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Endoscopic Submucosal Dissection of Gastric Superficial Lesions: Predictors for Time of Procedure in a Portuguese Center

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Abstract

Background: Endoscopic submucosal dissection (ESD), an endoscopic technique used for treatment of gastric superficial lesions, has been gaining importance on western countries. Procedural times have an impact on various outcomes.

Aim: To define which factors from patients, lesions and procedure can predict longer procedural times.

Methods: In a cohort of 127 lesions resected by ESD with IT-knife, after using needle-knife for submucosal layer access, by experienced gastroenterologists, characteristics from the patient (age, gender, presence of co-morbidities, usage and suspension of anti-platelet drugs and general physical condition), lesion (size, histopathological diagnosis at biopsy, location, macroscopic type and submucosal invasion) and procedure (adverse events) were retrospectively analyzed for its impact on time of procedure. Univariate and multivariate analysis were performed.

Results: Lesions larger than 20 mm ($p < 0.001$), on the upper third of the stomach ($p = 0.035$) and with an ASA score of 3 ($p = 0.031$) were considered influential factors for a longer procedure time and specifically for a time of procedure longer than 90 min. Existence of intra-procedure adverse events was also a predictor for a procedure time >90 min. Lesion's size >20 mm and location in the upper third were independently associated with a procedure time longer than 90 min (OR 4.91 [95%CI 2.29–10.50] and OR 18.26 [95%CI 2.02–164.78], respectively).

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Conclusion: The time of procedure of ESD for gastric superficial lesions is influenced by size of lesion (>20 mm) and location (upper third of stomach), which predict a time longer than 90 min. This can be useful for better management of workflow, operation, training of teams and anesthesic procedures.

Dissecção Endoscópica da Submucosa de Lesões Superficiais Gástricas: Preditores do Tempo de Procedimento num Centro Português

Resumo
Introdução: A Disseção Endoscópica de Submucosa (ESD), uma técnica utilizada para o tratamento de lesões gástricas superficiais, tem ganho importância no Ocidente. O tempo de procedimento tem impacto nos *outcomes*.
Objetivo: Definir os fatores do paciente, da lesão e do procedimento que predizem um tempo de procedimento prolongado.
Métodos: Numa coorte de 127 lesões removidas por ESD com *IT-knife*, após utilização de *needle-knife* para acesso à camada submucosa, por gastrenterologistas experientes foram analisadas, retrospetivamente, características dos pacientes (idade, género, presença de co-morbidades, toma/suspensão de agentes anti-plaquetários e condição física), das lesões (tamanho, diagnóstico histopatológico na biopsia, localização, características macroscópicas e invasão submucosa) e do procedimento (complicações). Foi realizada análise univariada e multivariada.
Resultados: Lesões >20 mm (*p*<0,001), no terço superior do estômago (*p*=0,035) e em pacientes com um índice ASA 3 (*p*=0,031) foram considerados como fatores com influência para tempo de procedimento prolongado e, especificamente, para um tempo de procedimento superior a 90 minutos. A existência de complicações intra-procedimento também foi considerada como um preditor para um tempo >90 minutos. Uma lesão >20 mm e a localização no terço superior estiveram associadas independentemente com um tempo de procedimento superior a 90 minutos (OR 4.91 [IC 95% 2.29-10.50] e OR 18.26 [IC 95% 2.02-164.78], respetivamente)
Conclusões: O tempo de procedimento da ESD para lesões superficiais gástricas é influenciado pelo tamanho e localização das lesões, sendo preditores de um tempo de procedimento superior a 90 minutos. Estes dados são importantes para melhor gestão da dinâmica de trabalho, procedimento, formação das equipas e procedimentos anestésicos.

1. Introduction and background

Endoscopic submucosal dissection (ESD) is an endoscopic technique used for treatment of gastric superficial lesions.[1] It has been widely used in countries such as Korea and Japan, but its use only widespread in the Western countries in the last decade.[2] Although having successful results,[3–5] ESD requires a high level of expertise in order to reach the desired outcomes.[6–7]

Specifically, longer procedural times are related to a higher level of adverse events[8] such as delayed bleeding,[9] perforation,[10–11] post-operative pneumonia[11–13] and other clinical adverse events related to premedication and a heavy workload for patients.[7] Moreover, previous retrospective studies have shown that time of procedure can be influenced by different factors such as existence of fibrosis,[14–15] presence of ulceration,[7,15–17] area of the resected specimen,[7,16–19] location on the upper portion of the stomach,[7,16–19] adhesion[19] and presence of a scar.[7] Therefore, it is essential to take these factors into account in the pre-operatory period, since they can influence the workflow for ESD such as allocation of type of rooms and anesthesic procedures, and level of training of teams.[11]

Considering this impact of procedure time, the present work aims at addressing the procedure time of ESD for removal of superficial gastric lesions and to define which patients' characteristics, lesions' features and procedure variables may be predictors of longer procedural times.

2. Materials and methods

2.1. Type of study and selection of patients

Our study reports a retrospective cohort of 162 consecutively patients (with 195 gastric neoplastic lesions) that

were referred to the Portuguese Institute of Oncology – Porto (IPO) from March 2003 to April 2013 for assessment and treatment of gastric superficial neoplasias. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, in compliance with good clinical practice.

All patients were referred for endoscopic treatment after a multidisciplinary oncology group decision and full medical and anesthesiology evaluation. Both oral and written informed consent was given by patients. All the endoscopic procedures performed on IPO during this period were screened by their report on the institute database, followed by analysis of the clinical record of the patient.

Results related with other outcomes regarding the long-term follow-up of this cohort, that are outside the aim of this analysis, were already published by our team.[20]

Flowchart followed for patients' selection can be found in Fig. 1. For the purpose of this study, only cases treated by ESD, without ulcerative findings on the lesion, and technically performed with IT-knife were selected. Fifty-three

procedures were excluded because they were treated by endoscopic mucosal resection (EMRc). Of the ESD procedures, one was excluded because Flex-knife was used along with IT knife, six were excluded because diathermic loop was used along with IT-knife and two were excluded because we used a hybrid technique (ESD followed by EMRc). Six procedures were excluded due to incomplete information regarding time of procedure.

2.2. Description of endoscopic resection techniques

Two operators effectuated the endoscopic procedures (MDR and PPN). MDR received training in Japan and in live animal courses before introducing the technique in the Hospital. PPN had animal training and then gradually begun the endoscopic procedures under MDR supervision in 2010.[21-22]

Lateral margins of each lesion were always determined by chromoendoscopy with indigo carmine 1%[23-25] or with
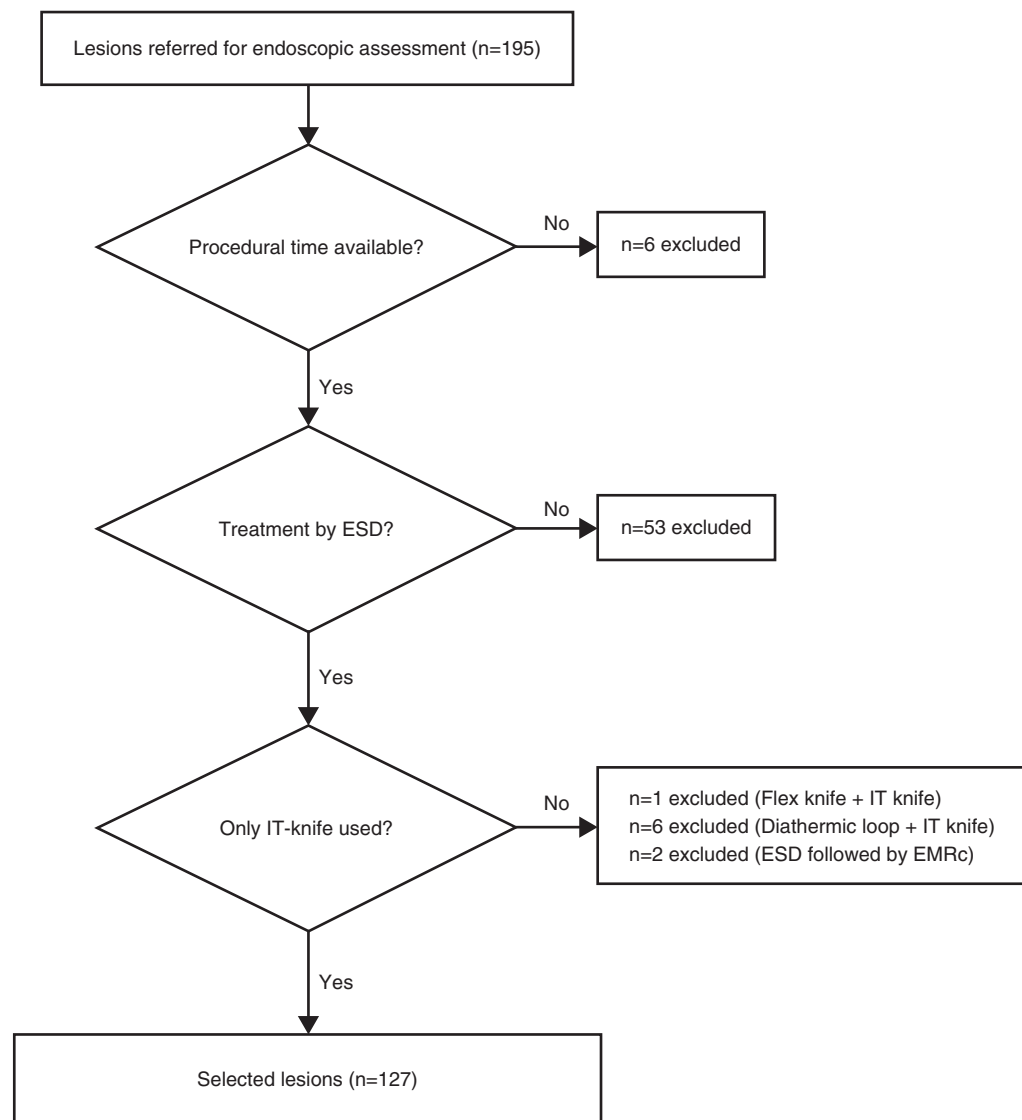

Figure 1   Flowchart for patients inclusion in the study.

virtual chromoendoscopy using HR-NBI (applying Pimentel-Nunes et al. classification for delimitation of lesions[26]) and small marks were made 2–5 mm from the edges of the lesion using needle-knife coagulation. The technique of endoscopic submucosal dissection (ESD) was initiated after the submucosal injection of the lesion with an epinephrine and saline solution (1:100,000) and a few drops of methylene blue. After that to obtain access to the submucosal layer 3–4 small mucosal incisions using needle-knife were made. Then, an IT-knife (Olympus, model KD-610L) in the endocut mode was used to do the circumference of the lesion outside the coagulation markers. Complete dissection of the lesion was performed using endocut mode (Olympus electrosurgical unit HF-120, 80/60 W) with further submucosal injections as needed being made throughout the procedure. CO_2 insufflation was not used as it is not available at our center.

All procedures were performed under deep sedation or general anesthesia (with propofol and fentanyl) supervised by an anesthesiology team.

2.3. Definitions: procedural time and potential predictive factors

Procedural time was defined as the time of anesthesia, in minutes, reported in patients' clinical files by the anesthesiology team. Thereafter, two groups were created according to a time shorter or longer than 90 min of procedure given that the median time of all the procedures was 85 min.

In order to determine the influential factors on procedure time the following variables were analyzed:

- *Regarding the lesion*: Gross cross-sectional dimension of the lesion at the diagnostic procedure (measured endoscopically) in millimeters, followed by sub-grouping in lesions ≤20 mm (absolute indication for endoscopic resection on differentiated lesions without ulcerative findings[27]) and >20 mm, histopathological findings at diagnostic biopsy (low-grade dysplasia, high grade dysplasia or T1a), location (upper, middle and lower third of the stomach), macroscopic type (organized by Paris classification,[28] followed by sub-grouping in depressed and non-depressed lesions) and histopathological definitive classification defined by the presence or absence of submucosal invasion.
- *Regarding the patient*: Age, gender, presence of comorbidities, previous suspension of anti-platelet drugs and general condition of the patient, evaluated by the American Society of Anesthesiology score (ASA 1, 2, 3, 4 or 5).[29]
- *Regarding the procedure*: Type of anesthesia (sedation *vs* general anesthesia); existence (and type) of adverse events; adverse events were defined as: perforation was defined as mesenteric fat or intra-abdominal space visible through the gastric wall during the procedure and/or postprocedural clinical and imagiologic signs of peritonitis due to perforation; bleeding was only considered as an adverse event when a procedural bleeding could not be managed without endoclips (significant intraprocedure bleeding) or required surgery and/or transfusion of red blood cells (acute bleeding) or as a postoperative

bleeding with a decrease of the hemoglobin level more than 2 g/dL and/or need for blood transfusions, endoscopic or surgical intervention because of hematemesis or melena (delayed bleeding).

2.4. Comparison with previous studies

For the purpose of comparison with previous studies we applied the formula developed by Goto et al.,[16] for prediction of time of procedure: predictive procedural time (min) = $2.384 \times$ (tumor size, mm) + $38.568 \times$ (location) + $40.333 \times$ (ulcerative findings) [location in the upper-third of the stomach, 1; the middle or the lower third of the stomach, 0; presence of ulcerative findings, 1; and the absence of ulcerative findings, 0].

2.5. Statistical analysis

Statistical Package for Social Sciences (SPSS 21.0 Package Facility, SPSS Inc., IL, USA) was used for data support and analysis. Analysis was performed using descriptive statistics methods, as well as Kruskal–Wallis test for analysis with time (when analyzed as a continuous variable), and Chi-square and Fisher's exact test for analysis of dichotomic variables (including time more or less than 90 min as a dichotomic variable). Logistic regression was used to estimate OR for individual variables in multivariate analysis. A value of $p < 0.05$ was considered to be statistically significant. Pearson's test was used for linear regression correlation analysis.

3. Results

3.1. Characteristics of lesions and procedure

Of the 127 lesions, 55% were performed on male patients with an average age of 69 (±10.9) years old and a median of 71 (IQR 61–77). Eight (6%) lesions were located on the upper third, 27 (21%) on the middle third and 92 (72%) were located on the lower third. The median time of procedure was of 85 min (IQR 55–130). The median lesion size was of 20 mm (IQR 15–30). Globally, 93% of the lesions were resected *en bloc* with R0 achieved in 91% of the cases. Adverse events (bleeding) occurred in 13% of the procedures.

3.2. Factors predictive of ESD procedure time

Tumor size, location and the ASA score were significantly associated with procedure time (Table 1). Specifically, a procedure for a lesion >20 mm, located at the upper third of the stomach and in a patient with an ASA of three were associated with longer procedure time, with results significantly different from the other characteristics on the same group. Other patients', lesions' and characteristics of procedure are shown in Table 1.

Procedures were furthermore analyzed in two different groups – those taking less than and those taking more than 90 min. These results are consistent with the findings on the previous analysis, as the majority of the cases (72%) with a lesion ≤20 mm lasted 90 min or less, while the majority of the cases with a lesion >20 mm (66%) lasted for more than

Table 1 Characteristics of patients, lesions and procedure with univariate analysis for predictors of longer procedure time and procedure time greater than 90 min. $p < 0.05$ was considered as statistically significant.

Characteristics	n	Time				
		Median (IQR)	p value	<90 min	>90 min	p value
Procedures (total)	127	85 (55–130)				
Gender			0.443			
Male	70	97.5 (50–140)		34 (49%)	36 (51%)	0.065
Female	57	80 (60–120)		37 (65%)	20 (35%)	
Age[a]	71 (61–77)		0.705			
≤65	42	85 (43.75–121.25)		25 (60%)	17 (40%)	0.564
>65	85	90 (60–140)		46 (54%)	39 (46%)	
ASA			**0.011**[*]			**0.031**[*]
ASA 1	31	65 (40–95)		23 (74%)	8 (26%)	
ASA 2	71	90 (55–130)		38 (54%)	33 (46%)	
ASA 3	25	120 (62.50–165)		10 (40%)	15 (60%)	
Co-morbidities			0.125			
Yes	92	90 (30–112.75)		47 (51%)	45 (49%)	0.076
No	35	72.5 (55–140)		24 (69%)	11 (31%)	
Anti-platelets			0.153			
Yes	25	105 (60–187.5)		12 (48%)	13 (52%)	0.374
No	102	85 (48.75–126.25)		59 (58%)	43 (42%)	
Suspension of anti-platelets			0.764			
Yes	14	117.5 (60–200)		5 (36%)	9 (64%)	0.416
No	8	102.5 (52.50–201.25)		4 (50%)	4 (50%)	
Size of lesion			**<0.001**			**<0.001**
≤20 mm	74	65 (45–110)		53 (72%)	21 (28%)	
>20 mm	53	120 (80–147.5)		18 (34%)	35 (66%)	
Histopathology at biopsy			0.521			
LGD	40	75 (46.25–125)		26 (65%)	14 (35%)	0.367
HGD	57	90 (52.50–137.50)		29 (51%)	28 (49%)	
Adenocarcinoma	30	90 (60–130)		16 (53%)	14 (47%)	
Type of lesion			0.891			
Naive	121	85 (55–130)		68 (56%)	53 (44%)	0.542
Recidive	6	95 (29.75–156)		3 (50%)	3 (50%)	
Location			**0.022**[**]			**0.035**[**]
Upper third	8	145 (115–253.75)		1 (12%)	7 (88%)	
Middle third	27	90 (60–180)		15 (56%)	12 (44%)	
Lower third	92	80 (46.25–120)		55 (60%)	37 (40%)	
Macroscopic features			0.833			
Depressed lesions	60	87.5 (60–130)		36 (60%)	24 (40%)	0.379
Non depressed lesions	67	85 (45–140)		35 (52%)	32 (48%)	
Submucosal invasion			0.289			
Yes	14	115 (72.5–135)		6 (43%)	8 (57%)	0.297
No	113	85 (52.50–130)		65 (58%)	48 (42%)	
Adverse events			0.069			
Yes	17	130 (50–200)		5 (29%)	12 (71%)	**0.018**
No	110	84 (53.75–122.75)		66 (60%)	44 (40%)	

IQR, interquartile range; min, minutes; LGD, low-grade dysplasia; HGD, high-grade dysplasia.
Bold signifies statistically significant values.
[*] Statistically significant for comparison between ASA1 and ASA3.
[**] Statistically significant for comparison between upper third and lower third.
[a] Median age (IQR).

90 min ($p < 0.001$). Also, lesions located on the upper third took more than 90 min (88%), compared to lesions at other locations ($p < 0.035$) and gross majority of lesions in patients with ASA1 took less than 90 min to remove (74%) while lesions on patients with ASA 3 took more than 90 min on 60% of the cases ($p = 0.031$). Moreover, this analysis also shows that intra-procedure adverse events pushed the procedure time to more than 90 min as 71% of the procedures with adverse events took more than 90 min ($p = 0.018$). Characteristics with a statistically significant difference at univariate analysis ($p < 0.05$) were then computed for multivariate analysis (Table 2). Those patients harboring lesions larger than 20 mm and located to the upper third showed an increased risk of 4.91 times [95%CI 2.29–10.50] and 18.26 times [95%CI 2.02–164.78], respectively and independently with $p < 0.05$. The occurrence of adverse events during the procedure and the ASA score do not seem to be independently predicting procedural time longer than 90 min. Furthermore, type of anesthesia did not influence procedure time.

Trends for time of procedure according to lesion's size and location can be found in Fig. 2.

3.3. Comparison with previous studies

Correlation between the registered time of procedure and the predicted time of procedure is shown in Fig. 3 (Pearson's $r = 0.430$).

4. Discussion

To the best of our knowledge this is the first study relating ESD time of procedure with factors from the lesion,

Table 2 Multivariate analysis of predictors for longer procedure time (>90 min). $p < 0.05$ was considered as statistically significant.

	OR	(95%CI)	
Size			
≤20 mm	1		
>20 mm	**4.91**	**(2.29–10.50)**	**<0.001**
Location			
Lower third	1		
Middle third	1.182	(0.46–3.07)	0.731
Upper third	**18.26**	**(2.02–164.78)**	**0.01**
Adverse events			
No	1		
Yes	2.84	(0.84–9.63)	0.093
ASA			
1–2	1		
3	1.713	(0.63–4.65)	0.292

OR, odds ratio; CI, confidence interval.
Bold signifies statistically significant values.

patient and the procedure itself in Western countries. We showed that lesions with more than 20 mm, located on the upper third of the stomach have a time of procedure significantly higher than smaller lesions, on middle and lower stomach. Co-morbidities should be taken into account but only larger lesions and lesions on the upper third are independent predictors for longer procedure time. Our results
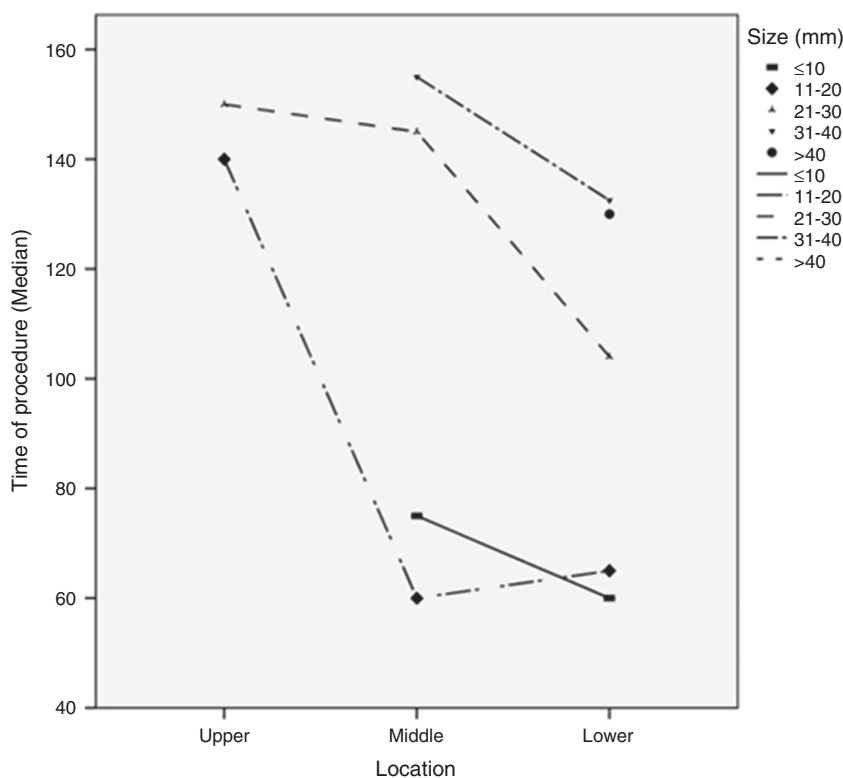

Figure 2 Time of procedure (median) according to location and size of lesion.
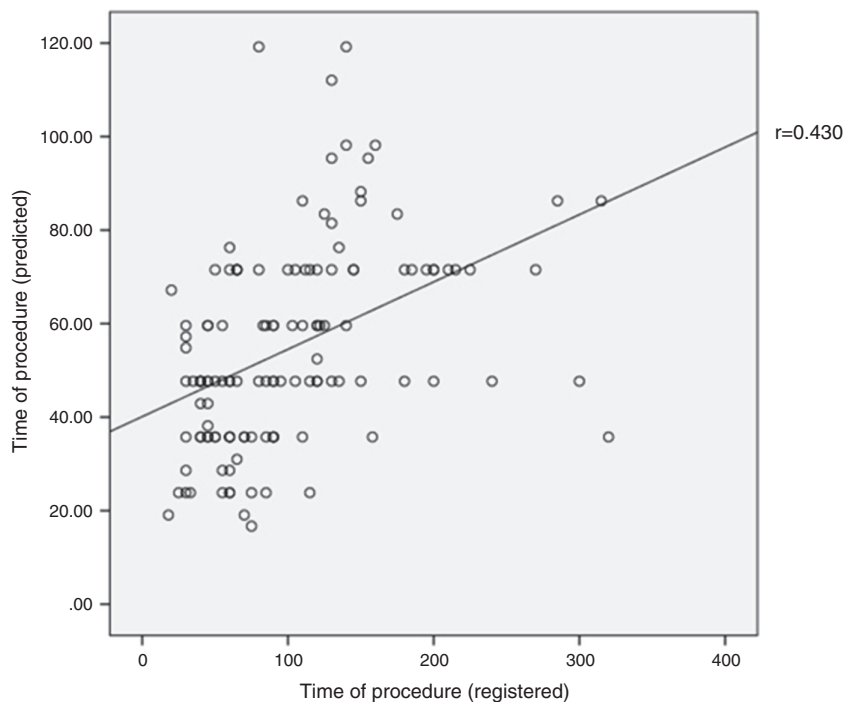
Figure 3 Correlation between registered time of procedure and the predicted time of procedure by Goto *et al*. formula.

may permit to establish these factors relevant for planning and management of these patients.

4.1. Predictive factors of prolonged time of procedure

Comparing the different characteristics of the lesions, a cross sectional dimension >20 mm had longer procedure times when compared to lesions ≤20 mm (120 (IQR 80–147.50) min *vs* 65 (IQR 45–110) min, *p* < 0.001). Moreover, when the lesion was located on the upper third the median time was of 145 (IQR 115–253.75) min, significantly different from times recorded for lesions on the lower third with a median time of 80 (IQR 46.25–120) min, *p* = 0.022. In what relates to the general condition of the patient, measured by the ASA score, ASA 3 patients had a median procedure time of 120 (IQR 62.5–165) min, clearly longer than patients with ASA 1 with a median time of 65 (IQR 40–95) min, *p* = 0.011. We also showed that these same characteristics tend to be associated with a procedure longer than 90 min. In fact, the size and location were independently associated with a time longer than 90 min whereas the risk profile of patients and/or the evidence of adverse events (bleeding) during the procedures were not independent.

The reasons why the first two factors can act as predictors for a longer time of procedure can be easily explained – a larger lesion will obviously require a higher area to be dissected and therefore more time; the location at the upper third, due to the position required for the scope and the wall characteristics, require more technical skills.[7,30,31] Nevertheless, for the other two factors we may have different reasons not to observe them as independent predictive factors – bleeding is expected more often in lesions in the upper third[32] and ASA 3 patients prevalence is very low and they

tend to be older [median age of 75 (IQR 69.5–80) *vs* 70 (IQR 59–76) on ASA 1 and 2, *p* = 0.005] what may lead to larger [median dimension of 30 mm (IQR 18–30) on ASA 3 *vs* 20 mm (IQR 15–25) on ASA 1 and 2, *p* = 0.037] and more advanced lesions.

4.2. Predictive factors compared to eastern series

Moreover, the majority of our findings are in accordance with previous findings in eastern series, specifically in what regards to size and location of lesion.[7,15-19]

Goto et al,[16] developed a formula to predict the time of procedure based on size of lesion, location on the upper third and presence of ulceration. Comparing to our results, and considering the non-existence of ulcerated lesions on this series, for a lesion of 20 mm or more and located on the upper third, its predicted time of procedure is never less than 86 min which is in accordance with our findings that those two factors are associated with a procedure time longer than 90 min. The correlation between the registered time of procedure and the predicted time of procedure on this formula is shown in Fig. 3 (Pearson's *r* = 0.430).

Our results are also consistent with previous findings by Ahn et al,[18] as the predicted times of procedure for lesions on the upper third with more than 30 mm are always superior to 90 min. However, it does not have the same conclusion to lesions between 21 and 30 mm.

Regarding the intra-procedure adverse events predicting a longer time of procedure (>90 min) it is in agreement with previous findings by Yamamoto et al,[33] stating that uncontrolled hemorrhagic makes the procedure lengthier.

We have also linked a higher ASA score to a prolonged procedure time. However, this finding contradicts Kim et al.,[34] if we assume that a ASA 3 is similar to their's high risk group

defined as having one or more co-morbidity states. However, it is not clear if this contradiction is real or if it is due to different classification systems and it was not confirmed as an independent factor. Interestingly we did not find that any medication, including anticoagulants, interfere with procedure time.

4.3. Limitations

One of the limitations of our study has to do with the standard used to calculate time of procedure, based on the time of anesthesia. This means that our times of procedure can be slightly superior to the ones found on other studies that, for instance, count the time only on the beginning of lesion's marking and that the procedure chosen for the anesthesia can also have a different impact on the global time itself. Nevertheless, the mean time of procedure on this series is similar to times reported on different eastern series and for purposes of human resources and room allocation it is interesting to consider the time of anesthesia as a time of procedure as it is more accurate.

However, it can have an impact on the finding of the relation with the ASA score, as this one could relate directly to time of anesthesia and not with time of procedure. Also, it has also been reported on literature that many times the ASA score is subjective to inter-observer variations.[35] Therefore, this finding should be looked with special attention.

However, future studies should focus on the analysis of time of anesthesia and time of procedure itself alone, evaluated at the same time, to give us a perspective on the impact of adverse events of the procedure itself or anesthesic adverse events on the global time.

Another limitation has to do with the evaluation of size being done with a cut-off point in the 20 mm, a methodological option that has to do with the size of our series not allowing comparisons in smaller groups.

A different limitation has to do with the fact that we only considered IT-knife for analysis for the scope of this study as previous studies refer that different knives have different times of procedure associated.[36] However, the option here was purely methodological as we had cases on our series with other knives, but the choice of other knives or concomitant knives with IT-knife was based on the fact that lesions were identified as more complicated and lengthy, that made us to opt to focus on only one knife, so this bias was not present on this study. Anyway, further studies comparing times of procedure with different knives can be an interesting area for research.

Finally, we do not have consistently recorded data for fibrosis and existence of scar throughout the observation period, bringing to the surface the limitation of this study being a retrospective study and subsequently the comparisons with other works. The definition of long-term prospective studies on this area with the focus on studying factors influencing time of procedure are the key for obtaining consistent and comparable data worldwide.

5. Conclusion

In summary, we found that lesions on the upper stomach, greater than 20 mm and in patients with significant co-morbidities can increase the time of procedure and it is expected that it will last more than 90 min, with the first two being independent predictors. It is important to keep in mind if these three factors are present on a certain lesion before the procedure, so an adequate planning of operation, human resources and anesthetic method can be performed, therefore allowing an increased efficacy and efficiency.

Conflicts of interest

The authors have no conflicts of interest to declare.

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