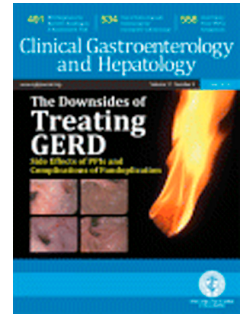# Journal Pre-proof

Effectiveness of capsule endoscopy and double-balloon enteroscopy in suspected complicated celiac disease

Francesca Ferretti, Federica Branchi, Stefania Orlando, Leda Roncoroni, Giulio Barigelletti, Sabrina Fabiano, Maurizio Vecchi, Roberto Penagini, Luisa Doneda, Luca Elli
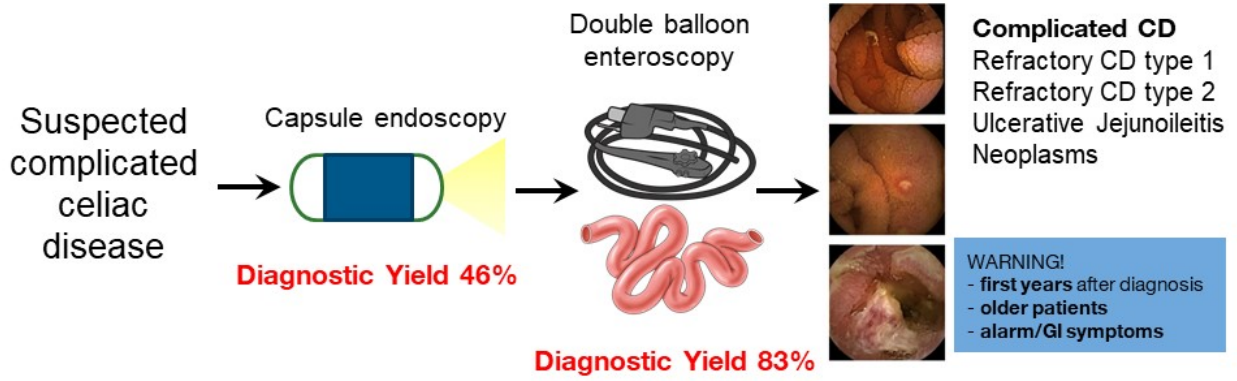
Suspected complicated celiac disease

Capsule endoscopy

Diagnostic Yield 46%

Double balloon enteroscopy

Diagnostic Yield 83%

Complicated CD
Refractory CD type 1
Refractory CD type 2
Ulcerative Jejunoileitis
Neoplasms

WARNING!
- **first years** after diagnosis
- **older patients**
- **alarm/GI symptoms**

Up to **40%** of lesions are unreachable at traditional upper GI endoscopy.

Clinical Gastroenterology and Hepatology

Effectiveness of capsule endoscopy and double-balloon enteroscopy in suspected complicated celiac disease

Short title: Enteroscopy and celiac disease

Francesca Ferretti[1], Federica Branchi[1], Stefania Orlando[1], Leda Roncoroni[1,2], Giulio Barigelletti[3], Sabrina Fabiano[3], Maurizio Vecchi[4], Roberto Penagini[4], Luisa Doneda[2], Luca Elli[1]

[1] Center for the Prevention and Diagnosis of Celiac Disease, Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy;

[2] Department of Biomedical, Surgical and Dental Sciences, Università degli Studi di Milano, Milan, Italy;

[3] Cancer Registry Unit, Fondazione IRCCS Istituto Nazionale dei Tumori Milano, Milan Italy;

[4] Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico and Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy.

Corresponding author:

Luca Elli MD PhD

Center for the Prevention and Diagnosis of Celiac Disease

Gastroenterology and Endoscopy Unit

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

E-mail: luca.elli@policlinico.mi.it

Tel.: +39 02 55033418

Abbreviations

CCD: Complicated celiac disease; CE: Capsule endoscopy; SB: Small bowel; DBE: Double-balloon enteroscopy; DY: Diagnostic yield.

ABSTRACT

Background and Aims. Complicated celiac disease (CCD) is a rare but severe condition with a poor prognosis. Guidelines recommend use of capsule endoscopy (CE) to explore the small bowel (SB), followed by a double-balloon enteroscopy (DBE) in selected cases with suspected CCD. Our study aims to evaluate the diagnostic yield of CE and DBE in identifying and monitoring CCD.

Methods. Consecutive suspected CCD patients were prospectively enrolled to undergo CE and/or DBE in the presence of persistent symptoms despite gluten-free diet (GFD), increased anti-transglutaminase antibodies titer, lack of adherence to GFD and CCD follow-up. The diagnostic yields (DY) of CE and DBE were calculated. The incidence of neoplastic complications and mortality were assessed.

Results. In total, 130 patients (97 females, age 49±16 years) underwent 151 CE and 23 DBE. The DY of CE was 46%. Patients age >50 years (at CE examination or at CD diagnosis) with a disease duration <5 years were at higher risk of positive CE (RR 1.6, 1.7 and 1.5 respectively, $p<0.05$) than their counterparts. Up to 40% of SB lesions were unreachable by upper endoscopy. At the end of the diagnostic work-up, 25 patients with pre-malignant/malignant lesions were identified: 12 type-1 refractory CD (RCD-1), 7 type-2 RCD (RCD-2), 6 enteropathy-associated T-cell lymphoma (EATL). Six patients (2 RCD-2 and 4 EATL) died.

Conclusions. In case of suspected CCD, CE should be the first-line approach to detect complications and to identify patients deserving DBE. Older and symptomatic patients with suspected CCD deserve a careful evaluation of small bowel especially during the first years after CD diagnosis.

WHAT YOU NEED TO KNOW

Background

- Capsule endoscopy and double-balloon enteroscopy can be used to diagnose small-bowel (SB) diseases.

- Their utility in celiac disease (CD) is not standardized and large prospective studies are unavailable to date; thus, the role of capsule endoscopy and double-balloon enteroscopy in monitoring patients with CD remains unclear.

Findings

- Capsule endoscopy identified small bowel lesions in 46% of patients with suspected CCD. Up to 40% of detected lesions were beyond the Treitz ligament

- Capsule endoscopy followed by double-balloon enteroscopy allowed early diagnosis of pre-neoplastic and neoplastic CD complications.

Implications for patients' care

- Sequential capsule endoscopy followed by double-balloon enteroscopy should be considered in patients with suspected CD complications.

INTRODUCTION

Even if a benign course is described in the natural history of treated celiac patients,[1,2] up to 20% of such patients show persistent or recurrent symptoms despite 6 to12 months of following strict gluten-free diet (GFD).[3] This "non-responsive" form of celiac disease (NRCD) requires a careful diagnostic work-up to identify and discriminate complicated forms of CD (CCD), which includes pre-neoplastic and neoplastic complications, such as refractory forms of CD (RCD, ulcerative jejunoileitis (UJI), enteropathy-associated T-cell lymphoma (EATL) and small-bowel (SB) adenocarcinoma. The clinical, histological and molecular distinction between RCD type 1 (RCD-1) and type 2 (RCD-2) is particularly important because RCD-2 is less frequent but characterized by a severe prognosis with mortality of up to 50% in 5 years and at higher risk of neoplastic evolution.[5]

In the setting of suspected CCD, several diagnostic strategies, including endoscopy and radiology, have been proposed.[11] In particular, the introduction of enteroscopy has facilitated the effective and complete exploration of SB in celiac patients through the combination of capsule endoscopy (CE) and double-balloon enteroscopy (DBE).[12–14] Accordingly to the European Society of Gastrointestinal Endoscopy (ESGE) recommendations,[15] CE can be performed for suspected CCD with persistent malabsorption as well as in case of elevated antibodies despite at least one year on strict GFD.[12,16,17] Subsequently, DBE can be necessary to allow a definitive diagnosis through direct visualization and biopsy .[14,18,19]

With this premise, the main aims of this study were: a) to evaluate the diagnostic performance of CE and DBE in patients with suspected CCD in terms of DY; b) to identify the main factors influencing CE results; c) to define the concordance between CE and DBE. Additionally, we

aimed to define the rates of pre-neoplastic and neoplastic complications and mortality in this large cohort of CD patients.

METHODS

Design of the study and patients

We prospectively enrolled all consecutive CD patients seen at the "Center for Prevention and Diagnosis of Celiac Disease-Fondazione IRCCS Ca' Granda-Milano" between November 2014 and March 2018. According to the main indications for enteroscopy in CD, reported in the literature,[15] the patients were enrolled in the study and divided into four groups on the basis of: a) persistence or recurrence of gastrointestinal (diarrhea, abdominal pain) and/or alarm signs/symptoms (fever, unexplained weight loss, gastrointestinal bleeding and/or persisting iron-deficiency anemia, malabsorption) after at least 6 months on strict GFD *(Symptoms group)*; b) increased anti-tissue transglutaminase antibodies (TTG) despite strict GFD *(TTG group)*; c) lack of adherence to GFD, defined as "conscious and regular gluten ingestion during the previous year" *(Non-adherent group);* d) follow-up of known CCD *(CCD group).*

In case of multiple indications for enteroscopy, group allocation was chosen by the clinicians according to a criterion of priority in the diagnostic thinking (*i.e.* alarm symptoms > TTG positivity).

The exclusion criteria were: age <18 years, contraindications to undergo enteroscopy, pregnancy, absence of the patient's written informed consent to participate in the study.
RCD-1 or RCD-2 were defined accordingly to international guidelines.[10]
In case of positive CE, DBE was to be performed within a month, if biopsies or tattooing were needed, as for multiple sampling in the case of severe or extensive atrophy (Marsh-Oberhuber graded),[20] in UJI, conflicting histological results and suspected neoplastic lesions or polyps.

Capsule endoscopy and double-balloon enteroscopy

CE and DBE were performed as previously described.[18,21] Further information about enteroscopies and recorded technical data are reported in Supplemental digital content 1.

The DY was calculated as the percentage of positive enteroscopy according to its indication. Thus, in our study, the presence of CD-related findings was considered, to include atrophy, ulcers, erosions, mass lesions/stenosis and non-specific signs of inflammation (including edema, hyperemia or isolated aphtoid erosions). Particular attention was given to atrophy, which was suspected in case of: mosaicism, scalloping, granular mucosa and/or flattened folds (Supplemental digital content 2).[22] The sensitivity and specificity of the abovementioned endoscopic markers for duodenal atrophy at histology (samples obtained by upper endoscopy and/or DBE) were investigated. The duodenal mucosa was evaluated at histology according to the Marsh-Oberhuber scale.[20]

Follow-up data

The patients had an outpatient visits scheduled at least on a yearly basis. In case of CCD the patients were extensively evaluated after CE at scheduled outpatient visits (at least 3 per year), including laboratory tests and hospitalization when needed. Newly diagnosed CCD was defined at CE and/or DBE execution. In case of suspected neoplasms, radiological examinations were performed (including CT or MR enterography and/or PET) in order to confirm or exclude the diagnosis and to establish the correct work-up.

The rate of SB neoplasms was compared to that of the general population. Standardized Incidence Ratio Analysis (*i.e.* the observed number of incidence cases against the expected number of incidence cases in the study population) was carried out to identify the variation of incidence between the study population and the general population. The incidence values were

driven from the Tumor Registry of Varese (Italy) for the 2000–2012 period. The incidences of SB adenocarcinoma and lymphoma were considered and compared.

Statistical analysis

All the statistical analysis of our study was performed by computer software: SPSS ver. 18 (IBM SPSS, Milan, Italy), GraphPad Prism ver. 6 (GraphPad Software Inc, La Jolla, CA, USA), SeerStat ver. 8.3.4 (https://seer.cancer.gov/seerstat), RStudio ver. 1.1.463 (2009-2018, RStudio, Inc.) and SurvSoft ver. 2.0 (http://www.krebsregister-bayern.de/software_e.html, Cancer Registry Bavaria).

The data were described as mean ± standard deviation (SD) or median with inter-quartile range (IQR).

A $p<0.05$ value was considered statistically significant. Categorical variables were compared with the χ^2 or Fisher's exact test, while the independent t-test or Mann-Whitney's test were used for continuous variables. Cohen's kappa coefficient (κ) was used to define the concordance between CE and DBE. The relative risk (RR) ratio defined the probability of an event occurring in the exposed *vs.* non-exposed group. Multivariate analysis was conducted by logistic regression (step-by-step method); the analyzed parameters were: age at diagnosis and at enrolment, anemia (hemoglobin levels <12 g/dL in females, <13 g/dL in males, adherence to the GFD; positivity of TTG antibodies, duration of disease (< or ≥ 5 years).

The study was approved by the local Ethics Committee (167/2012) and carried out in accordance with the Declaration of Helsinki.

RESULTS

Among 3,324 patients followed up with regular visits at our tertiary referral "Center for the Prevention and Diagnosis of Celiac Disease" every 12-18 months (840 males, aged 47±15 years at enrolment, 36±16 at CD diagnosis), 130(3.9%) consecutive celiac patients with suspected CCD were enrolled (33 males, aged 49±16 years at enrolment, 39±18 at CD diagnosis). Their demographic and clinical data are provided in Table 1.

Globally, 151 CE and 23 DBE were performed. Eighteen patients underwent more than one CE examination (2 CE in 15 patients, 3 CE in 3 patients): the reason for repeating CE was either a previous incomplete CE (3 cases) or CCD follow-up (15 cases). In order of frequency, the indications for each CE were: persistence or recurrence of symptoms despite GFD (57, 38%), lack of adherence to GFD (43, 28%), CCD follow-up (26, 18%) and increased TTG values (25, 16%). In 21 cases CE positive required DBE because of extensive bioptic sampling (14), UJI (2), suspected neoplastic lesions (3) and polyps (2); in 2 cases, DBE was the first-line option because of clinical contraindications to CE. Enteroscopy was antegrade in 19 and retrograde in 4. The mean procedure time was 41±7 minutes with a mean 165±67 cm insertion depth. No complications were recorded.

Diagnostic yield of enteroscopy

The DY of CE was 46% (69/151). The main findings were atrophy, ulcers/erosions, masses/stenotic lesions or non-specific signs of inflammation (including edema, hyperemia or isolated aphtoid erosions) (Table 2). As expected, the DY was significantly higher in the follow-up of known CCD (p<0.05, Figure 1).

The localization of SB lesions is depicted in Figure 2. Interestingly, in 27/69(40%) cases the lesions could not be assessed by upper endoscopy and CE allowed their correct definition and extension,, including 2 cases of EATL, 1 of UJI and 11 findings of ulcers or erosions in the jejunum or ileum. Moreover, in 39/69(57%) cases CE excluded any SB involvement except for the duodenum.

In our study, the DY for CD-related lesions significantly varied according to age at CE execution, age at CD diagnosis and disease duration (< or $\geq$ 5 years), while no statistical differences were found in patients showing anemia, positive TTG antibodies and non-adherence to GFD. In particular, the DY was significantly higher in patients older than 50 years at enrolment or at CD diagnosis (p<0.05) with an increased RR of detecting lesions at CE of 1.6 (95% CI 1.1–2.2) and 1.7 (95% CI 1.3–2.3) respectively (Figure 3A and B). Moreover, in the first 5 years after CD diagnosis an increased DY was observed (RR 1.5, 95% CI 1.1–2.1) (Figure 3C). This result was also confirmed by multivariate logistic regression analysis showing that a duration of disease <5 years was related to an increased odds ratio (OR) of 2.4 (95% CI 1.18–5.04) (Supplemental Digital Content 3).

The DY of DBE was 83% (19/23 cases). The findings were: macroscopic signs of atrophy in 15/23 (65%), erosions/ulcers in 4 (17%), malignant stenosis in 3 (13%) and polyps in 2 (9%). The concordance of CE and DBE was substantial (κ coefficient = 0.62): in 2 cases the DBE did not confirm the macroscopic signs of atrophy described at CE.

By comparing the CE findings with histology obtained via EGDS, CE sensitivity and specificity for atrophy were 63% (95%CI 0.51–0.73) and 80% (95%CI 0.68–0.89), respectively. When compared to the following DBE, histology confirmed CE signs of atrophy in all the cases with a 100% sensitivity and 80% specificity and 95% accuracy (κ=0.86). Even in the presence of neoplastic lesions, there was substantial concordance between CE and DBE

(91% accuracy, κ=0.62): DBE was positive in one case, but biopsies were inadequate because of a serrated stenosis, and DBE was also positive in another case for an ulcer that histology revealed to be neoplastic.

Follow-up and clinical results

After a complete diagnostic work-up and a median 13-month follow-up (IQR 6–19), the CCD rate of our patient cohort was 19% (25/130). The overall CCD prevalence in our Center was 0.8%.

In the *Symptoms group, TTG group* and *Non-adherent group,* the sequential approach with CE and DBE allowed a new diagnosis of CCD in 16/119(13%) patients: 8 RCD-1, 3 RCD-2, 5 EATL cases (Table 3). A higher rate of complications was observed in the *Symptoms group* compared to the other groups, with a RR of 5.2 (95%CI 1.6–17.3). Consequently, according to the novel enteroscopic diagnosis, a different clinical management approach was adopted. In case of RCD-1 diagnosis corticosteroids were administered, including oral budesonide or prednisone for outpatients and intravenous prednisone for hospitalized patients. In case of RCD-2 and/or inadequate clinical and/or histological response to steroids, immunosuppressive therapy with azathioprine, cyclosporine or cladibrine was started. Patients with EATL were treated with chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone, CHOP); in one case etoposide was added to the CHOP regimen. In two cases, after the enteroscopic work-up the diagnosis of CCD was converted to uncomplicated CD, avoiding any further invasive and expensive investigations (Table 3).

The rate of RCD diagnosis in the entire cohort was 15% (19/130): 12 RCD-1 and 7 RCD-2. They were 16 females, median age 58 years (IQR 41–63). RCD was diagnosed after a median of 36 months after CD diagnosis (IQR 16–62).

SB neoplasia was detected in 6/130 (5%) subjects. EATL was the final diagnosis in all the cases, these being 4 females, median age 56 years (IQR 52–58) and belonging to the *Symptoms group* (5 cases) and the *CCD group* (1 case).

Six deaths occurred (4 females, median age 60 years, IQR 55–67) among the 25 CCD patients; 5/6 (83%) died during the first years after CCD diagnosis. In all the cases death was CD-related: in 4 patients a fatal complication occurred during the diagnostic/therapeutic approach to EATL, in the remaining 2 patients, who presented severe malabsorption syndrome in RCD-2, sepsis was the cause (see also Table 3 and supplementary file 4 for details).

The incidence of non-Hodgkin lymphoma in our selected cohort was higher than in the general population with a total SIR (adjusted by age, year and sex) of 115,683 (95 CI 42,453–251,794), with a total 6 cases observed *vs.* 0.00001 expected (p<0.01).

DISCUSSION

This is the first study evaluating a large cohort of celiac patients during clinical, serologic and endoscopic follow-up. For such patients a sequential CE-DBE approach was chosen to identify and monitor SB complications and neoplasms. According to our results, the prevalence of CCD in our tertiary referral center was about 0.8%, suggesting the rarity of the condition. However, a high incidence of pre-neoplastic and neoplastic complications compared to the general population was confirmed. Thus, an early thorough diagnostic approach is recommended.

Perez-Cuadrado et al.[17] have recently demonstrated that CE is a minimally invasive instrument to effectively evaluate the SB mucosa in patients with persistent or novel symptoms despite on-going GFD. In our cohort the global DY of CE was 46% with 68/151 SB atrophy cases, its being almost comparable to the DY of CE in other clinical settings, such as obscure gastrointestinal bleeding (OGIB) (46-62%)[23,24] and iron-deficiency anemia (30-66%)[25–27]. Interestingly, in this COVID-19 era the diagnostic approach with such a non-aerosol generating procedure as CE should be encouraged, even if personal protective equipment (PPE) and accurate disinfection of instruments are recommended.[28]

The concordance of macroscopic endoscopic markers with histology is controversial: among different studies, the overall specificity and sensitivity sway from 83% to 100%, and from 6% to 94%, respectively.[22,29,30] In our study CE sensitivity and specificity to identify duodenal atrophy were 63% and 80% respectively, comparable to the literature values.[31] Surprisingly, in those patients undergoing DBE after positive CE the concordance between CE and DBE was substantial (κ=0.62) and after DBE histology confirmed the endoscopic signs of atrophy in all the cases with 100% sensitivity and 80% specificity. In the presence of neoplastic lesions the degree of accuracy was 91%. However, the fair sensitivity of endoscopic markers requires that bioptic sampling be always performed: in this setting, the chance to explore and sample the

whole length of the SB mucosa by CE, firstly, and targeted DBE later can significantly extend the diagnostic accuracy of this invasive technique for selected patients.

Interestingly, up to 40% of patients presented lesions in the distal portions of SB that would have been missed at traditional upper endoscopy. Both neoplastic (2 EATL) and pre-neoplastic lesions (extensive atrophy/erosions and UJI) were correctly identified, allowing for the prompt modification of the patients' therapeutic management, for instance, with cladribine treatment for RCD-2 or chemotherapy protocols.

In our cohort almost all the neoplastic complications occurred in the presence of alarm or recurring symptoms with a high mortality rate after CCD diagnosis. Therefore, particular attention should be paid to alarm symptoms or persisting/recurring gastrointestinal symptoms despite correct GFD during the first months, as recently suggested in the literature.[17] According to our results, the persistence of atrophy is not related to TTG antibody positivity as demonstrated by a recent meta-analysis.[32] Similarly, non-adherence to GFD does not affect CE results and no complications were recorded among non-adherent patients. In this context the role of gluten remains unclear: contradictory reports have been published about the protective role of GFD against the development of malignancies in CD patients.[33–35] On the contrary, patients aged ≥ 50 years at both CE examination and CD diagnosis have shown an increased relative risk of positive CE, supporting the need for stricter follow-up (as reported by Biagi et al.[36]). Moreover, a shorter course of CD is seen among positive CE and EATL onsets, according to studies demonstrating both a higher rate of complications with higher risk of lymphoma during the first few years after CD diagnosis and the normalization of overall mortality rates 5 years after diagnosis.[37]

In conclusion, even if CCD is a rare condition affecting only a small portion of CD subjects,[6] the rates of neoplastic complications and mortality are significantly higher in this subgroup than in the general population or patients with non-complicated CD.[38] The first years after diagnosis seem to be most critical, especially for older patients, and those with alarm symptoms. We did not find any association between positive serology or non-adherence to GFD with CCD.[35] We also found that CE and DBE greatly improved the endoscopic DY for CD complications and these tests were valuable tools for managing symptomatic or at-risk CD patients.[18] Our results show that a sequential CE-DBE approach is effective and should be considered as the first-line approach to assess at-risk patients and detect CD-related complications.[13]

REFERENCES

1. Elli L, Ferretti F, Orlando S, et al. Management of celiac disease in daily clinical
    practice. Eur J Intern Med 2019;61:15-24.
    http://www.ncbi.nlm.nih.gov/pubmed/30528262. Accessed April 11, 2020.

2. Caio G, Volta U, Sapone A, et al. Celiac disease: a comprehensive current review.
    BMC Med 2019;17:1-20.

3. Leffler DA, Dennis M, Hyett B, et al. Etiologies and Predictors of Diagnosis in
    Nonresponsive Celiac Disease. 2007.

4. Elli L, Branchi F, Sidhu R, et al. Small bowel villous atrophy: celiac disease and
    beyond. Expert Rev Gastroenterol Hepatol 2017;11.

5. Malamut G, Cellier C. Refractory Celiac Disease. Gastroenterol Clin North Am
    2019;48:137-144.

6. Daum S, Cellier C, Mulder CJJ. Refractory coeliac disease. Best Pract Res Clin
    Gastroenterol 2005;19:413-424.

7. Ilus T, Kaukinen K, Virta LJ, et al. Refractory coeliac disease in a country with a high
    prevalence of clinically-diagnosed coeliac disease. Aliment Pharmacol Ther
    2014;39:418-425.

8. Al-toma A, Verbeek WHM, Hadithi M, et al. Survival in refractory coeliac disease
    and enteropathy-associated T-cell lymphoma: Retrospective evaluation of single-
    centre experience. Gut 2007;56:1373-1378.

9. Vaira V, Gaudioso G, Laginestra MA, et al. Deregulation of miRNAs-cMYC circuits
    is a key event in refractory celiac disease type-2 lymphomagenesis. Clin Sci

2020;134:1151-1166.

10. Al-Toma A, Volta U, Auricchio R, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United Eur Gastroenterol J 2019;7:583-613.

11. Branchi F, Locatelli M, Tomba C, et al. Enteroscopy and radiology for the management of celiac disease complications: Time for a pragmatic roadmap. Dig Liver Dis 2016;48:578-586.

12. Pennazio M, Spada C, Eliakim R, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2015;47:352-376.

13. Elli L, Casazza G, Locatelli M, et al. Use of enteroscopy for the detection of malignant and premalignant lesions of the small bowel in complicated celiac disease: a meta-analysis. Gastrointest Endosc 2017;86.

14. Tomba C, Sidhu R, Sanders DS, et al. Celiac disease and double-balloon enteroscopy: What can we achieve? J Clin Gastroenterol 2016;50.

15. Rondonotti E, Spada C, Adler S, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Technical Review. Endoscopy 2018;50:423-446.

16. Yung DE, Rondonotti E, Giannakou A, et al. Capsule endoscopy in young patients with iron deficiency anaemia and negative bidirectional gastrointestinal endoscopy.

United Eur Gastroenterol J 2017;5.

17. Perez-Cuadrado-Robles E, Lujan-Sanchis M, Elli L, et al. Role of capsule endoscopy in alarm features and non-responsive celiac disease: A European multicenter study. Dig Endosc 2018.

18. Tomba C, Elli L, Bardella MT, et al. Enteroscopy for the early detection of small bowel tumours in at-risk celiac patients. Dig Liver Dis 2014;46.

19. Fukumoto A, Tanaka S, Shishido T, et al. Comparison of detectability of small-bowel lesions between capsule endoscopy and double-balloon endoscopy for patients with suspected small-bowel disease. Gastrointest Endosc 2009;69:857-865.

20. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: Time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol 1999;11:1185-1194.

21. Brotz C, Nandi N, Conn M, et al. A validation study of 3 grading systems to evaluate small-bowel cleansing for wireless capsule endoscopy: a quantitative index, a qualitative evaluation, and an overall adequacy assessment. Gastrointest Endosc 2009;69.

22. Ianiro G, Gasbarrini A, Cammarota G. Endoscopic tools for the diagnosis and evaluation of celiac disease. World J Gastroenterol 2013;19:8562-8570.

23. Shishido T, Oka S, Tanaka S, et al. Diagnostic yield of capsule endoscopy vs. double-balloon endoscopy for patients who have undergone total enteroscopy with obscure gastrointestinal bleeding. Hepatogastroenterology 2012;59:955-959.

24. Teshima CW, Kuipers EJ, van Zanten SV, et al. Double balloon enteroscopy and

capsule endoscopy for obscure gastrointestinal bleeding: An updated meta-analysis. J Gastroenterol Hepatol 2011;26:796-801.

25.   Koulaouzidis A, Rondonotti E, Giannakou A, et al. Diagnostic yield of small-bowel capsule endoscopy in patients with iron-deficiency anemia: A systematic review. Gastrointest Endosc 2012;76:983-992.

26.   Sidhu R, Sanders DS, Morris AJ, et al. Guidelines on small bowel enteroscopy and capsule endoscopy in adults. Gut 2008;57:125-136.

27.   Pasha SF, Leighton JA. Evidence-Based Guide on Capsule Endoscopy for Small Bowel Bleeding. Gastroenterol Hepatol (N Y) 2017;13:88-93.

28.   Elli L, Rimondi A, Scaramella L, et al. Endoscopy during the Covid-19 outbreak: experience and recommendations from a single center in a high-incidence scenario. Dig Liver Dis 2020.

29.   Smith AD, Graham I, Dudfield J, et al. A prospective endoscopic study of scalloped folds and grooves in the mucosa of the duodenum as signs of villous atrophy. Gastrointest Endosc 1998;47:461-465.

30.   Bardella MT, Minoli G, Radaelli F, et al. Reevaluation of duodenal endoscopic markers in the diagnosis of celiac disease. Gastrointest Endosc 2000;51:714-716.

31.   Barret M, Malamut G, Rahmi G, et al. Diagnostic yield of capsule endoscopy in refractory celiac disease. Am J Gastroenterol 2012;107:1546-1553.

32.   Silvester JA, Kurada S, Szwajcer A, et al. Tests for Serum Transglutaminase and Endomysial Antibodies Do Not Detect Most Patients With Celiac Disease and Persistent Villous Atrophy on Gluten-free Diets: a Meta-analysis. Gastroenterology

2017;153:689-701.e1.

33. Elli L, Bonura A, Garavaglia D, et al. Immunological comorbity in coeliac disease: Associations, risk factors and clinical implications. J Clin Immunol 2012;32.

34. Elli L, Discepolo V, Bardella MT, et al. Does gluten intake influence the development of celiac disease-associated complications? J Clin Gastroenterol 2014;48.

35. Elli L, Bascuñán K, Di Lernia L, et al. Safety of occasional ingestion of gluten in patients with celiac disease: A real-life study. BMC Med 2020;18.

36. Biagi F, Schiepatti A, Maiorano G, et al. Risk of complications in coeliac patients depends on age at diagnosis and type of clinical presentation. Dig Liver Dis 2018;50:549-552.

37. Eigner W, Bashir K, Primas C, et al. Dynamics of occurrence of refractory coeliac disease and associated complications over 25 years. Aliment Pharmacol Ther 2017;45:364-372.

38. Malamut G, Afchain P, Verkarre V, et al. Presentation and Long-Term Follow-up of Refractory Celiac Disease: Comparison of Type I With Type II. Gastroenterology 2009;136:81-90.

FIGURE LEGENDS

Figure 1. Diagnostic yield of capsule endoscopy (CE) according to the clinical indication: a) persistence or recurrence of gastrointestinal and/or alarm symptoms after at least 6 months on strict GFD *(Symptoms group)*; b) increased anti-tissue transglutaminase antibodies (tTG) despite strict GFD *(TTG group)*; c) lack of adherence to GFD, defined as "conscious and regular gluten ingestion in the previous year" *(Non-adherent group)*; d) follow-up of known CCD *(CCD group)*.

Figure 2. Localization of lesions identified by capsule endoscopy (CE) throughout the small bowel. Dotted lines: separation of the three tertiles of the small bowel (proximal, middle, and distal) defined on the basis of the capsule passage time. In the lower panel the distribution of atrophy and erosive lesions (%) along the small bowel is reported.

Figure 3. Diagnostic yield of capsule endoscopy according to the age of patients at enrolment (A), the age at diagnosis of celiac disease (B) and the duration of celiac disease (C).

SUPPLEMENTARY FILES – LEGENDS

Supplemental digital content 1. Evaluated technical parameters of Capsule Endoscopy (CE) and Double-Balloon Enteroscopy (DBE)

Supplemental digital content 2. Endoscopic findings suggestive of small bowel atrophy: A) flattened folds; B) mosaic pattern; C) scalloping; D) granular mucosa

Supplemental digital content 3. Multivariate analysis of the variables associated with positive Capsule Endoscopy (CE). Age_dg: age at diagnosis; Age: age at enrolment; Anemia: Hemoglobin levels <12 g/dL in females, <13 g/dL in males; GFD: non-adherence to gluten-free diet; TTGA Pos: positivity of antitransglutaminase antibodies; Duration: duration of disease < or ≥ 5 years

Supplemental digital content 4. Clinical characteristics of the 6 patients deceased in the enrolled cohort.

Table 1. Demographic and clinical data of the patients undergoing CE and/or DBE.

	CD patients
Patients, n	130
Sex M/F, n (%)	33/97 (25/75)
Age at enrolment (years)*	49±16
Age at diagnosis (years)*	39±18
BMI (kg/m^2)*	22±4
Patients with autoimmune co-morbidities, n (%)	30 (25)
Patients with other co-morbidities, n (%)	53 (52)
Anemic patients**, n (%)	20 (15)
TTG Ab positivity, n (%)	47 (36)
GFD adherence, n (%)	89 (68)
CD duration (years)*	10±9
Autoimmune co-morbidities (n)	Hashimoto's thyroiditis (16)
	Autoimmune hepatitis/PBC (6)
	Dermatitis herpetiformis (5)
	Vitiligo (3)
	Sjogren syndrome (2)
	Lichen (1)
	Lupus (1)
	Autoimmune hypoparathyroidism (1)
Non-autoimmune co-morbidities (n)	Osteoporosis/osteopenia (27)
	Hypertension (9)
	Previous extra-intestinal cancer (8)
	Cirrhosis/chronic liver disease (6)
	Neurological disease (5)
	Cardiovascular disease (4)
	Hematological disease (3)
	Lymphocytic colitis (2)
	Kidney disease (2)
	Previous gastrointestinal cancer (1)
	Common variable immunodeficiency (1)
	Chronic obstructive pulmonary disease (1
	Down syndrome (1)
Upper gastrointestinal endoscopy (n)	123
Macroscopic signs of atrophy, n (%)	54 (43)
Histological atrophy***, n (%)	74 (60)

CD, celiac disease; M, males; F, females; BMI, Body Mass Index; TTG Ab, anti-transglutaminase antibodies; GFD, gluten-free diet; PBC, primary biliary cholangitis

* Mean ± standard deviation

** Hemoglobin <12 g/dL in females, <13 g/dL in males

*** Marsh 3a, 3b or 3c according to the Marsh-Oberhuber classification

Table 2. Capsule endoscopy (CE) findings.

Overall CE, n	151
Positive CE, n (%)	69 (46)
Atrophy	68 (45)
Ulcers/erosions	18 (12)
Masses/stenotic lesions	2 (1)
Signs of inflammation	8 (5)
Markers of mucosal atrophy	
Mosaicism, n (% atrophy)	39 (57)
Scalloping	61 (90)
Granular mucosa	29 (43)
Flattened folds	12 (18)
Other pathological findings, n (%)	11 (7)*
Complete examination, n (%)	145 (96)**
Adequate bowel preparation, n (%)	145 (96)
Gastric transit time	
Median time (IQR)	16 minutes (8–32)
SB transit time	
Median time (IQR)	282 minutes (IQR 233–372)
Complication rate, n (%)	1 (0.7)***

* Gastric erosion (1), SB angiectasia (5), SB diverticulum (1), sub-mucosal bulgings (4)

** SB exploration was incomplete in 6 cases: 1 for insufficient bowel preparation, 1 for stenotic lesion and 4 for slow transit time.
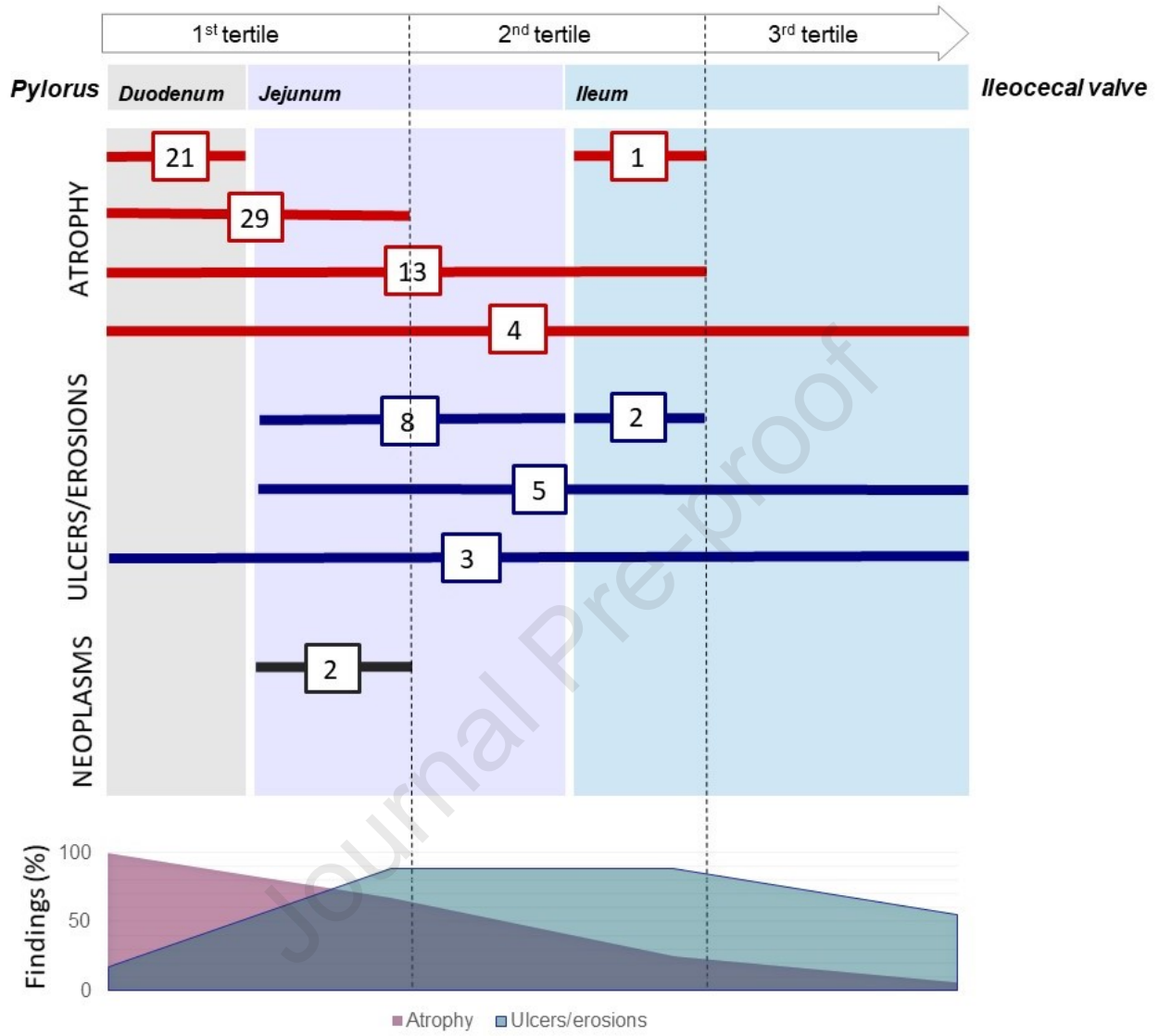
*** Capsule retention in a poorly symptomatic neoplastic stenosis; the capsule was retrieved during surgery for intestinal resection.
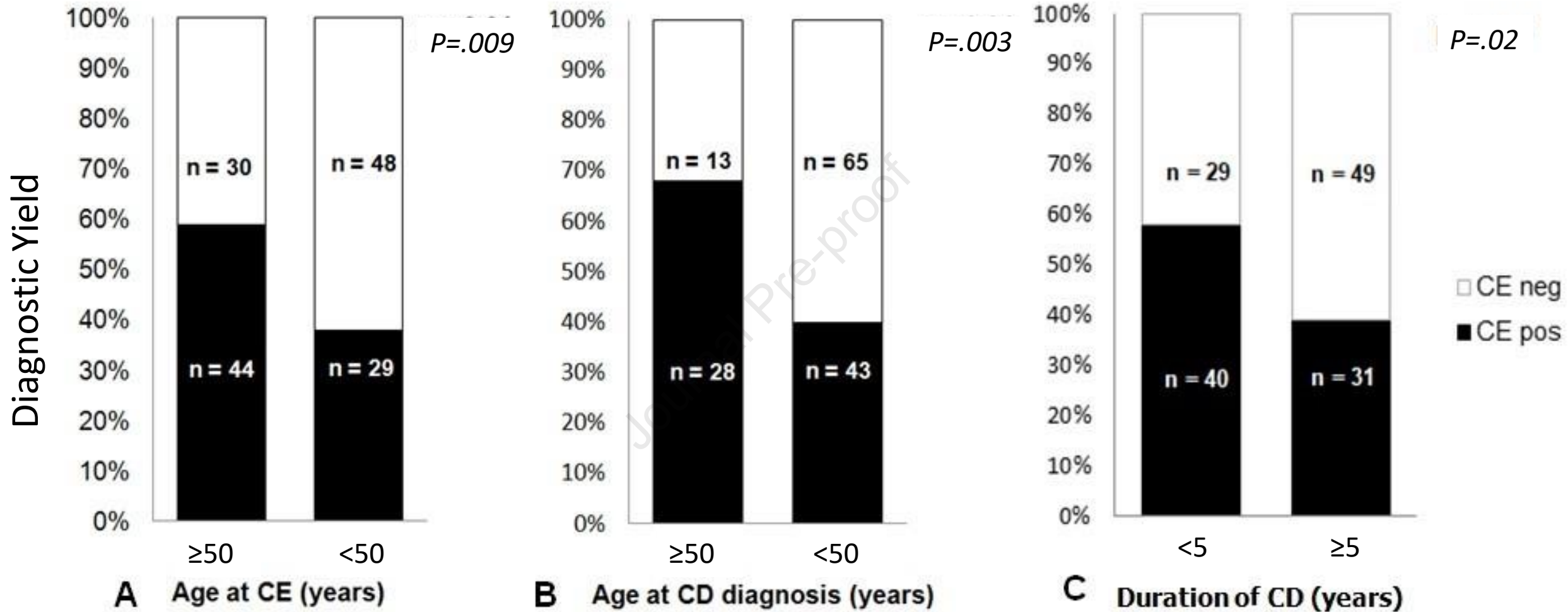
Table 3. Number of complications and deaths in the study population according to clinical indications: a) persistence or recurrence of gastrointestinal and/or alarm symptoms after at least 6 months on strict GFD (*Symptoms group*); b) increased anti-tissue transglutaminase antibodies (TTG) despite strict GFD (*TTG group*); c) lack of adherence to GFD, defined as "conscious and regular gluten ingestion in the previous year" (*Non-adherent group*); d) follow-up of known CCD (*CCD group*).

GROUP	PTS	CE	DBE	UCD	CCD			DEATHS
					RCD-1	RCD-2	EATL	
Symptoms	54	57	12	41	5	3	5	3
TTG	23	25	3	20	3	0	0	0
Non-adherent	42	43	3	42	0	0	0	0
CCD	11	26	5	2*	4	4	1	3
Total	130	151	23	112	12	7	6	6

Pts: patients; CE: capsule endoscopy; DBE: double-balloon enteroscopy; UCD: uncomplicated celiac disease; CCD: complicated celiac disease; RCD-1: refractory celiac disease type 1; RCD-2: refractory celiac disease type 2; EATL: enteropathy-associated T-cell lymphoma.

*2 patients were reclassified after enteroscopic work-up

Diagnostic Yield

A — Age at CE (years): ≥50 (n = 30 CE neg, n = 44 CE pos), <50 (n = 48 CE neg, n = 29 CE pos), P=.009

B — Age at CD diagnosis (years): ≥50 (n = 13 CE neg, n = 28 CE pos), <50 (n = 65 CE neg, n = 43 CE pos), P=.003

C — Duration of CD (years): <5 (n = 29 CE neg, n = 40 CE pos), ≥5 (n = 49 CE neg, n = 31 CE pos), P=.02

☐ CE neg
■ CE pos
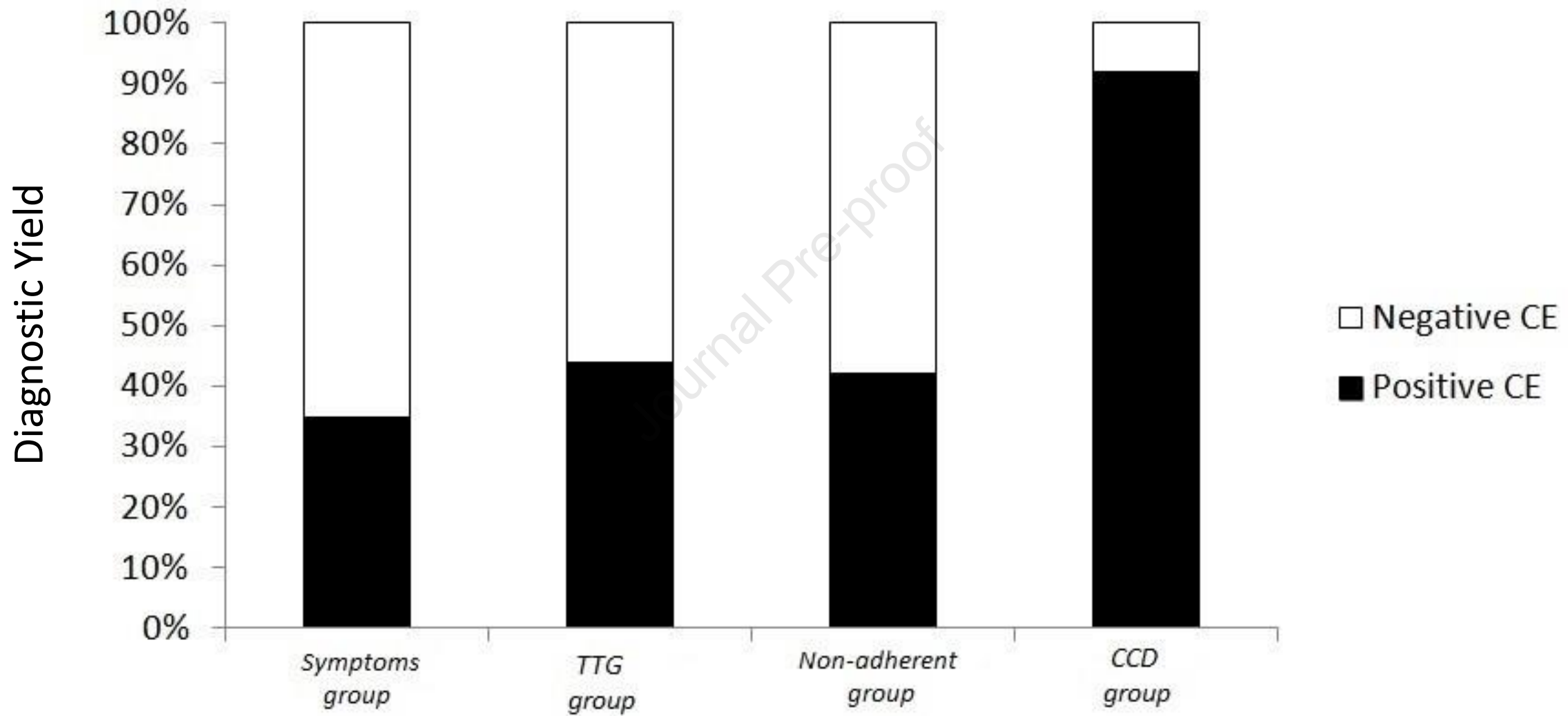
Supplemental Digital Content 1.

Capsule endoscopy and double balloon enteroscopy techniques

Capsule endoscopy (Pillcam SB3, Given Imaging, Yoqneam, Israel) was performed after intestinal cleaning with a 2-litre polyethylene-glycol (PEG) based solution, taken the day before procedure and with overnight fasting. Before ingesting the capsule, the Given Imaging recording system was positioned according to the manufacturer's instructions; data were downloaded on a dedicated computer workstation and analyzed by software (Given Imaging, Yoqneam, Israel). For those patients who had undergone major abdominal surgery or presented symptoms suggesting a possible intestinal obstruction, CE was preceded by patency capsule (Agile, Given Imaging, Yoqneam, Israel). According to the Given Imaging specifications, the examination by Pillcam SB3 lasted at least 9 hours. All the registrations were conducted till battery exhaustion

The CE imaging results were defined as "adequate" following Brotz et al.[1]

Double-balloon enteroscopy (DBE) (Fujifilm, EN-580T) was performed via oral or anal route according to the previous findings and clinical decision. The suggested preparation for oral DBE was 12 hours of food and approximately 4 hours of clear liquid fasting. Standard colonoscopy preparation with restricted diet and laxatives was necessary for retrograde examination. Conscious or deep sedation was administered (midazolam and/or pethidine, propofol).

Three CE readers with great experience (>100 videos per year reviewed, with a high prevalence of celiac patients) examined CE.

The following table describes the evaluated technical parameters of Capsule Endoscopy (CE) and Double Balloon Enteroscopy (DBE).

Capsule Endoscopy	Double-balloon enteroscopy
Clinical indication	Clinical indication
CE completeness	Type of procedure (antegrade or
Bowel preparation	retrograde)
Gastric and small bowel transit time	Type of anesthesia
Diagnostic yield (extension and	Duration of the procedure (minutes)
localization of findings)	Depth of insertion (cm)
Presence of mucosal atrophy	Diagnostic yield (extension and
(localization and extension)	localization of findings)
Presence of other pathological findings	Histological results
Complication rate	Complication rate

Reference

1.   Brotz C, Nandi N, Conn M, et al. A validation study of 3 grading systems to evaluate small-bowel cleansing for wireless capsule endoscopy: a quantitative index, a qualitative evaluation, and an overall adequacy assessment. Gastrointest Endosc 2009;69.

Supplemental digital content 3. Multivariate analysis of the variables associated with positive Capsule Endoscopy (CE). Age_dg: age at diagnosis; Age: age at enrolment; Anemia: Hemoglobin levels <12 g/dL in females, <13 g/dL in males; GFD: non-adherence to gluten-free diet; TTGA Pos: positivity of antitransglutaminase antibodies; Duration: duration of disease < or ≥ 5 years

		P	OR	95% CI
STEP 1	Age_dg	0.52	0.68	0.21-2.17
	Age	0.54	0.73	0.27-2.00
	Anemia	0.32	1.67	0.60-4.83
	GFD	0.52	1.36	0.53-3.49
	TTGAPos	0.81	1.10	0.51-2.36
	Duration<5years	0.05	2.26	0.99-5.19
	Constant	0.33	0.48	
STEP 2	Age_dg	0.50	0.67	0.21-2.15
	Age	0.56	0.74	0.27-2.01
	Anemia	0.33	1.67	0.59-4.73
	GFD	0.53	1.36	0.53-3.47
	Duration<5years	0.05	2.28	1.00-5.22
	Constant	0.35	0.51	
STEP 3	Age_dg	0.16	0.54	0.22-1.29
	Anemia	0.36	1.62	0.58-4.56
	GFD	0.60	1.28	0.51-3.22
	Duration<5years	0.06	2.19	0.97-4.92
	Constant	0.36	0.52	
STEP 4	Age_dg	0.17	0.54	0.22-1.30
	Anemia	0.39	1.58	0.57-4.39
	Duration<5years	0.07	2.03	0.95-4.36
	Constant	0.44	0.67	
STEP 5	Age_dg	0.16	0.54	0.22-1.29
	Duration	0.06	2.10	0.99-4.49
	Constant	0.91	0.96	
STEP 6	Duration<5years	**0.02**	**2.44**	1.18-5.04
	Constant	0.30	0.77	
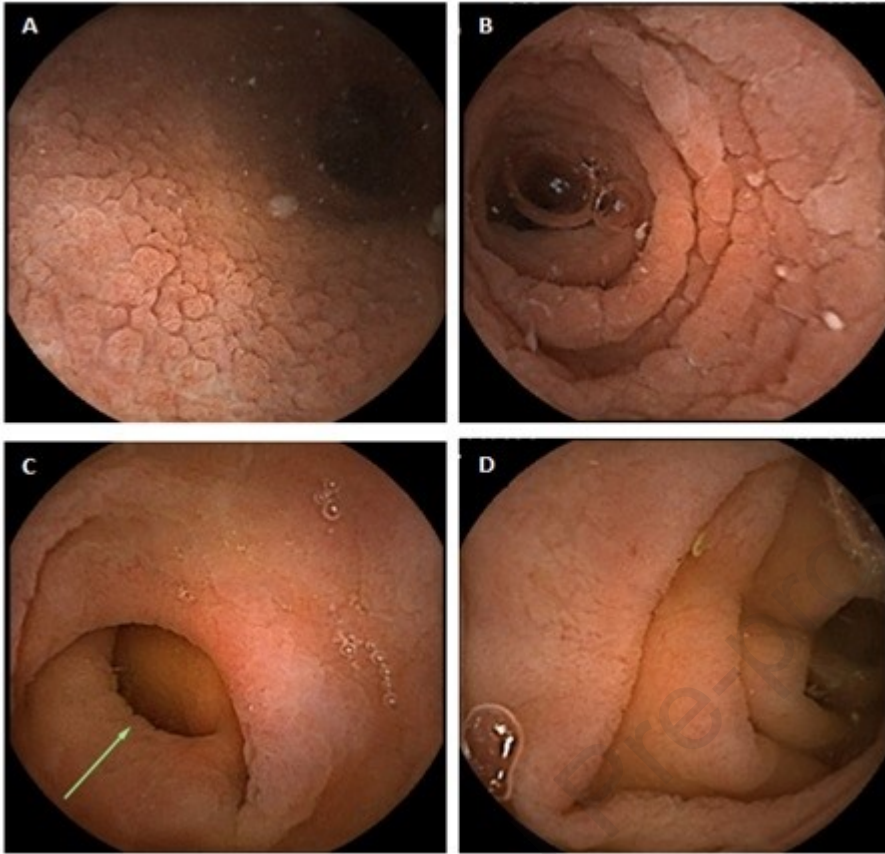
Supplemental content 4. Clinical characteristics of the 6 patients deceased in the enrolled cohort

PT	Gender	Age at diagnosis (years)		Death (years)	BMI (kg/m²)	Comorbidities	Duodenal histology	Monoclonal TCR/CD3s-cyt+ IELs	Findings		Diagnosis	Cause of death
		CD	CCD						VCE	DBE		
#1	M	62	63	64	16	None	3c	Yes	Ulcerative jejunoileitis and diffuse small bowel atrophy		RCD2	Sepsis, severe malnutrition
#2	M	68	69	69	18	Cardiaomyopathy	3c	Yes	NA	Extensive jejunal atrophy and ulcers	EATL	Cardiac Failure
#3	F	55	56	57	27	Previous rectal cancer	3c	Yes	Jejunal ulcerated mass and extensive atrophy		EATL	Hemorragic shock
#4	F	53	56	72	15	Osteoporosis, HCV hepatitis, neuropathy	3c	Yes	Duodenal and jejunal severe mucosal atrophy		RCD2	Sepsis, severe malnutrition
#5	F	32	33	33	19	Autoimmune hepatitis	3c	Yes	Diffuse and severe small bowel atrophy and ileal ulcers		EATL	Sepsis, multiorgan failure
#6	F	56	57	58	27	None	3b	Yes	NA	Mucosal atrophy and jejunal ulcerated stenosis	EATL	Fatal complication during neurological investigation

CD, celiac disease; CCD, complicated celiac disease, BMI, Body Mass Index; GFD, gluten-free diet; TCR, T-cell receptor; IELs, intraepithelial lymphocytes; VCE, videocapsule endoscopy; DBE, double-balloon enteroscopy; M, male; F, female; RCD2, refractory celiac disease type 2; EATL, enteropathy-associated T-cell lymphoma; NA, not available.

WHAT YOU NEED TO KNOW

Background

● Capsule endoscopy and double-balloon enteroscopy can be used to diagnose small-bowel (SB) diseases.

● Their utility in celiac disease (CD) is not standardized and large prospective studies are unavailable to date; thus, the role of capsule endoscopy and double-balloon enteroscopy in monitoring patients with CD remains unclear.

Findings

● Capsule endoscopy identified small bowel lesions in 46% of patients with suspected CCD. Up to 40% of detected lesions were beyond the Treitz ligament

● Capsule endoscopy followed by double-balloon enteroscopy allowed early diagnosis of pre-neoplastic and neoplastic CD complications.

Implications for patients' care

● Sequential capsule endoscopy followed by double-balloon enteroscopy should be considered in patients with suspected CD complications.