vs. 32.4 %; $P < 0.001$). Strikingly, a higher proportion of missed cancers than prevalent cancers followed EGDs that were performed in a primary care unit (44.9 % vs. 37.2 %; $P < 0.001$). Finally, a higher fraction of missed UGICs presented at an advanced stage compared with prevalent cancers (42.2 % vs. 36.2 %; $P < 0.001$) (▶ **Table 2**).

Within the esophagus, more EACs were missed than prevalent (24.2 % vs. 18.6 %; $P < 0.001$) (▶ **Table 3**). Specifically, the rates of missed EACs and ESCCs were 6.1 % and 4.2 %, respectively, and the relative risk for missing EAC compared with ESCC was 1.4 (95 %CI 1.1–1.8; $P = 0.01$). The male:female ratio for prevalent EAC and ESCC was 4.2:1 and 3.6:1, respectively, whereas for missed EAC and ESCC the ratio was lower at 3.0:1 and 2.3:1, respectively.

In the stomach, missed cancers were less often adenocarcinomas (75.0 % vs. 83.2 %; $P < 0.001$), and the overall miss rate for gastric adenocarcinomas was 5.7 %. Among a subset of poorly differentiated gastric tumors (Lauren's diffuse type/SRCCs), there was no clinically significant difference between missed and prevalent cancers (13.2 % vs. 13.7 %; $P = 0.86$). Anatomically, the proportion of missed cancers within the proximal and distal stomach was comparable (4.9 % vs 5.1 %, respectively) (**Table 4 s**). However, cancers in the proximal region of the stomach were more often advanced compared with distal cancers (34.6 % vs 29.5 %, respectively).

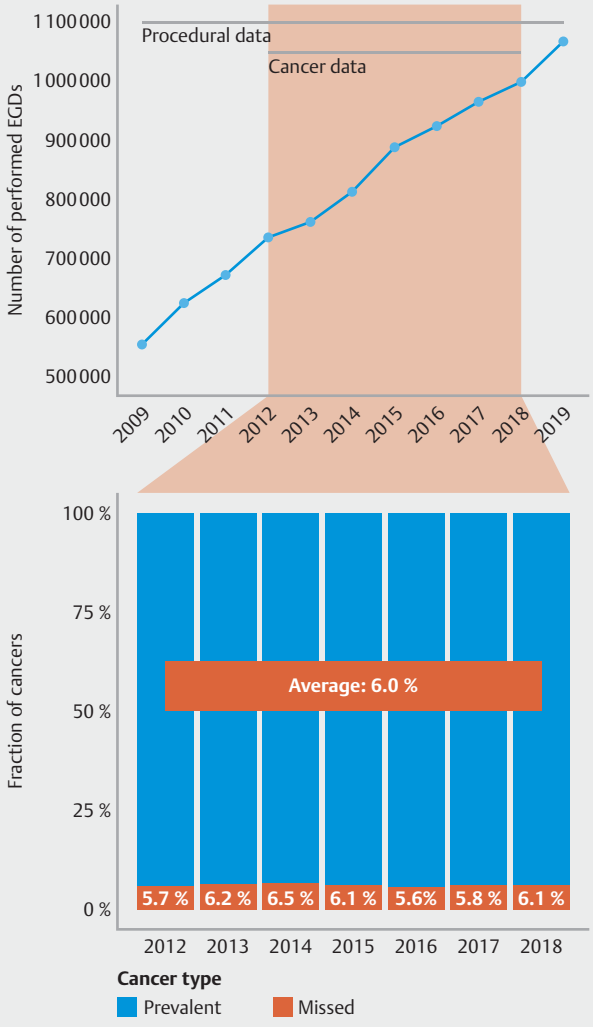
Risk factors for missed cancers

Using a multivariable logistic regression model, we found that initial EGD performed within a primary (vs. secondary) care endoscopy unit (OR 1.3, 95 %CI 1.2–1.5), female sex (OR 1.3, 95 %CI 1.2–1.4), and higher comorbidity index (CCI 1–2 OR 2.7 [95 %CI 2.4–3.0], CCI 3–4 OR 4.2 [95 %CI 3.6–4.9], and CCI ≥ 5 OR 6.0 [95 %CI 4.7–7.5], respectively, vs. CCI 0) were all independently associated with risk of missed UGICs ($P < 0.001$). The model was adjusted for age (OR 0.99, 95 %CI 0.99–0.99 for each life-year). The model results are presented in **Table 5 s**.

▶ **Table 1** Characteristics of procedures and patients undergoing esophagogastroduodenoscopy between 2009 and 2018.

Demographic characteristics	
Patients, n	4105399
Age, years	
▪ Mean (SD)	56.0 (17.4)
▪ Median	58.0
Sex, n (%)	
▪ Male	1743215 (42.5)
▪ Female	2362184 (57.5)
Charlson comorbidity index, n (%)	
▪ 0	2526430 (61.5)
▪ 1–2	1165743 (28.4)
▪ 3–4	307587 (7.5)
▪ ≥5	105639 (2.6)
Residence type, n (%)	
▪ Urban areas	2751379 (67.0)
▪ Rural areas	1354020 (33.0)
Endoscopy characteristics	
EGD procedures, n	5877674
Type of endoscopy facility, n (%)	
▪ Primary care (ambulatory)	2911806 (49.5)
▪ Secondary care (hospital)	2965868 (50.5)
Type of endoscopy procedure, n (%)	
▪ Diagnostic	5681662 (96.7)
▪ Therapeutic	196012 (3.3)

EGD, esophagogastroduodenoscopy.



▶ **Fig. 3** Esophagogastroduodenoscopies (EGDs) and cancers included in the study. **a** The overall number of EGDs performed in 2009–2018. **b** Proportion of missed and prevalent cancers in 2012–2018.

Discussion

This nationwide registry-based study showed that, within the public healthcare service, 6 % of UGICs were missed during a preceding endoscopic examination. Despite the growing utility of endoscopy services nationwide, the proportion of cancers missed did not significantly improve over the study period (2012–2018), and ranged between 5.6 % and 6.5 %. Concerningly, EGDs performed within outpatient units had a nearly 30 % higher risk of a missed cancer diagnosis than those performed in secondary care (inpatients) facilities. This finding highlights the need for better quality control in ambulatory endoscopy centers.

Within histological subtypes, EACs were most commonly overlooked (miss rate of 6.1 %), followed by gastric adenocarcinomas (5.7 %) and ESCCs (4.2 %). Within the esophagus, the proportion of missed EAC cases was about 1.4 times the proportion of missed ESCC cases. Moreover, patients with EAC more often presented at an advanced stage compared with patients with ESCC. The reason for this is unclear, as we did not find significant differences in other clinical features between these two subsets of patients. We may assume that Barrett's esophagus and EACs remain relatively new clinical challenges in Poland, and are not yet sufficiently recognized. These data are of particular importance given the systematically growing incidence of EAC in the Western world [24] – a trend that has inevitably reached central and eastern parts of Europe.

Our report used a previously established definition for missed UGIC – a malignancy diagnosed from 6 to 36 months after a nondiagnostic EGD. This definition relies on the hypothesis that gastric cancers have a 2–3-year tumor doubling time [25]. Consequently, it is presumed that any cancerous lesion within the stomach should be visible for at least 3 years prior to the initial presentation. To simplify, we included esophageal and duodenal cancers within the scope of this definition, as in previous studies on the topic [7, 13, 22, 26–29].

▶ **Table 2** Features of prevalent and missed upper gastrointestinal cancers.

	Prevalent UGIC	Missed UGIC	*P* value
Cases, n	30270	1993	NA
Patient data			
Age, mean (SD); median, years	67.4 (11.6); 67	68.2 (12.5); 68	0.082
Sex, n (%)			<0.001
▪ Male	20470 (67.6)	1203 (60.4)	
▪ Female	800 (32.4)	790 (39.6)	
Residence type, n (%)			<0.001
▪ Urban areas	18760 (62.0)	1338 (67.1)	
▪ Rural areas	11510 (38.0)	655 (32.9)	
Charlson comorbidity index, n (%)			<0.001
▪ 0 (no comorbidities)	13777 (45.5)	432 (21.7)	
▪ 1–2 (mild)	12307 (40.7)	1004 (50.4)	
▪ 3–4 (moderate)	3536 (11.7)	442 (22.1)	
▪ ≥5 (severe)	650 (2.1)	115 (5.8)	
▪ Mean (SD)	1.1 (1.3)	1.8 (1.5)	<0.001
▪ Median (IQR)	1.0 (2)	2.0 (2)	
Endoscopy data			
Time to diagnosis, mean (SD), days	17.9 (29.4)	507.7 (260.2)	NA
Type of endoscopy unit, n (%)			<0.001
▪ Primary care	11267 (37.2)	894 (44.9)	
▪ Secondary care	19003 (62.8)	1099 (55.1)	
Cancer data			
Origin, n (%)			<0.001
▪ Esophagus	6433 (21.3)	331 (16.6)	
▪ Stomach	23527 (77.7)	1623 (81.4)	
▪ Duodenum	310 (1.0)	39 (2.0)	
TNM classification (simplified), n (%)			<0.001
▪ Localized	9982 (33.0)	624 (31.3)	
▪ Regional	9321 (30.8)	528 (26.5)	
▪ Advanced	10967 (36.2)	841 (42.2)	

UGIC, upper gastrointestinal cancer; NA, not applicable; IQR, interquartile range.

▶ **Table 3** Esophageal and gastric cancer characteristics.

	Prevalent UGIC	Missed UGIC	*P* value
Esophagus	n = 6433	n = 331	
Histological subtype, n (%)			
▪ ESCC	4675 (72.7)	213 (64.3)	0.002
▪ EAC	1201 (18.6)	80 (24.2)	<0.001
▪ Other	557 (8.7)	38 (11.5)	<0.001
Location1, n (%)			
▪ Proximal	464 (7.2)	23 (6.9)	>0.99
▪ Middle	1227 (19.1)	57 (17.2)	0.23
▪ Distal	1136 (17.6)	45 (13.6)	0.03
▪ Unspecified	3790 (58.9)	206 (62.2)	0.32
Stomach	n = 23527	n = 1623	
Histological subtype, n (%)			
Adenocarcinoma	19584 (83.2)	1217 (75.0)	<0.001
▪ Nondiffuse	16367 (69.5)	1003 (61.8)	<0.001
▪ Diffuse/SRCC	3217 (13.7)	214 (13.2)	0.86
Other	3943 (16.8)	406 (25.0)	<0.001
Location*, n (%)			
▪ Cardia	4045 (16.6)	196 (12.1)	0.02
▪ Fundus	438 (1.8)	27 (1.7)	>0.99
▪ Body	4930 (20.2)	276 (17.0)	0.28
▪ Pylorus	1779 (7.3)	93 (5.7)	0.55
▪ Unspecified	13216 (54.1)	1031 (63.5)	<0.001

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; SRCC, signet-ring cell carcinoma.
* Some cancers extended into more than one location.

The available reports on missed UGICs have been conducted using two different general approaches. The first approach, typically based on cancer registries, includes a retrospective audit of cancer cases to identify individuals who underwent a recent nondiagnostic EGD. This approach allows evaluation of the "cancer miss rate," proven to range from 4.3% to 9.8% [26, 28]. A second approach, defining the "procedural miss rate," is based on a prospective review of endoscopy data. The EGD miss rate has been shown to vary widely, from 0.4% to 25.8% [6, 30].

In our study, we used two high quality, nationwide databases – KRN and NFZ – to link the procedural and cancer data in order to identify patients with robust UGIC diagnoses (double reported at KRN and NFZ) with any previous exposure to upper endoscopy. Taken together, our study was based on a retrospective audit of cancer data. Following this methodology, we could demonstrate that approximately 6% of the UGICs were overlooked during a preceding endoscopic examination – a number that is within the previously reported rates in studies with a comparable design [7, 13, 22, 26–29].

While the issue of missed cancers during endoscopy has been increasingly recognized, most of the evidence to date has originated from colonoscopy studies. Clearly, the risk of missed UGICs is a more complex issue than for colorectal cancer. While post-colonoscopy colorectal cancers have been predominantly linked to operator skills and technical aspects of the procedure

[31, 32], factors contributing to missed UGICs presumably fall outside of merely procedural aspects. This complexity may be attributed to a more heterogeneous histological landscape of UGI malignancies. In fact, our study has shown significantly different miss rates for the most common histological UGIC subtypes, and the highest miss rate was demonstrated for esophageal adenocarcinomas (6.1 %).

Within the stomach, however, missed cancers were less often adenocarcinomas (75.0 % vs. 83.2 %, $P<0.001$) and more commonly harbored a nonspecific ("other") histology. Interestingly, there was no significant difference in diffuse/SRCC histology rate between the missed and prevalent gastric tumors (13.2 % vs. 13.7 %; $P=0.86$) and there was no difference in the rate of missed cancers between proximal vs. distal parts of the stomach.

Risk factors for missing cancer during endoscopy can be broadly divided into operator-dependent and patient/disease-related factors. Regarding the former, a study from Scotland showed that > 70 % of missed UGICs can be attributed to endoscopist errors, such as missing a lesion, taking insufficient biopsies, or providing inappropriate follow-up [13]. It was also proven that nongastroenterologists tend to have higher miss rates than specialists [9, 21, 22]. Moreover, our group demonstrated that the rate of obtaining biopsies during EGD ("endoscopists biopsy rate") is inversely associated with the risk of overlooked gastric cancers [33]. As the lowest risk of missed tumors was shown for operators with a ≥ 44 % biopsy rate, our report may highlight a possible lack of EGD quality at a national level, as biopsies were performed in only about 30 % of the procedures. At an institutional level, endoscopy lists with more procedures per day have been associated with higher rates of missed UGICs [28]. As the primary care setting was the leading institutional factor contributing to missed UGICs, we calculated the annual endoscopy volume separately for inpatient and outpatient units. The mean annual number of procedures was notably higher in secondary care providers than in primary care (682.3 vs. 572.0 EGDs yearly, respectively). We believe that this difference in volume may highlight the varying degrees of experience, hence quality, between these two types of health care providers. In addition, despite having no registered data on use of sedation, we may safely assume that it was more commonly applied in a hospital setting than in primary care units (there is no funding coverage from the public health care system for general anesthesia in outpatient endoscopy).

The previously postulated patient-related factors included increased comorbidity, female sex, and younger age [9, 21–23]. These findings are broadly in line with our results. By evaluating the CCI index for each patient, we could demonstrate that those with higher comorbidity carry a greater risk of a missed cancer. For instance, patients with severe comorbidities (CCI ≥ 5) had a nearly sixfold higher risk of missed cancer than those with no comorbidities (OR 6.0, 95 %CI 4.7–7.5). We also showed that females had a 30 % higher risk of missed cancer than males (OR 1.3, 95 %CI 1.2–1.4), a finding that applies to all UGICs regardless of their subtype. The male:female ratio was lower within missed EACs, ESCCs, and gastric cancers, respectively, when compared with prevalent cancers. As discussed in previous reports, this could be potentially explained by a lower tolerance for EGD examination among women [34, 35] and usually lower expectation of UGIC in female patients. This finding highlights the need to standardize the upper endoscopy procedure and apply a uniform approach to all patient profiles. Although significant in the multivariable model, the association of age and missed UGIC was relatively poor in our study. A minimal effect (OR 0.99) on the risk was noted, and, although statistically significant, we do not find this difference clinically relevant.

Our study constitutes the most extensive nationwide report to date on UGICs missed during endoscopy. We based our findings on well-established, high-quality data from two large national databases with high data completeness. The report was carried out in cross-disciplinary collaboration with Poland's Ministry of Health analytical and statistical experts, and we have used previously established definitions of prevalent and missed UGICs.

We are, however, aware of certain limitations of our study. First, the study findings are based on administrative data and claims records that may carry a degree of oversimplification. Despite having a wide range of data, we lacked specific details on the procedures and operators. For example, we did not have data on procedural time, and type/model of endoscopes, as well as the specialties of physicians providing endoscopy services. Moreover, we were lacking indications for the procedure; hence, we were unable to identify patients undergoing regular surveillance, such as for premalignant conditions (e. g. Barret's esophagus). In addition, more than half of ICD-10 codes on cancer location were reported as "unspecified" (53.3 % in the esophagus, 52.8 % in the stomach); therefore, we could not provide any reliable conclusions on the specific location of missed pathology within the upper GI tract. Finally, simplifying the missed cancer definition by grouping all UGICs could lead to overgeneralized results. On the other hand, we followed established methodologies from previous studies, and generalizations were inevitable to handle such large databases as the ones used in our study.

In conclusion, we highlighted the critical issue of cancers missed during upper endoscopy in this nationwide registry-based study. Results showed that missed cancers are relatively common and occur more frequently within primary care units. We found that the rate of missed esophageal adenocarcinomas was the highest among all UGIC subtypes. Moreover, female sex and higher comorbidity scores were significantly associated with missed cancers, underscoring the need for a uniform and standardized approach to the EGD procedure.

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Competing interests

The authors declare that they have no conflict of interest.

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