

Primary Gastrointestinal Tract Cancers in Nigeria, Epidemiological and Histopathological Study

Obiora Jude Uchendu¹, Emmanuel Esaba Akpo²

¹Department of Histopathology, Delta State University, Abraka, Nigeria. ²Department of Surgery, Delta State University, Abraka, Nigeria.

Abstract

Background: Cancer is a low priority health concern in Nigeria. Epidemiological and histopathological profile of primary gastrointestinal tract cancer (PGITC) is poorly characterized in this region. **Aims:** This paper addresses the trend, age, gender, and histological profile of PGITC in Delta State, Nigeria. **Materials and method:** The study is a 75-month (2014-2020) descriptive, retrospective analysis of gastrointestinal (esophagus, stomach, intestinal and anal) cancers in Delta State University Teaching Hospital, Nigeria. Duplicate copies of histopathology reports of PGITC were examined for age, sex, site and histological diagnosis, and the results analyzed using Excel spreadsheet version 2016. **Results:** PGITC accounts for 15.6% of all cancers. Equal gender distribution was observed. The age range and mean age of affected patients were 23-90 years and 53.4 ±14.16 years respectively. The yearly trend undulated with two peaks in 2015 and 2019. The 3rd, 4th, 5th, 6th, 7th, 8th, 9th and 10th decades accounted for 5 (4.6%), 13 (12.0%), 21 (19.4%), 32 (29.6%), 24 (22.2%), 9 (8.3%), 3 (2.8%) and 1 (0.9%) of cases respectively. Esophageal, stomach, small intestinal, colorectal and anal cancers accounted for 6 (5.6%), 13 (12.0%), 5 (4.6%), 82 (75.9%), and 2 (1.9%) of the cases. Most colorectal and stomach cancers were adenocarcinomas. Squamous cell cancers are the most common esophageal and anal cancers while sarcomas were mostly from the small intestine. **Conclusion:** PGITC are relatively common in this study and mostly carcinoma with mean age and peak in the 6th decade. Colorectal cancers are distinctly the most common. There is a need for routine imaging screening to prevent gastrointestinal cancer in this region.

Keywords: Cancer- gastrointestine- age- gender- Nigeria

Asian Pac J Cancer Care, 6 (1), 3-7

Submission Date: 06/10/2020 Acceptance Date: 02/02/2021

Introduction

Cancer, is a major cause of mortality in most countries, but a low public health concern in Nigeria. Globally, gastrointestinal tract (esophagus, stomach, small intestine, large intestine and anus) cancer accounts for 3.5 million (19.2%) of newly confirmed cancer cases and 2.2 million (22.7%) cancer related death [1].

The more common Primary gastrointestinal tract Cancers (PGITC) are esophageal cancer, gastric cancer, and colorectal cancer accounting for 3.2%, 5.7% and 10.0% of global cancers, although with striking inter-regional variations [1].

Epidemiologic and histopathological profile of PGITC in Nigeria is poorly characterized, because of unavailability of population-based studies and poor record

keeping. Till date, no such study has been done in Delta State, Nigeria. This paper therefore analyzes the gender, age and histopathological pattern of PGITC among cancer patients in the apex hospital of Delta State.

Materials and Methods

Delta State University Teaching Hospital (DELSUTH) is a tertiary care hospital facility, located in Delta State of Nigeria. Its Pathology Department provides histopathological services to both the hospital and other hospitals within and around the state.

The present study is a descriptive, retrospective study of the entire histologically confirmed PGITC in the

Corresponding Author:

Dr. Obiora Jude Uchendu

Department of Histopathology, Delta State University, Abraka, Nigeria.

Email: ojlinksent@yahoo.com

department of Pathology of DELSUTH from the January 1, 2014 to March 31, 2020.

The information used for this study was obtained from the duplicate copies of histopathology reports of these patients. These include age and gender of the patients, and the corresponding anatomical location and histological diagnosis of these cancers. The tissue blocks were also pulled out, fresh tissue sections made, hematoxylin and eosin, periodic acid-Schiff and alcian blue stains applied where necessary to confirm the present diagnosis or specific histological features.

Cases with inconclusive diagnosis, incomplete information, metastatic diseases and cancer from the liver, gall bladder and pancreas were excluded from the study. The results were analyzed using excel spreadsheet version 2016 and presented in tables and figures.

Ethical approval was granted prior to the commencement of this work. Its reference number is HREC/PAN/2019/063/0345.

Results

One hundred and eight (15.6%) PGITC were encountered among 692 cancers seen over the period of this study. The patients had equal gender distribution, with an average age and age range of 53.4±14.16 years and 23-90 years, respectively. The corresponding mean age for male and female cases are 53.9 and 52.8 years respectively. The average number of cases was 17 cases annually.

The regional and age distribution of PGITC is shown in Table 1. We encountered 5 (4.6%), 13 (12.0%), 21 (19.4%), 32 (29.6%), 24 (22.2%), 9 (8.3%), 3 (2.8%) and 1 (0.9%) cases in the 3rd, 4th, 5th, 6th, 7th, 8th, 9th and 10th decades respectively. Male predominance was observed among patients within the age range of 40-70 years, while female dominance was observed in the rest of the age group. Esophageal, stomach, small intestine, colorectal and anal cancers accounted for 6 (5.6%), 13 (12.0%), 5

(4.6%), 82 (75.9%), and 2 (1.9%) of the cases. The peak for esophageal, gastric and colorectal cancer was in the 6th decade, while small intestine and anal cancers peaked at the 5th and 9th decades, respectively. The mean age for esophageal, gastric, small intestine, colorectal and anal cancers were 63.2, 53.1, 53.8, 52.0, and 80.0 years respectively.

Distribution of the histological types of PGITC is shown in Table 2. Carcinoma, sarcoma and neuroendocrine tumors accounted for 101 (93.5%), 6 (5.6%) and 1 (0.9%) cases respectively. The carcinomas comprised 95 (94.1%) adenocarcinoma and 6 (5.9%) squamous cell cancer (SCC) distributed in the colorectum (80 [79.2%]), stomach (12 [11.9%]), esophagus (6 [5.9%]) and small intestine (1 [1.0%]). The sarcoma comprised small intestinal Gastrointestinal stromal tumors (GIST) (4 [66.7%]), gastric GIST (1[16.7%]), and colorectal leiomyosarcoma (1 [16.7%]). The only case of carcinoid was among the colorectal cancers. The gastric carcinoma comprised eight cases of diffuse type, four cases of intestinal type and two cases of mixed type.

Discussion

PGITCs are relatively common, accounting for 15.6% of all cancers in this study which is higher than 6.5-8.4% reported previously in Nigeria [2-3] but lower than the total global rate of 19.2% [1]. Report by Singh et al. in Sub-Saharan Africa (SSA) showed that colorectal cancer, esophageal cancer and gastric cancer are the 5th, 6th and 9th most common cancers in this region [4]. There is some evidence that the incidence of PGITC are increasing, with a projected 73% increase ahead of 58% global increase by 2030 [4-5]. The relatively lower incidence in Nigeria may be attributed to lack of diagnostic capacity at various district hospitals, limiting the cases referred to Nigerian reference centers.

In our series, we noted an annual rate of 17 cases per annum (1.4 cases/month). This is however higher than 8.4

Table 1. Regional and Age Distribution of Gi Cancers

Age group	EC		SC		SIC		CRC		Anus		No of cases (%)
	M	F	M	F	M	F	M	F	M	F	
20-29							2	3			5 (4.6%)
30-39				1			4	8			13 (12.0%)
40-49			1	2		3	7	8			21 (19.4%)
50-59	2	1	2	3			14	10			32 (29.6%)
60-69	1		2	1		1	13	6			24 (22.2%)
70-79	2			1	1		1	3		1	9 (8.3%)
80-89								2		1	3 (2.8%)
90-99							0	1			1 (0.9%)
Total	5	1	5	8	1	4	41	41	0	2	108 (100%)
% of cases	(4.6)	(0.9)	(4.6)	(7.4)	(0.9)	(3.7)	(40)	(40)	0%	(1.9)	
M:F ratio	5:01		01:01.6		1:04		1:01		0:02		1:01
Total	6 (5.6%)		13 (12.0%)		5 (4.6%)		82 (75.9%)		2 (1.9%)		108 (100%)
Mean age (yrs)	63.2		53.1		53.8		52		80		53.4

M, Male; F, Female; EC, Esophageal cancer; SIC, Small intestinal cancer; CRC, Colorectal cancer; Yrs, Years

Table 2. Regional Distribution of Histological Types of PGITC

Histology group	Histological type	EC	SC	SIC	CRC	Anus	Total	%
Carcinoma	SCC	4				2	101	93.5
	Adenocarcinoma							
	No special type	2		1	80			
	Diffuse type		8					
	Intestinal type		2					
	Signet ring type		2					
Sarcoma	Leiomyosarcoma				1		6	5.6
	GIST		1	4				
Neuroendocrine	Carcinoid				1		1	0.9
Total		6	13	5	82	2		

EC, esophageal cancer; SC, Stomach cancer; SIC, Small intestinal cancer; CRC, Colorectal cancer; SCC, Squamous cell cancer; GIST, Gastrointestinal stromal tumor

cases yearly recorded in Uyo [3], and 7.9 cases per year in Port Harcourt, Nigeria [2]. These indices may not be a true reflection of the incidence as they may vary with the size of the catchment area of the facility investigated, and the general health-seeking behavior of the populace served by the health facility. There is therefore the need for a population-based study approach, which until now is still not possible in our region. Most developed countries have highly organized cancer data collection and screening system. As a result, cancers in those regions appear to be apparently higher than in under-developed countries [1].

The trend of PGITC in this report is constantly undulating with two peaks (2015 and 2019). These variations underscore the influence of many odds against single hospital-based cancer epidemiology, such as health-seeking behavior, patients' hospital preference, and recurrent industrial actions in Nigerian government hospitals. However, the observation of a peak in the last complete year of study is a positive sign that PGITC incidence is rising. There is therefore a need for a cancer documentation system that enlists all cancer cases irrespective of where the diagnosis is made and a more stable health sector in Nigeria.

Although our study showed an overall equal gender distribution of PGITC, we observed a sharp gender disparity at different times of the life cycle and in different regions of the gut. The male dominance, which was limited to 40-70 years of age group in this study, is a remarkable observation that calls for further studies. Contrary to our study, however, local reports, SSA and global reports have favored male dominance for esophageal, stomach and colorectal cancers [1-2-3-4]. Female predominance for PGITC in Iran [3] and equal gender distribution for esophageal cancer in North Africa [7] are few exceptions. This general observation may be related to male preponderance in exposure to certain risk factors such as smoking, alcohol, red and processed meat consumption, and propensity to deposit visceral fat and weak, unhealthy nutrition [8-9]. While the local differences in our study may be related to some yet unidentified genetic and/or biological differences, the prevalent diet pattern in this region, which is low in

fiber and rich in oil (Banga soup, starch etc), a non-gender dependent factor, might be contributory.

The order of gastrointestinal cancer incidence is colorectal, gastric cancer, esophageal cancer, small intestinal and anal cancer (in decreasing incidence). Other researchers have reported a similar trend in Nigeria [2-5-6-10]. This is at variance with a report in Uyo, Nigeria where small intestinal cancer was the second to colorectal cancer in incidence [3]. Across Europe and US, colorectal cancers have consistently been among the top 3 cancers [1-11]. However, in Northern Iran, China and South Africa, Sudan, Uganda, Ethiopia, Tanzania, Kenya and India, esophageal cancers are the most common [2-3-9-12]. Gastric cancer is the leading PGITC in Iran, Togo and Saudi Arabia [3-13]. Very high rate of colorectal cancer may be ascribed to westernized lifestyle, physical inactivity, diet pattern and other earlier mentioned risk factors. Remarkably, the slower transit time in the colorectum and its large bacteria load, invariably exposes it to carcinogenic effect of bile acid and fatty acid metabolites, possibly contributing to its higher cancer risk. On the contrary, relatively low rate of small intestine cancer is a general observation despite being the largest part of the gastrointestinal tract. This paradox may be attributed to the short transit time of food particles, low bacterial load, high IgA concentration and less exposure to carcinogens.

CRC accounted for 11.9% of all cancers studied, which is higher than 4.5% and 10% in SSA [4] and the global incidence [1] respectively, depicting the seriousness of the situation. Discouraging reports from western countries show that it is the 2nd leading cause of cancer mortality [11], and therefore calls for serious concern. These western countries have proof of reducing its colorectal cancer incidence and mortality through National Screening programmes using fecal occult blood testing and colonoscopy/sigmoidoscopy [14]. Such programmes will be of immense benefit in this region and should be adopted as part of National health policy. Also, public health education towards more fiber diet, more physical activity, less alcohol beverage, reduced red and refined meat and less smoking will be a desirable move.

The mean age and peak age for colorectal cancer is at the 6th decade which correlates with local publications, [10-15] but is a decade earlier than is observed in western countries, [4] possibly because of our younger population structure or some yet unidentified genetic difference.

Gastric cancer accounted for 1.9% of all cancers, which correlates favorably with 1.4-1.9% reported in other Nigerian histopathology series [2-16]. Our report is lower than the SSA [3%] [4] and global incidence [1] despite the high serological prevalence of *Helicobacter pylori* reported in this region, and the evidence of its strong association with gastric cancer [6-10]. This paradox calls for further studies. This disparity may be attributed to genetic differences and are the subject of further study. There is however no doubt that our weak cancer data and diagnostic capacity alongside absence of screening programme may favor under-reporting of gastric cancer cases. Global reduction of gastric cancer in high-risk countries has been attributed to mass endoscopic screening and reduced intake of salted, smoked and chemically preserved foods, improved refrigeration, increased consumption of vegetables and fruits, and greater antibiotics coverage against *Helicobacter pylori* [17]. Despite the apparently low incidence, there is need to integrate routine endoscopic screening for gastric cancer in our health programme and create an awareness of its preventive measure through public health campaign.

Esophageal cancer accounted for 0.9% of all cancers in our study, which is higher than 0.2% reported in Port Harcourt [2] but relatively lower than SSA [4%] [4] and global incidence [1]. The mean age in our study correlates with the reported mean age of 65.4 years in other Nigerian studies [18]. Significantly, no esophageal cancer was encountered before the age of 50 years in our series. Globally, it is the 7th most common cancer, and the 6th most fatal, [1] a reflection of its poor prognostic index. This scenario may be worse in this part of the globe, where imaging diagnostic techniques are scarce and diagnosis often made at advanced stages of the disease.

Very little is known about the epidemiology of small intestine cancer in our region, probably because of its rarity.

Anal cancer is the least common PGITC in our study. There is also limited information on anal cancer in this part of the world, probably because of its rarity. The two patients in our study were in their eighties. In South Africa, an average age of 50.1 years was observed among patients with anal cancer [19]. Anal cancer is strongly associated with sexually transmissible Human papilloma virus and Human immunodeficiency virus [20-21]. In Nigeria, anal sex is criminalized and this may account for the low incidence of anal cancer [22]. A report however showed a 4.3-37.8% prevalence among those practicing anal sexual intercourse among adults and adolescents in SSA [23]. On the other hand, the prevalence of anal cancer is on the rise in developed countries most likely because of increasing incidence of anal sex and homosexuality.

Carcinoma is expectedly the most common histological type of PGITC in this paper, because the primary lining of the gut is epithelial. This also explains why squamous

cell cancer was encountered in the esophagus and anus in this report, and why adenocarcinoma is the most frequent histological type of colorectal cancer. Two-third of esophageal cancer encountered in our study was squamous cell cancer, which correlates favorably with the leading histological variant across the globe. Studies have also shown that the incidence of SCC has been on the decline in the last decade while that of the adenocarcinomas has been on the increase [9]. As an exception, in US, adenocarcinomas is relatively more common, accounting for 80% of esophageal cancer [24].

Our report showed preponderance of diffuse-type of gastric cancer. On the contrary, the intestinal type was more common in other parts of Nigeria [10-16-25].

Typically, anal cancer may be adenocarcinoma or squamous cell carcinoma in line with the normal epithelium of the proximal and distal 3rd of anal canal [26]. Our cases were solely the later. No report was made in the histological pattern of anal cancer in Nigerian literature. In a study in South Africa, 85% of cases were SCC, and this histological type has been shown to have poorer prognosis [19].

In this study, small intestinal cancers are predominantly sarcomas (GIST). No lymphoma was observed in our study, and similar reports in this region has also shown that lymphoma is generally less common [2-3-6-10].

Limitation

The major limitation is that the study was done in a referral center, and by implication, cases that were not managed in this center were missed. We also considered only histologically diagnosed cases, and may have missed cancer cases diagnosed using only imaging techniques or other laboratory techniques. Our study may, therefore, be an under-representation of the true incidence.

In conclusion, PGITC are relatively common with colorectal cancer being the distinctly most abundant. Adenocarcinoma is the overall most common histological variant, although squamous cell cancer is the most common esophageal and anal cancers. There is equal gender distribution although male dominance is seen in 40-70 years; and peak and mean age in the 6th decade. Routine endoscopy and colonoscopy screening and fecal occult blood examination is recommended for early detection and prevention of PGITC. There is however a need for increased healthcare funding to accommodate this necessity.

Acknowledgements

Special thanks to Professor Odokuma E I and the entire staff of the Department of Pathology, Delta State University Teaching Hospital, Oghara, Nigeria without whom completing this work would have been impossible.

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018 09 12;68(6):394-424. <https://doi.org/10.3322/caac.21492>
- Obiorah C, Ray-Offor E. Epidemiology of Gastrointestinal Malignancies in Nigeria:Port Harcourt Cancer Registry Study. *Oncology Journal of India*. 2020;4(1):1. https://doi.org/10.4103/oji.oji_30_19
- Abudu EK, Akinbami OS. Histopathologic Prolife of Primary Gastrointestinal Malignancies in Uyo City (Niger-Delta Region of Nigeria). *Rare Tumors*. 2016 03 31;8(1):27-29. <https://doi.org/10.4081/rt.2016.6183>
- Singh P, Griffiths E, Irabor D, Adedeji O. Gastrointestinal Cancers in Sub-Saharan Africa. In O.A. Adedeji (ed.), *Cancer in Sub-Saharan Africa*. Springer. 2017;:125-37.
- Iliyasu Y, Ladipo JK, Akang EEU, Adebamowo CA, Ajao OG, Aghadiuno PU. A twenty-year review of malignant colorectal neoplasms at University College Hospital, Ibadan, Nigeria. *Diseases of the Colon & Rectum*. 1996 05;39(5):536-540. <https://doi.org/10.1007/bf02058707>
- Habeebu M, Salako O, Okediji P, Mabadeje B, Awofeso O, Ajekigbe A, Abdulkareem F. The distribution, histologic profile and clinical presentation of gastrointestinal malignancie in Lagos, Nigeria. *JWACS*. 2017;7(1):9-27.
- Asombang AW, Chishinga N, Nkhoma A, Chipaila J, Nsokolo B, Manda-Mapalo M, Montiero JFG, Banda L, Dua KS. Systematic review of esophageal cancer in Africa: Epidemiology, risk factors, management and outcomes. *World Journal of Gastroenterology*. 2019 08 21;25(31):4512-4533. <https://doi.org/10.3748/wjg.v25.i31.4512>
- White A, Ironmonger L, Steele RJC, Ormiston-Smith N, Crawford C, Seims A. A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK. *BMC Cancer*. 2018 09 20;18(1). <https://doi.org/10.1186/s12885-018-4786-7>
- Hassanipour S, Mohammadian-Hafshejani M, Ghoncheh M, Salehiniya H. The incidence and mortality of esophageal cancer and its relationship with development in the world. *Biomed Res Ther*. 2017;4(9):1607-23.
- Abdulkareem F, Faduyile F, Daramola A, Rotimi O, Banjo A, Elesha S, Anunobi C, Akinde O, Abudu E. Malignant Gastrointestinal Tumours in South Western Nigeria: A Histopathologic Analysis of 713 Cases. *West African Journal of Medicine*. 2009 Dec 02;28(3). <https://doi.org/10.4314/wajm.v28i3.48478>
- Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh J, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. *European Journal of Cancer*. 2013 04;49(6):1374-1403. <https://doi.org/10.1016/j.ejca.2012.12.027>
- Obayo S, Lukwago L, Orem J, Faulx AL, Probert CS. Gastrointestinal malignancies at five regional referral hospitals in Uganda. *African Health Sciences*. 2018 01 05;17(4):1051. <https://doi.org/10.4314/ahs.v17i4.13>
- Alahmadi R, Hamour O, H A, A T. Incidence of gastric carcinoma at King Faisal Specialist Hospital- Jeddah Saudi Arabia: a hospital-based study. *Integrative Molecular Medicine*. 2016;3(2):606-611. <https://doi.org/10.15761/imm.1000211>
- Altobelli E, Lattanzi A, Paduano R, Varassi G, di Orio F. Colorectal cancer prevention in Europe: Burden of disease and status of screening programs. *Preventive Medicine*. 2014 05;62:132-141. <https://doi.org/10.1016/j.ypmed.2014.02.010>
- Aliyu S, Ningi A, Babayo U. The Burden of Colorectal Cancers in Nigeria: Patterns and Presentations in North-Eastern Nigeria. *J Cancer Res Oncobiol*. 2020;3(1):128.
- Ebili H, Oluwasola A, Akang E, Ogunbiyi J. Clinicopathological features of gastric carcinoma in Ibadan, Nigeria, 2000-2011. *Nigerian Medical Journal*. 2015;56(2):126. <https://doi.org/10.4103/0300-1652.150700>
- Danwang C, Bigna JJ. Epidemiology of gastric cancer in Africa: a systematic review and meta-analysis protocol. *Systematic Reviews*. 2019 Nov 13;8(1). <https://doi.org/10.1186/s13643-019-1214-2>
- Abdulkareem F, Onyekwere C, Awolola N, Banjo A. A clinicopathologic review of oesophageal carcinoma in Lagos. *Nigerian Quarterly Journal of Hospital Medicine*. 2009 08 11;18(2). <https://doi.org/10.4314/nqjhm.v18i2.44979>
- Ntombela X, Sartorius B, Madiba T, Govender P. The clinicopathologic spectrum of anal cancer in KwaZulu-Natal Province, South Africa. *Cancer Epidemiology*. 2015 08;39(4):528-533. <https://doi.org/10.1016/j.canep.2015.05.005>
- Newsom-Davis T, Bower M. HIV-associated anal cancer. *F1000 Medicine Reports*. 2010 Dec 08;2. <https://doi.org/10.3410/m2-85>
- Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. *International Journal of Epidemiology*. 2016 Oct 27;:dyw276. <https://doi.org/10.1093/ije/dyw276>
- Strömdahl S, Onigbanjo Williams A, Eziefule B, Emmanuel G, Iwuagwu S, Anene O, Orazulike I, Beyrer C, Baral S. An assessment of stigma and human right violations among men who have sex with men in Abuja, Nigeria. *BMC International Health and Human Rights*. 2019 03 05;19(1). <https://doi.org/10.1186/s12914-019-0190-x>
- Morhason-Bello IO, Kabakama S, Baisley K, Francis SC, Watson-Jones D. Reported oral and anal sex among adolescents and adults reporting heterosexual sex in sub-Saharan Africa: a systematic review. *Reproductive Health*. 2019 05 06;16(1). <https://doi.org/10.1186/s12978-019-0722-9>
- Napier KJ. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. *World Journal of Gastrointestinal Oncology*. 2014;6(5):112. <https://doi.org/10.4251/wjgo.v6.i5.112>
- Mandong B, Manasseh A, Tanko M, Echejoh G, Madaki A. Epidemiology of gastric cancer in jos university teaching hospital jos a 20 year review of cases. *Nigerian Journal of Medicine*. 2010 Nov 15;19(4). <https://doi.org/10.4314/njm.v19i4.61975>
- Turner J. The gastrointestinal tract. In:Kuma, Abbas, Aster. *Robins and Cotran Pathologic Basis of disease 9ed*. Elsevier-Saunders. 2015, Philadelphia;:749-817.



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