

RESPONSE TO THE REVIEW

On behalf of the authors, I would like to thank the reviewers for their thorough review of our manuscript.

All the comments from the reviewers have been carefully addressed. This has allowed us to update the manuscript, and therefore to increase the quality of the layout.

Below please find the answers to the reviewers' comments.

Reviewer #1:

Specific Comments to Authors: Patients with gastric mucosa atrophy, intestinal metaplasia and dysplasia have an increased risk of gastric cancer. *Helicobacter pylori* infection plays an important role in the occurrence and development of gastric mucosa inflammation, atrophy, intestinal metaplasia, and gastric cancer. *Helicobacter pylori* eradication therapy can reduce the risk of gastric cancer. For patients with atrophic and intestinal metaplasia of gastric mucosa, even if *Helicobacter pylori* has been successfully eradicated, close endoscopic follow-up is still required for these patients. The authors present a retrospective case series and analysis of the available literature evidence on gastric mucosal precancerous lesion characteristics preceding gastric adenocarcinoma development. They proposed subtyping of intestinal metaplasia have an important role in the risk stratification for surveillance decisions. There are some problems: Out of 1681 subjects in the Biobank, gastric adenocarcinoma was detected in five cases. It is recommended to supplement the following information: The baseline demographic characteristics of the 1681 subjects. Such as age, sex, positive family history, stage of atrophic gastritis, history of *Helicobacter pylori* infection, etc. Mean follow-up time of these patients. Demographic information of 5 patients with gastric cancer: family history of gastric cancer, smoking history, drinking history, *Helicobacter pylori* infection status, etc.

The baseline demographic characteristics of the 1681 patients has been added

Additional information of the 5 patients having developed gastric cancer has been added.

Reviewer #2:

Specific Comments to Authors: Dear Authors, I have read your article in its

entirety. I reviewed your informative and interesting article with interest. I suggest you to carefully check the misspellings in your text. King Regards,

The manuscript has been checked and corrected by an English-speaking professional in the field

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a **native English-speaking expert** to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

The manuscript has been checked and corrected by an English-speaking professional in the field

On behalf of the authors

Mārcis Leja

Name of Journal: *World Journal of Clinical Cases*

Manuscript Type: MINIREVIEWS with a retrospective case series analysis

The role of pre-existing incomplete intestinal metaplasia in gastric adenocarcinoma – a retrospective case series analysis

Short title:

Bogdanova I *et al.* Incomplete gastric intestinal metaplasia/gastric adenocarcinoma/risk

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Author contributions: Bogdanova I designed the outline and performed all the pathology evaluation, including specific staining for intestinal metaplasia subtypes, performed the analysis of the obtained results and design of the tables;

Aleksandraviča I coordinated the biobanking activities and data acquisition; Tolmanis I reviewed the endoscopy reports; Leja M coordinated the research and participated in the outline design and writing of the paper, all authors were involved in writing and final approval of the manuscript.

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Abstract

Background: Risk stratification for patients with gastric precancerous lesions for endoscopic surveillance remains controversial. Here we are presenting a retrospective analysis of patients having developed gastric adenocarcinoma during the period of follow-up.

Methods: We conducted a retrospective study on patients having undergone upper endoscopy prior to the development of gastric adenocarcinoma. The presence and stage of precancerous lesions as well as subtype of intestinal metaplasia at the baseline endoscopy got evaluated. Literature mini-review was performed.

Results: Out of 1681 subjects in the Biobank, gastric adenocarcinoma was detected in five cases in whom previous endoscopy data with biopsies either from the corpus or antral part were available. All of the patients had incomplete intestinal metaplasia during the baseline endoscopy; all three subjects in whom intestinal metaplasia subtyping was performed according to Filipe et al, had Type III intestinal metaplasia. Two of the five cases had low OLGA and OLGIM stages (I-II) at the baseline.

Conclusions: The presence of incomplete intestinal metaplasia, in particular, that of Type III is a better predictor for gastric adenocarcinoma development than OLGA/OLGIM staging system. Subtyping of intestinal metaplasia have an important role in the risk stratification for surveillance decisions.

Key words: minireview, gastric adenocarcinoma, precancerous lesions, retrospective study, subtypes of intestinal metaplasia, OLGA/OLGIM staging

Bogdanova I, Poļaka I, Aleksandraviča I, Dzērve Z, Anarkulova L, Trone V, Tolmanis I, Leja M. The role of pre-existing incomplete intestinal metaplasia in gastric adenocarcinoma – a retrospective case series analysis

Core tip: We present a retrospective case series and analysis of the available literature evidence on gastric mucosal precancerous lesion characteristics preceding gastric adenocarcinoma development. The obtained data are strongly suggesting that subtyping of gastric intestinal metaplasia, in particular that of Type III is an important predictor for the development of adenocarcinoma. The subtype of intestinal metaplasia appears to be a better predictor for cancer than OLGA and OLGIM staging system, however larger studies would be required to confirm this.

INTRODUCTION

Atrophy, intestinal metaplasia and dysplasia are defined as precancerous lesions for gastric cancer, however the magnitude of risk for developing cancer may be substantially variable^[1]. Surveillance strategies, i.e. repeated endoscopies in patients with such lesions is recommended in Europe^[2]; yet substantial differences between the currently existing guidelines have to be noted^[3]. The Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis Intestinal Metaplasia Assessment (OLGIM) have been suggested for easier use, and claimed to be a tool for better risk-stratification^[4, 5].

Based on a long-term follow-up study on 7436 patients in Italy, OLGA staging system was suggested to be a good predictor for gastric cancer development since most of the overall 28 incident neoplasia occurred in stages III and IV^[6]. In another cohort study by the Italian investigators involving 1755 consecutive patients incident neoplastic lesions (prevalence - 0.4%; low-grade intraepithelial neoplasia - 4; high-grade intraepithelial neoplasia - 1; gastric cancer - 2) developed exclusively in patients with OLGA stages III-IV. A prospective, longitudinal multicenter study in Singapore involving 2980 subjects undergoing screening upper endoscopy with standardized gastric mucosal biopsy sampling has suggested patients with OLGIM III-IV lesions to be the highest risk-group for gastric neoplasia development (adjusted hazard ratio 20.7; 95% CI 5.04 to 85.6) whereas OLGIM II group was identified to bear an intermediate risk^[7].

A meta-analysis of six case-control studies and two cohort studies, comprising 2700 subjects has also demonstrated a significant association between the OLGA/OLGIM stages III/IV and gastric cancer risk^[8].

The potential role of gastric intestinal metaplasia subtyping has been debated for decades. The landmark study by Filipe et al.^[9] has suggested the role of a specific high-iron diamine alcian-blue (HID-AB) staining technique for assessing the presence of sialomucins and sulfomucins. However, currently the HID-AB method

is available only in a few specialized laboratories. Intestinal metaplasia can be more broadly subtyped in complete and incomplete metaplasia based on the standard hematoxylin and eosin (H&E) staining method. Incomplete intestinal metaplasia corresponds to Type II and Type III intestinal metaplasia by Filipe taken together (see Figure 1).

Based on the above, we have decided to check in our retrospective surveillance cohort the role of intestinal metaplasia subtypes in gastric cancer development as well as to review the studies in the literature that have assessed subtypes of intestinal metaplasia prior to cancer development. The secondary objective was to assess the correlation to high-risk OLGA/OLGIM stages for assuring whether OLGA and/or OLGIM staging system could serve as the single reliable parameter for risk assessment.

MATERIALS AND METHODS

General design

We requested data on gastric cancer (C16) entries to the Cancer Registry of Latvia from individuals having been enrolled to the Biobank of the Clinical and Preventive Medicine, University of Latvia and having undergone upper endoscopy in the Digestive Diseases Centre GASTRO, Riga, Latvia. Patient enrolment to the biobank was initiated in 2007, the follow-up period according to the Registry data was ending December, 2020. At the time of enrolment to the Biobank all the study subjects have provided their signed consent allowing their data to be analysed following the enrolment.

For the selected cases, the medical history available in the Digestive Diseases Centre GASTRO was analyzed; this included preceding and follow-up endoscopy data. Only patients having undergone upper endoscopy prior to the diagnosis of gastric cancer and having been biopsied from the corpus and antrum during the endoscopy were included to the analysis. Those having been diagnosed with other type of malignancies than gastric adenocarcinoma were excluded.

Consequently, in the selected group of patients, endoscopy biopsy results were re-evaluated in the Academic Histology Laboratory, Riga, Latvia.

Assessment of gastric precancerous lesions

Only cases with biopsies available from the corpus and antrum were included to the analysis; incisura biopsy was also available as the standard. Routinely, staining with H&E was used for the clinical work-up.

Whenever available, all the slides from the selected cases were re-analysed. Whenever the paraffin blocks were available, additional slides for HID-AB staining were produced, and the subtypes of intestinal metaplasia according to Filipe *et al.* were analysed.

Approaches for subtyping gastric intestinal metaplasia

Complete intestinal metaplasia is known also as small intestinal type, is characterized by the presence of absorptive cells with brush borders, goblet cells and occasionally Paneth cells, while incomplete intestinal metaplasia, known also as colonic type intestinal metaplasia – by the presence of hybrid mucous cells with large vacuoles of different sizes, without features of absorptive cells or goblet cells^[10]. When both subtypes are present (mixed intestinal metaplasia), the case is classified according the lesions of the highest risk, i.e. incomplete metaplasia.

According to the HID-AB stain, in Type I intestinal metaplasia sialomucins are present in goblet cells with no mucins in columnar cells; in Type II – sialomucins are present in goblet and columnar cells, while in Type III - sulfomucins predominate in columnar cells, and goblet cells may contain sialomucins or sulfomucins^[11].

RESULTS

Out of 1681 subjects in the Biobank (median age 59 years, 68% women, *H.pylori* positivity – 56.8% according to histology, 13% had reported gastric cancer among the 1st degree relatives, median follow-up period 9.1 years), gastric adenocarcinoma was detected in five cases fulfilling the inclusion criteria described above. Of those, 4 were women, 1 man, one woman was a current smoker, while another one – past smoker; three have reported modest use of alcohol, one had a first degree relative with a gastric cancer; the mean age at cancer development was 75.6 years (range 53-90 years). The mean period of cancer detection was 52 months (range 25-70 months) following the initial endoscopy. In all, but one case several upper endoscopies have been performed during the follow-up period. Four of the five cases were *H.pylori* positive according to the histology of the preceding endoscopy, the only *H.pylori* – negative subject was not self-reporting previous eradication therapy. For more details, see Table 1.

Patient No. 2 was the only case in which early gastric cancer was diagnosed, got the diagnosis set within a surveillance program, and was successfully managed by endoscopic submucosal resection.

At the reference endoscopy, i.e. an endoscopy prior to the cancer diagnosis with the highest-risk lesion, two patients were diagnosed with a high-grade dysplasia while the remaining three did not have any degree of dysplasia. One of the two with high-grade dysplasia was also classified as OLGA and OLGIM Stage III, while the other one – OLGA and OLGIM Stage I only. In the entire group, only two patients were stages as OLGA III (one of them – OLGIM II), whereas the majority, i.e. three cases were low OLGA and OLGIM risk stages (I and II).

In three cases in the group the material was available for an additional HID-AB staining: all three cases were diagnosed as Type III intestinal metaplasia according to Filipe et al.

DISCUSSION

Our retrospective cohort analysis was suggesting that incomplete intestinal metaplasia of the stomach mucosa, in particular, that of Type III according to Filipe *et al*, is a key predictor of gastric adenocarcinoma development.

The results in our case series of five patients having developed gastric cancer during the follow-up period is confirming the rationale for endoscopic surveillance strategies of patients with gastric precancerous lesions as suggested by the current guidelines^[2]. Three of these patients had clearly high-risk precancerous lesions (high grade dysplasia in two cases, and an addition subject with a high-risk OLGA/OLGIM stage) at the initial investigations, whereas in two cases surveillance would not been indicated unless considering the subtype of intestinal metaplasia. Both were diagnosed as OLGA and OLGIM II stage cases at the enrolment. In all the five cases incomplete intestinal metaplasia was present at the enrolment, and in all the subjects in whom HID-AB staining was available – the intestinal metaplasia was subtyped as Type III. Therefore, based on this very small cohort, subtyping of intestinal metaplasia seems to be a more important factor for risk stratification that OLGA and OLGIM staging.

Increasing evidence is becoming available on the role of intestinal metaplasia subtyping for gastric cancer risk stratification. A 20-year follow-up study of the population-based cohort in Colombia has suggested that the presence of incomplete intestinal at baseline substantially increased the risk (OR, 13.4; 95% CI, 1.8-103.8) for gastric cancer development when compared to subjects with a complete intestinal metaplasia at the enrolment.^[12]

In the Spanish multi-center study having involved 649 patients with gastric precancerous lesions at baseline 24 patients had developed gastric adenocarcinoma during the mean follow-up period of 12 years. The hazards ratio of progression to gastric cancer was 2.75 (95% CI 1.06-6.26) for those with

incomplete compared with those with complete intestinal metaplasia at baseline, after adjusting for sex, age, smoking, family history of gastric cancer and the use of non-steroidal anti-inflammatory medication^[10]. HID-AB staining was not used in the study.

These observations are supported by other studies. In France, a low gastric cancer risk country, progression towards gastric cancer was observed in two cases, both of them – had antrum limited disease (one was OLGA II, the other, - OLGA III stage), but incomplete intestinal metaplasia at the initial endoscopy^[13].

In a study from Japan altogether 4 patients have been progressing to gastric cancer during the observational period following *H.pylori* eradication; all of these patients had incomplete intestinal metaplasia in the antral part of the stomach at the enrolment^[14]. This group of researchers were using immunohistochemical staining for differentiating between the subtypes of intestinal metaplasia. Interestingly, the key objective of the study was addressing the reversibility of intestinal metaplasia; the obtained results were suggesting that incomplete intestinal metaplasia in the antrum was regressing within a 10-year period following the eradication whereas complete intestinal metaplasia did not regress either in the antrum or corpus^[14].

The study that has been conducted by our group in healthy individuals from Kazakhstan, a country with high incidence of gastric cancer, has suggested that limiting the patient surveillance of those with high OLGA or OLGIM stages may result in substantial downgrading of the risk, and therefore missing patients with high risk for surveillance as a substantial proportion of subjects with low stages according to the above classifications had incomplete intestinal metaplasia ^[15].

Recently two meta-analysis on the subtypes of gastric intestinal metaplasia and neoplasia risk have been published by researchers from China – Du et al. ^[16] has been including cohort studies (published until May 15, 2021) while Wei et al.^[17] included also case-control studies, and the analysis period was ending March 2020.

Both analysis obtained similar findings. Pooled relative risk for gastric cancer development of incomplete intestinal metaplasia when compared to complete type was 5.16 (95% CI, 3.28–8.12) in the study by Du et al.^[16], and 4.96 (95% CI 2.72–9.04) in the study by Wei et al.^[17] Both studies revealed the highest risk of progression to cancer in Type III intestinal metaplasia, i.e. 6.27 (95% CI 1.89–20.77) in the analysis by Wei et al.^[17] when compared Types I and II combined, while 6.42 (95% CI, 3.03–13.62) in the analysis by Du et al.^[16] when compared to Type I intestinal metaplasia.

There are certain limitations to our and other studies. The numbers of study subjects either in our case series or in other cohorts, including the study from France^[13], are low. Besides, there is a very limited number of laboratories that are currently using the HID-AB staining method; also in some of our patients the material was not available to apply this staining method in all. Larger series would be required for definite conclusions; European-level data collaborative for pooling the results from various studies whether published or unpublished, would be a powerful tool for the purpose.

Finally, the relevance of intestinal metaplasia subtyping has been gradually acknowledged by international guidelines. There is limited awareness among gastroenterologists of the potential prognostic value of the histological subtyping of IM^[11], and therefore, the pathologists are frequently not reporting the subtypes even though this would be important for setting the most appropriate surveillance endoscopy intervals. The latest version of MAPS (II) guideline acknowledges the role of incomplete intestinal metaplasia^[2], while this was discouraged in the initial version^[18]. Although referring to MAPS II, the recent Maastricht VI guideline suggests subtyping of intestinal metaplasia is clinically redundant if using OLGA/OLGIM staging systems^[5], which actually contradicts our findings and the above discussed evidence. We expect that increasing knowledge in the field should result in changes to upcoming editions of these guidelines.

CONCLUSION

Proper risk stratification of precancerous lesions of the stomach mucosa is important for determining the optimal surveillance strategies. The presence of incomplete intestinal metaplasia, in particular that of Type III is a better predictor for gastric adenocarcinoma development than OLGA/OLGIM staging system. Subtyping of intestinal metaplasia may have an important role in the risk stratification for surveillance decisions. Large-scale international data collaborative may be of importance to address the above issues.

ACKNOWLEDGEMENTS

We acknowledge the patients having supported their longitudinal data to be analysed as well as the services of the Biobank commonly run by the Institute of Clinical and Preventive Medicine, University of Latvia and Riga East University Hospital. Our thanks to Maria Blanca Piazuelo who has supported the implementation of HID-AB staining at the Academic Histology Laboratory and Sergejs Isajevs for the implementation of the method.

ETHICS

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Medical and Biomedical Research Ethics Committee of the Riga East University Hospital Support Foundation, protocol 18-A/16, October 6th, 2016.

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Footnotes

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other co-authors contributed their efforts in this manuscript.

Figure Legends

Figure 1 Relationships between subtypes of intestinal metaplasia (complete/incomplete; subtypes I, II, III according to Filipe et al.)

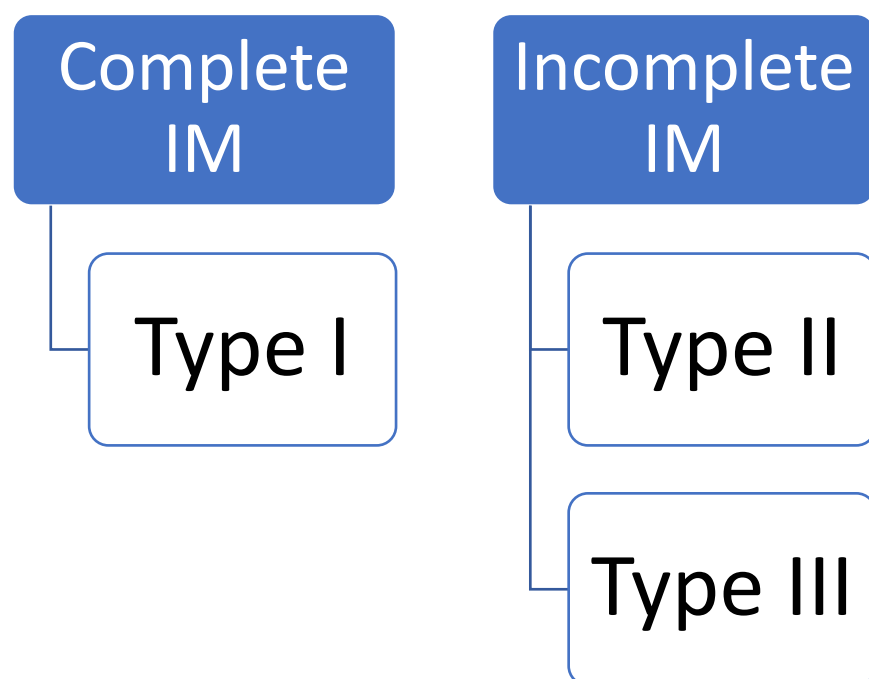


Table 1 Characteristics of the subjects having developed gastric adenocarcinoma following a previous upper endoscopy with biopsies

No	Gender	Age at cancer development	Year of enrolment	Year of cancer diagnosis	Year of death	No of preceeding upper endoscopies	Number of months of the reference endoscopy prior to cancer development	Reference endoscopy (highest risk lesion in the case of several preceeding endoscopies)					Grade of the cancer
								Dysplasia	OLGA stage	OLGIM stage	Complete/ incomplete intestinal metaplasia	Intestinal metaplasia according to <i>Filipe</i> (highest grade)	
1	Female	88	2008	2012	2013	1	52	No	II	II	Incomplete	NA	NA
2	Male	53	2011	2016	Alive	3	70	High-grade	III	III	Incomplete	III	Grade 1
3	Female	72	2010	2014	2015	3	48	High-grade	I	I	Incomplete	NA	Grade 3
4	Female	90	2008	2019	2020	4	65	No	III	II	Incomplete	III	Grade I
5	Female	75	2007	2021	Alive	2	25	No	II	II	Incomplete	III	Grade 1

Name of Journal: *World Journal of Clinical Cases*

Manuscript Type: MINIREVIEWS with a retrospective case series analysis

The role of pre-existing incomplete intestinal metaplasia in gastric adenocarcinoma – a retrospective case series analysis

Short title:

Bogdanova I *et al.* Incomplete gastric intestinal metaplasia/gastric adenocarcinoma/risk

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subtypes, performed the analysis of the obtained results and design of the tables; Aleksandraviča I coordinated the biobanking activities and data acquisition; Tolmanis I reviewed the endoscopy reports; Leja M coordinated the research and participated in the outline design and writing of the paper, all authors were involved in writing and final approval of the manuscript.

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Abstract

Background: Risk stratification for patients with gastric precancerous lesions for endoscopic surveillance remains controversial. Here we are presenting a retrospective analysis of patients having developed gastric adenocarcinoma during the period of follow-up.

Methods: We conducted a retrospective study on patients having undergone upper endoscopy prior to the development of gastric adenocarcinoma. The presence and stage of precancerous lesions as well as subtype of intestinal metaplasia at the baseline endoscopy got evaluated. Literature mini-review was performed.

Results: Out of 1681 subjects in the Biobank, gastric adenocarcinoma was detected in five cases in whom previous endoscopy data with biopsies either from the corpus or antral part were available. All of the patients had incomplete intestinal metaplasia during the baseline endoscopy; all three subjects in whom intestinal metaplasia subtyping was performed according to Filipe et al, had Type III intestinal metaplasia. Two of the five cases had low OLGA and OLGIM stages (I-II) at the baseline.

Conclusions: The presence of incomplete intestinal metaplasia, in particular, that of Type III is a better predictor for gastric adenocarcinoma development than OLGA/OLGIM staging system. Subtyping of intestinal metaplasia have an important role in the risk stratification for surveillance decisions.

Key words: minireview, gastric adenocarcinoma, precancerous lesions, retrospective study, subtypes of intestinal metaplasia, OLGA/OLGIM staging

Bogdanova I, Poļaka I, Aleksandraviča I, Dzērve Z, Anarkulova L, Trone V, Tolmanis I, Leja M. The role of pre-existing incomplete intestinal metaplasia in gastric adenocarcinoma – a retrospective case series analysis

Core tip: We present a retrospective case series and analysis of the available literature evidence on gastric mucosal precancerous lesion characteristics preceding gastric adenocarcinoma development. The obtained data are strongly suggesting that subtyping of gastric intestinal metaplasia, in particular that of Type III is an important predictor for the development of adenocarcinoma. The subtype of intestinal metaplasia appears to be a better predictor for cancer than OLGA and OLGIM staging system, however larger studies would be required to confirm this.

INTRODUCTION

Atrophy, intestinal metaplasia and dysplasia are defined as precancerous lesions for gastric cancer, however the magnitude of risk for developing cancer may be substantially variable^[1]. Surveillance strategies, i.e. repeated endoscopies in patients with such lesions is recommended in Europe^[2]; yet substantial differences between the currently existing guidelines have to be noted^[3]. The Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis Intestinal Metaplasia Assessment (OLGIM) have been suggested for easier use, and claimed to be a tool for better risk-stratification^[4, 5].

Based on a long-term follow-up study on 7436 patients in Italy, OLGA staging system was suggested to be a good predictor for gastric cancer development since most of the overall 28 incident neoplasia occurred in stages III and IV^[6]. In another cohort study by the Italian investigators involving 1755 consecutive patients incident neoplastic lesions (prevalence - 0.4%; low-grade intraepithelial neoplasia - 4; high-grade intraepithelial neoplasia - 1; gastric cancer - 2) developed exclusively in patients with OLGA stages III-IV. A prospective, longitudinal multicenter study in Singapore involving 2980 subjects undergoing screening upper endoscopy with standardized gastric mucosal biopsy sampling has suggested patients with OLGIM III-IV lesions to be the highest risk-group for gastric neoplasia development (adjusted hazard ratio 20.7; 95% CI 5.04 to 85.6) whereas OLGIM II group was identified to bear an intermediate risk^[7].

A meta-analysis of six case-control studies and two cohort studies, comprising 2700 subjects has also demonstrated a significant association between the OLGA/OLGIM stages III/IV and gastric cancer risk^[8].

The potential role of gastric intestinal metaplasia subtyping has been debated for decades. The landmark study by Filipe et al.^[9] has suggested the role of a specific high-iron diamine alcian-blue (HID-AB) **staining technique for assessing** the presence of sialomucins and sulfomucins. However, currently the HID-AB method

is available only in a few specialized laboratories. Intestinal metaplasia can be more broadly subtyped in complete and incomplete metaplasia based on the standard hematoxylin and eosin (H&E) staining method. Incomplete intestinal metaplasia corresponds to Type II and Type III intestinal metaplasia by Filipe taken together (see Figure 1).

Based on the above, we have decided to check in our retrospective surveillance cohort the role of intestinal metaplasia subtypes in gastric cancer development as well as to review the studies in the literature that have assessed subtypes of intestinal metaplasia prior to cancer development. The secondary objective was to assess the correlation to high-risk OLGA/OLGIM stages for assuring whether OLGA and/or OLGIM staging system could serve as the single reliable parameter for risk assessment.

MATERIALS AND METHODS

General design

We requested data on gastric cancer (C16) entries to the Cancer Registry of Latvia from individuals having been enrolled to the Biobank of the Clinical and Preventive Medicine, University of Latvia and having undergone upper endoscopy in the Digestive Diseases Centre GASTRO, Riga, Latvia. Patient enrolment to the biobank was initiated in 2007, the follow-up period according to the Registry data was ending December, 2020. At the time of enrolment to the Biobank all the study subjects have provided their signed consent allowing their data to be analysed following the enrolment.

For the selected cases, the medical history available in the Digestive Diseases Centre GASTRO was analyzed; this included preceding and follow-up endoscopy data. Only patients having undergone upper endoscopy prior to the diagnosis of gastric cancer and having been biopsied from the corpus and antrum during the endoscopy were included to the analysis. Those having been diagnosed with other type of malignancies than gastric adenocarcinoma were excluded.

Consequently, in the selected group of patients, endoscopy biopsy results were re-evaluated in the Academic Histology Laboratory, Riga, Latvia.

Assessment of gastric precancerous lesions

Only cases with biopsies available from the corpus and antrum were included to the analysis; incisura biopsy was also available as the standard. Routinely, staining with H&E was used for the clinical work-up.

Whenever available, all the slides from the selected cases were re-analysed. Whenever the paraffin blocks were available, additional slides for HID-AB staining were produced, and the subtypes of intestinal metaplasia according to Filipe *et al.* were analysed.

Approaches for subtyping gastric intestinal metaplasia

Complete intestinal metaplasia is known also as small intestinal type, is characterized by the presence of absorptive cells with brush borders, goblet cells and occasionally Paneth cells, while incomplete intestinal metaplasia, known also as colonic type intestinal metaplasia – by the presence of hybrid mucous cells with large vacuoles of different sizes, without features of absorptive cells or goblet cells^[10]. When both subtypes are present (mixed intestinal metaplasia), the case is classified according the lesions of the highest risk, i.e. incomplete metaplasia.

According to the HID-AB stain, in Type I intestinal metaplasia sialomucins are present in goblet cells with no mucins in columnar cells; in Type II – sialomucins are present in goblet and columnar cells, while in Type III - sulfomucins predominate in columnar cells, and goblet cells may contain sialomucins or sulfomucins^[11].

RESULTS

Out of 1681 subjects in the Biobank (median age 59 years, 68% women, *H.pylori* positivity – 56.8% according to histology, 13% had reported gastric cancer among the 1st degree relatives, median follow-up period 9.1 years), gastric adenocarcinoma was detected in five cases fulfilling the inclusion criteria described above. Of those, 4 were women, 1 man, one woman was a current smoker, while another one – past smoker; three have reported modest use of alcohol, one had a first degree relative with a gastric cancer; the mean age at cancer development was 75.6 years (range 53-90 years). The mean period of cancer detection was 52 months (range 25-70 months) following the initial endoscopy. In all, but one case several upper endoscopies have been performed during the follow-up period. Four of the five cases were *H.pylori* positive according to the histology of the preceding endoscopy, the only *H.pylori* – negative subject was not self-reporting previous eradication therapy. For more details, see Table 1.

Patient No. 2 was the only case in which early gastric cancer was diagnosed, got the diagnosis set within a surveillance program, and was successfully managed by endoscopic submucosal resection.

At the reference endoscopy, i.e. an endoscopy prior to the cancer diagnosis with the highest-risk lesion, two patients were diagnosed with a high-grade dysplasia while the remaining three did not have any degree of dysplasia. One of the two with high-grade dysplasia was also classified as OLGA and OLGIM Stage III, while the other one – OLGA and OLGIM Stage I only. In the entire group, only two patients were stages as OLGA III (one of them – OLGIM II), whereas the majority, i.e. three cases were low OLGA and OLGIM risk stages (I and II).

In three cases in the group the material was available for an additional HID-AB staining: all three cases were diagnosed as Type III intestinal metaplasia according to Filipe et al.

DISCUSSION

Our retrospective cohort analysis was suggesting that incomplete intestinal metaplasia of the stomach mucosa, in particular, that of Type III according to Filipe *et al*, is a key predictor of gastric adenocarcinoma development.

The results in our case series of five patients having developed gastric cancer during the follow-up period is confirming the rationale for endoscopic surveillance strategies of patients with gastric precancerous lesions as suggested by the current guidelines^[2]. Three of these patients had clearly high-risk precancerous lesions (high grade dysplasia in two cases, and an addition subject with a high-risk OLGA/OLGIM stage) at the initial investigations, whereas in two cases surveillance would not been indicated unless considering the subtype of intestinal metaplasia. Both were diagnosed as OLGA and OLGIM II stage cases at the enrolment. In all the five cases incomplete intestinal metaplasia was present at the enrolment, and in all the subjects in whom HID-AB staining was available – **the** intestinal metaplasia was subtyped as Type III. Therefore, based on this very small cohort, subtyping of intestinal metaplasia seems to be a more important factor for risk stratification that OLGA and OLGIM staging.

Increasing evidence is becoming available on the role of intestinal metaplasia subtyping for gastric cancer risk stratification. A 20-year follow-up study of the population-based cohort in Colombia has suggested that the presence of incomplete intestinal at baseline substantially increased the risk (OR, 13.4; 95% CI, 1.8-103.8) for gastric cancer development when compared to subjects with a complete intestinal metaplasia at the enrolment.^[12]

In the Spanish multi-center study having involved 649 patients with gastric precancerous lesions at baseline 24 patients had developed gastric adenocarcinoma during the mean follow-up period of 12 years. The hazards ratio of progression to gastric cancer was 2.75 (95% CI 1.06-6.26) for those with

incomplete compared with those with complete intestinal metaplasia at baseline, after adjusting for sex, age, smoking, family history of gastric cancer and the use of non-steroidal anti-inflammatory medication^[10]. HID-AB staining was not used in the study.

These observations **are** supported by other studies. In France, a low gastric cancer risk country, progression towards gastric cancer was observed in two cases, both of them – had antrum limited disease (one was OLGA II, the other, - OLGA III stage), but incomplete intestinal metaplasia at the initial endoscopy^[13].

In a study from Japan altogether 4 patients have been progressing to gastric cancer during the observational period following *H.pylori* eradication; all of these patients had incomplete intestinal metaplasia in the antral part of the stomach at the enrolment^[14]. This group of researchers were using immunohistochemical staining for differentiating between the subtypes of intestinal metaplasia. Interestingly, the key objective of the study was addressing the reversibility of intestinal metaplasia; the obtained results were suggesting that incomplete intestinal metaplasia in the antrum was regressing within a 10-year period following the eradication whereas complete intestinal metaplasia did not regress either in the antrum or corpus^[14].

The study that has been conducted by our group in healthy individuals from Kazakhstan, a country with high incidence of gastric cancer, has suggested that limiting the patient surveillance of those with high OLGA or OLGIM stages may result in substantial downgrading of the risk, and therefore missing patients with high risk for surveillance as a substantial proportion of subjects with low stages according to the above classifications had incomplete intestinal metaplasia ^[15].

Recently two meta-analysis on the subtypes of gastric intestinal metaplasia and neoplasia risk have been published by researchers from China – Du et al. ^[16] has been including cohort studies (published until May 15, 2021) while Wei et al.^[17] included also case-control studies, and the analysis period was ending March 2020.

Both analysis **obtained** similar findings. Pooled relative risk for gastric cancer development of incomplete intestinal metaplasia when compared to complete type was 5.16 (95% CI, 3.28–8.12) in the study by Du et al.^[16], and 4.96 (95% CI 2.72–9.04) in the study by Wei et al.^[17] Both studies revealed the highest risk of progression to cancer in Type III intestinal metaplasia, i.e. 6.27 (95% CI 1.89–20.77) in the analysis by Wei et al.^[17] when compared Types I and II combined, while 6.42 (95% CI, 3.03–13.62) in the analysis by Du et al.^[16] when compared to Type I intestinal metaplasia.

There are certain limitations to our and other studies. The numbers of study subjects either in our case series or in other cohorts, including the study from France^[13], are low. Besides, there is a very limited number of laboratories that are currently using the HID-AB staining method; also in some of our patients the material was not available to apply this staining method in all. Larger series would be required for definite conclusions; European-level data collaborative for pooling the results from various studies whether published or unpublished, would be a powerful tool for the purpose.

Finally, the relevance of intestinal metaplasia subtyping **has** been gradually acknowledged by international guidelines. There is limited awareness among gastroenterologists of the potential prognostic value of the histological subtyping of IM^[11], and therefore, the pathologists are frequently not reporting the subtypes even though this would be important for setting the most appropriate surveillance endoscopy intervals. The latest version of MAPS (II) guideline acknowledges the role of incomplete intestinal metaplasia^[2], while this was discouraged in the initial version^[18]. Although referring to MAPS II, the recent Maastricht VI guideline suggests subtyping of intestinal metaplasia **is** clinically redundant if using OLGA/OLGIM staging systems^[5], **which** actually contradicts our findings and the above discussed evidence. We expect that increasing knowledge in the field should result in changes to upcoming editions of these guidelines.

CONCLUSION

Proper risk stratification of precancerous lesions of the stomach mucosa is important for determining the optimal surveillance strategies. The presence of incomplete intestinal metaplasia, in particular that of Type III is a better predictor for gastric adenocarcinoma development than OLGA/OLGIM staging system. Subtyping of intestinal metaplasia may have an important role in the risk stratification for surveillance decisions. Large-scale international data collaborative may be of importance to address the above issues.

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ETHICS

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Medical and Biomedical Research Ethics Committee of the Riga East University Hospital Support Foundation, protocol 18-A/16, October 6th, 2016.

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Footnotes

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other co-authors contributed their efforts in this manuscript.

Figure Legends

Figure 1 Relationships between subtypes of intestinal metaplasia (complete/incomplete; subtypes I, II, III according to Filipe et al.)

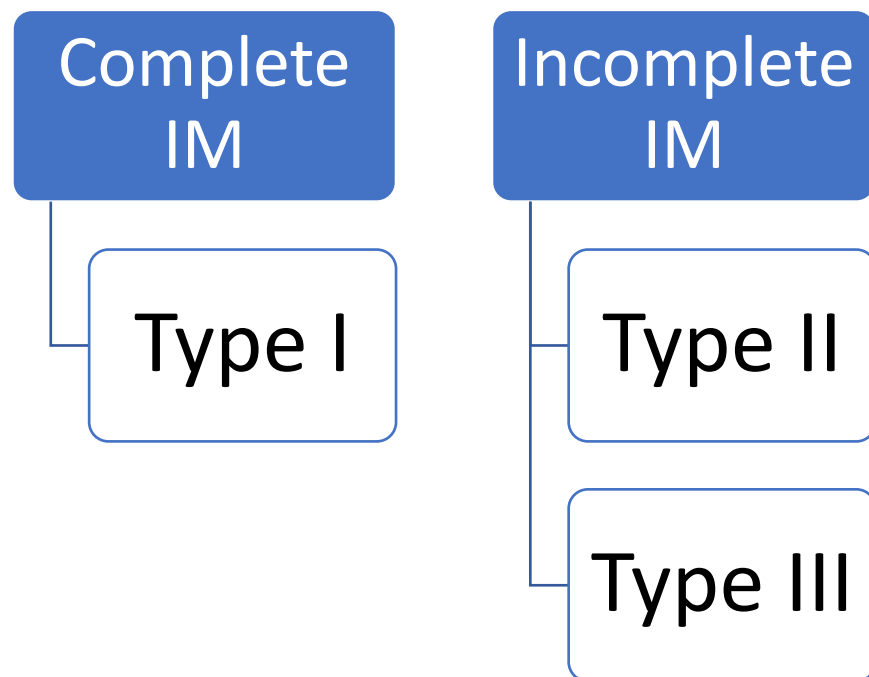


Table 1 Characteristics of the subjects having developed gastric adenocarcinoma following a previous upper endoscopy with biopsies

No	Gender	Age at cancer development	Year of enrolment	Year of cancer diagnosis	Year of death	No of preceeding upper endoscopies	Number of months of the reference endoscopy prior to cancer development	Reference endoscopy (highest risk lesion in the case of several preceeding endoscopies)					Grade of the cancer
								Dysplasia	OLGA stage	OLGIM stage	Complete/ incomplete intestinal metaplasia	Intestinal metaplasia according to <i>Filipe</i> (highest grade)	
1	Female	88	2008	2012	2013	1	52	No	II	II	Incomplete	NA	NA
2	Male	53	2011	2016	Alive	3	70	High-grade	III	III	Incomplete	III	Grade 1
3	Female	72	2010	2014	2015	3	48	High-grade	I	I	Incomplete	NA	Grade 3
4	Female	90	2008	2019	2020	4	65	No	III	II	Incomplete	III	Grade I
5	Female	75	2007	2021	Alive	2	25	No	II	II	Incomplete	III	Grade 1

