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Meta-Analysis

Diagnostic yield of upper endoscopy according to appropriateness: A systematic review

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ABSTRACT

Background/aim: Despite some official guidelines are available, a substantial rate of inappropriateness for upper gastrointestinal (UGI) endoscopies has been reported. This study aimed to estimate the inappropriate rate of UGI in different countries, also including the diagnostic yield.
Methods: A systematic review of studies on UGI endoscopy appropriateness was performed by adopting official guidelines as reference standard. Diagnostic yield of relevant endoscopic findings and cancers was compared between appropriate and inappropriate procedures. The Odd Ratio (OR) values and the Number-Needed-to-Scope (NNS) were calculated.
Results: Data of 23 studies with a total of 53,392 patients were included. UGI indications were overall inappropriate in 21.7% (95% CI = 21.4–22.1) of the patients. The inappropriateness rate significantly ($P < 0.0001$) decreased from 35.1% in the earlier studies to 22.1%–23% in the more recent ones. A relevant finding was found in 43.3% of appropriate and in 35.1% of inappropriate endoscopies ($P < 0.0001$; OR: 1.42, 95% CI = 1.36–1.49; NNS = 12). Prevalence of cancers was also higher in appropriate than in inappropriate UGIs (2.98% vs. 0.09%, $P < 0.0001$; OR = 3.33; NNS = 48). The prevalence of detected cancers significantly ($P < 0.004$) increased from 1.38% in the earlier studies to 2.11% in the more recent ones, whilst prevalence of other relevant findings remained similar.
Conclusions: Rate of inappropriate UGI endoscopies is still high. Diagnostic yield of appropriate endoscopies is higher than that of inappropriate procedures, including upper GI cancers. Therefore, implementation of guidelines in clinical practice is urged.

1. Introduction

Upper gastrointestinal (UGI) endoscopy is a useful procedure for diagnosis, surveillance, or exclusion of relevant gastroduodenal diseases [1]. Therefore, it is widely used in clinical practice for investigating patients with different symptoms, and it is generally scheduled as open-access procedure in different countries. It was estimated that more than 2.5 millions UGIs were performed yearly in Italy [2]. Disappointingly, a substantial rate of inappropriateness for this procedure was also reported [3], despite some official guidelines and expert-based recommendations were available to guide physicians when planning an UGI endoscopy [4–8]. Noteworthy, inappropriate UGI endoscopies achieved significantly lower diagnostic yield as compared to appropriate procedures [3]. In addition, inappropriate UGIs resulted in a considerable increase in both overall cost and waiting lists [9]. Therefore, to update current estimates on the inappropriate rate of UGIs in different countries is necessary to optimize its use in clinical practice.

Our aim was to perform a systematic review of available data on the appropriateness and diagnostic yield of UGI endoscopies, with particular attention to prevalence of relevant endoscopic findings and cancers.

2. Methods

2.1. Literature review

The literature search was performed on 31 July 2018 in PubMed, starting since1992, i.e. when the first official guideline on appropriate indications for upper endoscopy was published by the ASGE

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Table 1
Characteristics of the included studies.

Author [Ref.]	Country	Year of publication	Year of enrollement	Centres	Guideline	N of patients	Males (%)	Mean age (years)
Gonvers et al. [22]	Switzerland	1996	1992	Single	ASGE	442	65	46 ± 11
Seematter-Bagnoud et al. [23]	Switzerland	1999	1995–1996	Multi	RAND	2885	52	49 ± 18
Charles et al. [24]	US	1999	1997	Single	ASGE	168	NA	56 ± 13
Froelhich et al. [25]	Switzerland	2000	1996–1997	Multi	RAND	1681	55	NA
Trevisani et al. [26]	Italy	2001	2000	Single	ASGE	697	51	63.6 ± 16.4
Manes et al. [27]	Italy	2002	1998	Multi	Maastricht	706	55	47 (18–86)
Rossi et al. [28]	Italy	2002	2000–2001	Single	ASGE	1777	52	60 ± 15.3
Boulton-Jones et al. [29]	UK	2003	1997–1999	Single	BSG	1000	NA	NA
Bersani et al. [30]	Italy	2004	2000–2001	Single	ASGE	2000	42	57 (18–99)
Chan et al. [31]	Malaysia	2004	2002–2003	Single	ASGE	1076	45	NA
Al Romaih et al. [32]	Saudi Arabia	2006	2000	Single	ASGE	80	59	38.3 ± 15
Fernández-Esparrach et al. [33]	Spain	2006	2005	Single	EPAGE	228	45	57 (16–94)
Kaliszan et al. [34]	France	2006	2002–2003	Single	RAND	522	57	55 ± 14.8
Hassan et al. [35]	Italy	2007	2003	Multi	ASGE	6270	51	59 ± 16
Cerqueira et al. [36]	Portugal	2008	2002–2004	Single	ASGE	2305	50	59 ± 17.9
Buri et al. [37]	Italy	2010	2007–2008	Multi	ASGE	8252	47	57 (18–99)
Keren et al. [38]	Israel	2011	2000–2008	Single	ASGE	20,620	44	58 ± 17.8
Mangualde et al. [39]	Portugal	2011	2005–2006	Single	ASGE	381	50	59.5 ± 15.1
Tachi et al. [40]	Ghana	2011	2007–2008	Single	ASGE	373	44	46 (14–95)
Mudawi et al. [41]	Sudan	2012	2011	Single	ASGE	220	57	46.5 ± 17.9
Ennaifer et al. [42]	Tunisia	2015	2011	Single	EPAGE	182	48	49 (14–91)
Algjebreen et al. [43]	Saudi Arabia	2013	2008	Single	ASGE	508	49	45.3 ± 18.1
Tahir et al. [44]	New Zealand	2016	2013–2014	Single	ASGE	1019	45	62.6 ± 17.4

NA: not available.

[10]. The exploded medical subjects 'Upper endoscopy', and 'appropriateness' were utilized. Boolean operators (NOT, AND, OR) were also used in succession to narrow and widen the search. No language restriction was used. The selection criteria were: (a) adoption of official guidelines (ASGE, EPAGE, BSG, RAND, and Maastricht) to assess the appropriateness for UGIs [4–8]; (b) definition of relevant endoscopic findings; (c) prevalence of relevant endoscopic findings and/or cancers reported according to the appropriateness; (d) UGIs performed in adult patients. Two investigators (AZ and RM) separately performed the search, selected the studies, and extracted data by using pre-defined data extraction forms. A third investigator (VDF) arbitrated in the event of a lack of agreement. The full paper of all relevant studies was retrieved, and manual searches of reference lists were also performed to identify any additional studies that may have been missed using the above-mentioned procedure. When more than one publication of the same investigator group was available, only the most updated version, including the entire sample size, was considered for this pooled data analysis.

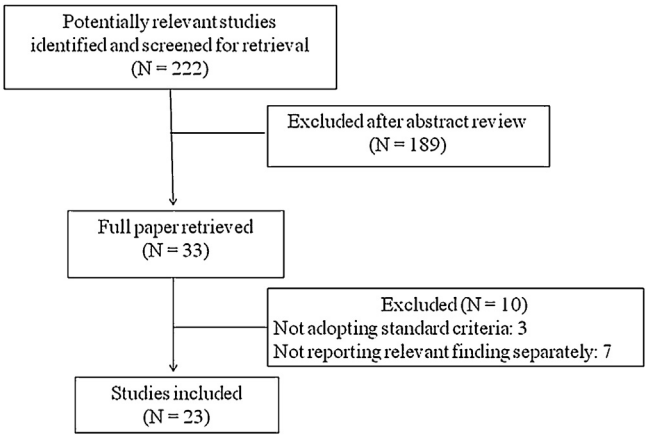

Fig. 1. Flow-chart of studies selection.

2.2. Statistical analysis

Data were calculated as mean or median with their 95% confidence intervals (CI). Comparisons among subgroups were performed by using the Chi-square test. The Odd Ratio values for differences and the Number-Needed-to-Scope (NNS) were calculated. Heterogeneity between trials was assessed calculating the I^2 statistic (random-effects model) on Excel, according to the method described elsewhere [11].

3. Results

3.1. Descriptive analysis

Study flow-chart is provided in Fig. 1. We identified 33 potentially relevant studies, but 10 were eventually excluded due to lack of standard criteria for appropriateness [12–14] or to the fact that the diagnostic yield was not reported accordingly [15–21]. The 23 included studies enrolled a total of 53,392 patients, with a median sample size of 706 (range: 80–20,620) patients, and were published during a 21-year period (1996–2016) [22–44]. ASGE guidelines were adopted in 16 series, EPAGE in 2, RAND criteria in 3 series, BSG in 1, and the Maastricht criteria in the remaining study. Five series were multicentre, whilst 18 studies were performed in only one endoscopic unit. A total of 61% studies were based in a European country, followed by African and Asian countries, while only 1 US series was found. The main characteristics of the studies included in this systematic review are provided in Table 1.

3.2. Appropriateness rates

According to the adopted guidelines, the indication for UGIs was rated as appropriate in 41,780 (78.3%; 95% CI = 77.9–78.6) cases, and inappropriate in the remaining 11,612 (21.7%; 95% CI = 21.4–22.1) patients. The inappropriateness rate widely ranged among different studies, with the lowest (10%) and the highest (61.7%) values both occurring in Italian series (Table 1). A substantial level of inter-study heterogeneity (I^2 = 62.3%) was also observed (Fig. 2). When stratifying studies in 3 enrolment periods, 2690 (35.1%; 95% CI = 34.1–36.2) out of 7659 endoscopies performed until to 2000, 3132 (22.1%; 95% CI = 21.3–22.7) out of 14,178 performed between 2001 and 2005, and 2516 (23%; 95% CI = 22.2–23.8) out of 10,935 performed after the 2006 were judged as inappropriate. Therefore, the inappropriateness rate significantly ($P < 0.0001$)

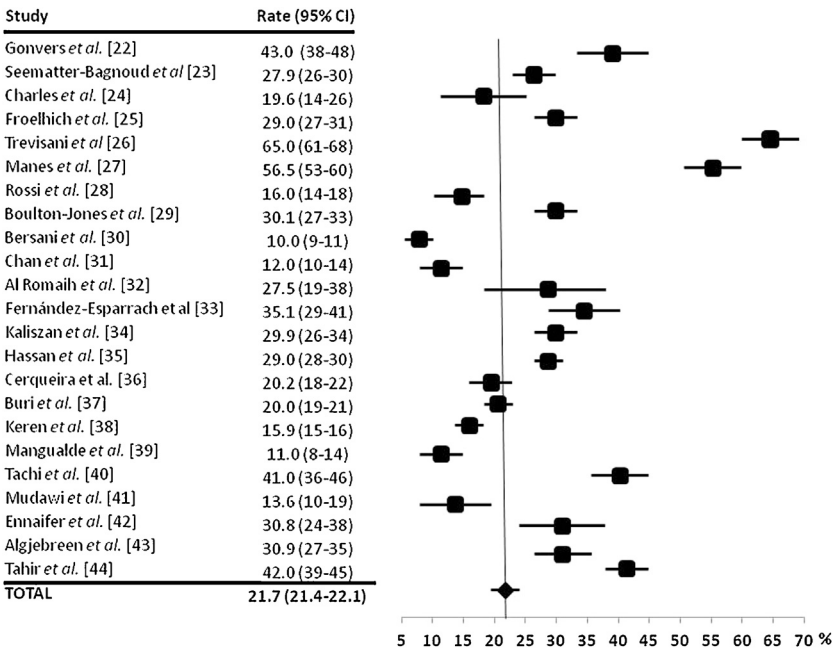

Fig. 2. Forrest plot of inappropriateness rates.

Table 2
Prevalence of relevant findings and cancers at upper endoscopy according to the appropriateness.

Author [Ref.]	Inappropriateness rate; N (%)	Relevant findings in appropriate; N (%)	Relevant findings in inappropriate; N (%)	Cancers in appropriate; N (%)	Cancers in inappropriate; N (%)
Gonvers et al. [22]	190 (43)	126 (50)	87 (46)	2 (0.8)	0 (0)
Seematter-Bagnoud et al. [23]	805 (39)	1081 (52)	386 (48)	NA	NA
Charles et al. [24]	33 (19.6)	44 (33)	6 (17)	NA	NA
Froelhich et al. [25]	487 (29)	716 (60)	180 (37)	29 (2.4)	0 (0)
Trevisani et al. [26]	453 (61.7)	167 (59.4)	169 (37.3)	NA	NA
Manes et al. [27]	399 (56.4)	140 (45)	198 (49.7)	6 (1.9)	0 (0)
Rossi et al. [28]	284 (16)	702 (47)	82 (29)	32 (2.1)	6 (2.2)
Boulton-Jones et al. [29]	301 (30)	486 (69.5)	191 (63.5)	17 (2.4)	0 (0)
Bersani et al. [30]	200 (10)	990 (55)	84 (42)	36 (2)	2 (1)
Chan et al. [31]	129 (12)	388 (41)	32 (25)	18 (1.9)	0 (0)
Al Romaih et al. [32]	22 (27.5)	21 (36)	6 (27)	0 (0)	0 (0)
Fernández-Esparrach et al. [33]	80 (35)	15 (10)	8 (10)	3 (2)	0 (0)
Kaliszan et al. [34]	156 (30)	179 (49)	37 (24)	9 (3.9)	0 (0)
Hassan et al. [35]	1818 (29)	2315 (52)	527 (29)	132 (2.7)	1 (0.1)
Cerqueira et al. [36]	465 (20)	1311 (71.3)	465 (61.7)	60 (3.3)	10 (2.1)
Buri et al. [37]	1650 (20)	NA	NA	129 (1.9)	3 (0.18)
Keren et al.[38]	3274 (15.9)	4805 (23.3)	865 (4.2)	655 (3.8)	69 (2.1)
Mangualde et al. [39]	42 (11.5)	129 (36.6)	5 (11.4)	10 (3.2)	0 (0)
Tachi et al. [40]	153 (41.1)	120 (54.5)	51 (33.3)	20 (9.1)	2 (1.3)
Mudawi et al.[41]	30 (14)	96 (93.2)	7 (6.8)	11 (6.1)	0 (0)
Ennaifer et al. [42]	56 (31)	74 (59)	30 (54)	4 (3.2)	0 (0)
Algjebreen et al. [43]	157 (31.3)	249 (71.4)	105 (66.1)	NA	NA
Tahir et al. [44]	428 (42)	379 (64.1)	145 (33.9)	17 (2.9)	0 (0)

NA: not available.

decreased from the first and second period, whilst it remained stable thereafter. Data of study by Karen et al. [38] were not included in this calculation because patients were enrolled through 2000–2008. When comparing different guidelines, a significantly ($P < 0.0001$) lower inappropriateness rate was observed following ASGE (20.2%; 95% CI = 19.8–20.6) as compared to the others (31.7%; 95% CI = 30.6–32.8).

3.3. Appropriateness and diagnostic yield

By considering the available data of 22 studies, a relevant finding was found in 14,553 (43.3%; 95% CI = 42.8–43.9) out of 33,528 appropriate and in 3488 (35.1%; 95% CI = 34.1–35.9) out of 9962 inappropriate UGIs ($P < 0.0001$; OR: 1.42, 95% CI = 1.36–1.49), with a NNS of 12. In detail, by taking into account the available data of 19 studies, the prevalence of cancers was significantly ($P < 0.0001$) higher in appropriate (1169 out of 39,214, 2.98%, 95% CI = 2.8–3.15) UGIs than in those inappropriate (93 out of 10,164; 0.09%, 95% CI = 0.73–1.1), with an OR of 3.33 (95% CI = 2.7–4.1) and a NNS of 48 (Table 2). When considering the enrolment period, the overall prevalence of detected cancers significantly ($P < 0.004$) increased from 1.38% (54 out of 3909) in the first period to 2.11% (309 out of 14,623) in second, and then it remained stable (196 out of 10,427, 1.88%; $P = 0.5$). The overall prevalence of relevant findings significantly ($P < 0.0001$) decreased from 52.3% (4004 out of 7659) to 49.1% (6957 out of 14,178), but it returned to 51.8% (1390 out of 2683) in the last period ($P = 0.7$). According to the guideline adopted, the overall diagnostic yield was significantly lower following ASGE

than others, both in appropriate (39.2% vs. 54.7%; $P < 0.0001$) and inappropriate (34.3% vs. 45.5%; $P < 0.0001$) procedures. On the contrary, prevalence of cancers was higher in ASGE than in others guidelines, both in appropriate (3.1%, 95% CI = 2.9–3.2 vs. 2.45%, 95% CI = 1.9–3.1; $P = 0.0495$) and inappropriate (0.1%, 95% CI = 0.87–1.31 vs. 0%, 95% CI = 0–0.26; $P < 0.0001$) endoscopies.

4. Discussion

UGI endoscopy represents the gold-standard for detecting mucosal abnormalities in the upper-GI tract, and it represents one of the most frequently performed diagnostic procedures worldwide. Multiple guidelines have been published in the last 20 years in order to prevent an inappropriate use of this procedure [4–8]. Despite this, a definite quote of UGIs with inappropriate indications remains [3]. This leads to both unacceptable consume of health resources and detrimental increase of waiting list in the open access endoscopic systems. By collecting 53,000 patients, this comprehensive review showed that more than 1 every 5 UGIs was performed for an inappropriate indication. A significant decrease in the inappropriateness rate occurred between data collected before and after the 2000, but disappointingly no further decrease was observed following the 2005. Our data also found that the prevalence of relevant findings was significantly higher when UGIs were performed for an appropriate rather than inappropriate indication. Indeed, 1 additional clinically relevant finding was detected every 12 endoscopic examinations performed for an appropriate rather than inappropriate indication. Noteworthy, the probability of finding an upper GI cancer was more than 3-fold higher in the appropriate than inappropriate procedures, with nearly 3 and less than 1 case every 100 endoscopies, respectively. Of note, in one series [36], 10 out of 70 GI cancers were detected in UGIs classified as inappropriate according to the ASGE guidelines only because of 'research of primitive tumour in patients with adenocarcinoma metastases'. However, the NICE guidelines on metastatic malignant disease of unknown primary origin in adults suggest performing the most appropriate investigations to search for a primary site, including symptom-directed endoscopy [45]. Therefore, to identify the primary tumour may still be relevant for patient's management by the oncologist. Based on these considerations, the appropriateness of such indication could at least be reconsidered, as occurred in the BSG guidelines updated on 2013 [46]. This would further lower the cancer detection rate in the inappropriate examinations. Moreover, a decision analysis model on upper GI cancers calculated an unacceptable incremental cost of $301,203 per life-year gained with inappropriate UGIs, while a favourable cost-effectiveness ratio of $16,577 per life-year gaied was computed for those with an appropriate indication[9]. Thus, cost-effectiveness of inappropriate endoscopies is largely unsatisfactory for cancer detection.

Although reduced in the last decades, the inappropriateness rate still remained higher than 20% in the most recent studies. This is a clinically relevant result of our analysis showing that implementation of guidelines is still needed, especially among the General Practitioners who are the most frequent referral phisicians for UGIs, as reported in all the included studies.

According to our data, the overall cancer detection rate significantly increased in the endoscopies performed following the 2000, reaching a plateau thereafter. This occurred despite the incidence of gastric cancer is reducing and it was not equally replaced by the relative increase of oesophageal cancer [47]. Likewise, virtually all UGI cancers become symptomatic – generally with alarm symptoms – so that undiagnosed tumours are really rare.

This analysis demonstrated that detection of relevant findings (including peptic ulcer, oesophagitis, erosions, etc.) did not significantly increase during the last decades, even though technical improvement of endoscopic techniques occurred. This may be justified by the reduction of *H. pylori* prevalence in the general population, as well as by a large use of proton pump inhibitor (PPI) therapy in clinical practice. [48]. When considering that as many as half of the patients undergoing UGI are actually on ongoing PPI therapy, the reduction of ulcerative/erosive lesions is far from being unexpected [49,50].

Finally, we showed that adopting the ASGE criteria, the inappropriateness rate is significantly reduced as compared to other guidelines, although the diagnostic rate was lower. Of note, no case of cancers occurred in the inappropriate procedures according to other guidelines, whilst a neoplastic lesion was detected in 0.1% inappropriate procedures following the ASGE criteria. Therefore, specific studies are needed for a 'head-to-head' comparison among guidelines.

In conclusion, our very large systematic review documented that the rate of inappropriate UGI endoscopy still remains substantially high. Diagnostic yield of appropriate endoscopy is distinctly higher than that of inappropriate procedures, including detection of upper GI cancers. These data suggest that implementation of guidelines in clinical practice is urged.

Conflict of interest

None declared.

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