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Prevalence of Microsatellite Instability in Upper Gastrointestinal Adenocarcinomas and Its Association with Demographic and Histopathological Parameters- A cross-sectional study.

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KEYWORDS

Microsatellite instability, Mismatch repair protein, Gastric cancer, MSI-H, MSI-L/ MSS.

ABSTRACT:

Introduction: Gastric cancer (GC) is a common global malignancy influenced by both genetic and environmental factors. In India, it is the fifth most common cancer in men and seventh in women, as per WHO's Globocan 2018 data. Esophageal and periampullary cancers are also among the more prevalent types. MMR genes maintain genomic stability, and microsatellite instability (MSI)—well-studied in colorectal cancer—also plays a role in GC. MSI-positive and MSI-stable GC differ in clinical behaviour. MSI testing may aid in diagnosis and guide personalised treatment for GC at any stage.

Objectives: To study MSI status in adenocarcinomas of the esophagus, gastroesophageal junction, gastric, and periampullary regions and their clinical and histopathological correlation.

Methods: A total of 47 cases were included in this study. Histology and immunohistochemistry for MMR protein were studied using standard protocols. Results were categorised and compared in various groups- MSI status, age, sex, tumour location, and histological subtype. They were analysed and compared using the chi-square test for categorical variables, and t-tests or one-way ANOVA were applied for continuous variables, as appropriate.

Results: A total of 47 specimens from excisional biopsies and resections of upper GI tract adenocarcinomas were analysed. MSI status was as follows: MSI-H status 27 cases (57.4%), MSI-L 09 cases (19.1%) and MSS 11 cases (23.4%). In this study, 16 out of 19 periampullary cancer cases showed moderately differentiated adenocarcinoma, with 81.2% displaying intestinal morphology. MSI-H was observed in 68.4% (13 cases).

Conclusions: Studies have shown that IHC is a surrogate procedure for molecular expression of the MMR gene with sensitivity and specificity. This study highlights the detection of the expression of the MMR gene using IHC and its clinicopathological association.

1. Introduction

Gastric cancer (GC) is a prevalent malignancy around the globe. It is a disease influenced by multiple factors, including environmental and genetic elements, greatly impacting its development and progression. In India, stomach cancer ranks as the fifth most frequently diagnosed cancer in men and the seventh in women, based on data from the World Health Organisation's Globocan report of 2018. Oesophageal cancer holds the position of the sixth most common cancer, while periampullary cancer stands at thirteenth in terms of overall prevalence (1).

MMR genes are important for maintaining genomic stability. Microsatellite instability plays a role in carcinogenesis and has been studied widely in colorectal cancers. Recent studies have shown its role in GC. Microsatellite instability and microsatellite-stable GC show distinct features and clinical behaviour. The microsatellite instability (MSI) test could be appropriate for diagnosing GC regardless of the tumour stage. It may help give every patient the most precise and effective treatment (1,2,5,7).

Multiple retrospective studies and prospective clinical trials have demonstrated distinct differences between gastric cancers (GCs) with microsatellite stability and those with microsatellite instability. MMR genes

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comprise the proteins MLH1, PMS2, MSH2 and MSH6. MSI (Microsatellite instability) testing, which utilises IHC markers, has become the standard practice for colonic adenocarcinomas; it assists in providing targeted treatment for these patients. MSI testing might be suitable for inclusion as a standard of care in upper gastrointestinal adenocarcinomas, viz. oesophagus, gastro-oesophageal junction, gastric, and periampullary adenocarcinomas (3,5,4,6,10).

Microsatellite instability (MSI) studies on oesophageal and periampullary adenocarcinomas are even fewer than those of gastric adenocarcinomas. Therefore, it is worthwhile to study the MSI status of upper gastrointestinal adenocarcinomas in the Indian population.

This study aims to assess the role of Microsatellite instability (MSI) in upper gastrointestinal adenocarcinoma and its correlation with age, sex, location of tumour and histological subtype of gastric adenocarcinomas.

2. Objectives

The primary objective is to study MSI status in adenocarcinomas of the esophagus, gastroesophageal junction, gastric, and periampullary regions.

Secondary objectives were to correlate MSI status with age, sex, tumour location and histological subtypes of gastric adenocarcinomas. And to do a clinicopathological correlation of gastric adenocarcinomas with MMR protein expression.

3. Methods

The study was conducted in the department of Pathology, Bharati Vidyapeeth (Deemed To Be University) Medical College, Bharati Hospital and Research Centre, Pune. It was a cross-sectional, retrospective, and prospective study of 47 cases diagnosed with oesophageal, gastroesophageal junction, gastric and periampullary adenocarcinomas over a period from May 2021 to October 2024.

All endoscopic biopsies and resected specimens of esophageal, gastroesophageal junction, gastric and periampullary adenocarcinomas (e.g., Whipple resection), paraffin blocks of retrospective cases were included. Cases with a history of neoadjuvant chemotherapy were excluded.

Immunohistochemistry (IHC) was conducted on the appropriate tissue sections utilising antibodies targeting MLH1, MSH2, MSH6, and PMS2. Each IHC run included both positive and negative controls to verify the accuracy and reliability of the staining procedure.

Data analysis was conducted using SPSS (Statistical Package for the Social Sciences), version 25.0. Results were presented in both table and graph formats. Comparative analyses were performed using the chi-square test for categorical variables, and t-tests or one-way ANOVA were applied for continuous variables, as appropriate.

4. Results

This cross-sectional study uses immunohistochemistry markers to assess MMR protein expression in upper gastrointestinal adenocarcinomas. It categorises adenocarcinomas based on MSI status into MSI-H and MSS/MSI-L, and examines the clinicopathological correlation between gastric carcinomas and MMR protein expression.

47 cases of upper GI carcinomas, including biopsies and resections, were studied. The patients' average age was 57 (range 24-78), with 26 males (55.4%) and 21 females (44.6%), a male-to-female ratio of 1.24:1. (Table no.2)

The most common symptom was abdominal pain. Jaundice occurred in 21.3% of cases, while 14.9% had both pain and jaundice. Dysphagia was seen in 19.2%, vomiting and anorexia in 12.7%, and weight loss in 10.6% of cases. The commonest site of adenocarcinoma was the D2 part of the duodenum (periampullary region) in 19 cases (40.4%), followed by 07 cases each (14.9%) in the pylorus and stomach body. (Table no.2)

There were 30 cases (63.8%) of moderately differentiated adenocarcinomas, 12 cases (25.5%) of poorly differentiated adenocarcinomas, and 05 cases (10.6%) of well-differentiated adenocarcinomas. (Table no.2)

As per the Lauren classification for the gastric adenocarcinoma, out of 24 cases (51.1%) from the gastric region, 05 cases showed intestinal morphology (20.9%) and 19 (79.1%) cases showed diffuse type morphology.

In 19 cases (40.4%) from the periampullary region, a light microscopy study showed intestinal-type

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morphology in 14 cases (73.7%), pancreatobiliary type morphology seen in 03 cases (15.8%), and 2 cases showed mucinous areas (10.5%). 4 cases (8.5%) from the esophageal region showed diffuse type morphology.

The upper GI tract adenocarcinomas were classified using MSI status into MSI-H and MSS/MSI-L. The majority of the patients were classified as MSI-H, 27 cases (57.4%), followed by MSS, 11 cases (23.4%) and MSI-L, 09 cases. (Table no.1)

Out of a total of 47 cases, 36 cases (76.6%) had a loss of 1 or more of the MMR gene proteins, and 11 cases (23.4%) had intact expression. These include: MLH1 only (sporadic)- 01 cases (02%), MLH1 and PMS2 (Type 1)- 06 cases (12.7%), PMS2 only (Type 2)- 02 cases (04%), MSH2 and MSH6 only (Type 3)- 05 cases (10.6%), Loss of MSH6 (Type 4)- 07 cases (14.8%), pMMR- All antibodies are intact in 11 cases (23.4%).

The study found no significant link between MMR expression and age (cut-off 50 years). Loss of MSH6 was more common in males (14.8%), though not statistically significant (p = 0.30). MLH1 and MSH2 showed no gender difference, while PMS2 loss was more frequent in females (42.8%).

MMR expression was associated with tumour differentiation, notably MSI-H in moderately differentiated intestinal-type adenocarcinomas (p = 0.01). (Table no.1)

5. Discussion:

Upper GI cancer is a major global health challenge, with variations in its molecular features significantly affecting prognosis and treatment responses. Microsatellite instability (MSI), which signifies impaired DNA MMR, has become an important biomarker in gastric cancer, affecting tumour characteristics, treatment choices, and patient outcomes. This research sought to assess the occurrence of MSI in gastric cancer cases along with its pathological and clinical importance (10).

Two studies (MAGIC 2017, ARTIST 2019) in Asia and Europe reported a median age of 59 years (range 20–85) with male predominance. Similar findings were noted by Tetsuya Ito et al. (2021) in a Japanese hospital-based study and in this study (8).

In the comparison of the MSI-high subgroup and the MSS/MSI-low subgroup, the median ages were 66 and 58 years, respectively, with intestinal-type histology present in 67.5% of the MSI-high subgroup compared to 43.2% in the MSS/MSI-low subgroup (both P < .001), while gastric tumour localisation was noted in 96.7% versus 91.3% (P = 0.056).

The present study showed 79.1% of cases of gastric adenocarcinoma with a diffuse type of morphology, which is more in comparison to the other two studies by Elizabeth C. Smyth et al. and Rosalba Micelia et al.

MSI-H gastric cancers show better prognosis than MSS, likely due to higher neoantigen load and stronger immune response. Reduced lymph node metastasis also suggests less aggressive disease, highlighting MSI-H as a favourable prognostic marker.

Studies by Zhu L. and Choi Y. (May 2015) found MSI-H linked to better survival in gastroesophageal adenocarcinoma, especially in the intestinal subtype. However, no significant prognostic value was seen in diffuse or signet-ring cell types, possibly due to the small sample size (111cases) (9).

In the present study we found a maximum number of cases of loss of MSH6 only, followed by loss of MLH1 and PMS2 where Elizabeth C. Smyth et al. and Tetsuya Ito et al. found a similar result with maximum cases of loss of MLH1 and PMS2.

Conclusion:

This cross-sectional study investigates the expression of MMR proteins in the upper gastrointestinal tract through immunohistochemistry while categorising gastric adenocarcinomas based on their MSI status into MSI-H and MSI-L, along with examining their clinicopathological relationships regarding subtype, age, and gender.

A total of 47 specimens from excisional biopsies and resections of upper GI tract adenocarcinomas were analysed. Most of the cases of moderately differentiated adenocarcinomas (63.8%) followed by poorly differentiated adenocarcinomas (25.5%). The overall most common morphology seen was the intestinal type (42.5%). MSI-H status 27 cases (57.4%), MSI-L 09 cases (19.1%) and MSS 11 cases (23.4%).

This study found that 16 of the 19 periampullary patients had moderately differentiated adenocarcinoma, with intestinal morphology in 81.2% of the cases. MSI-H status was found in 13 cases, i.e. 68.4% of cases.

Studies have shown that IHC is a surrogate procedure for molecular expression of the MMR gene with sensitivity

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and specificity. This study showed that the majority of moderately differentiated adenocarcinoma cases were situated in the periampullary area and had intestinal morphology with MSI-H status. Our study showed a maximum number of cases with loss of MLH1 expression.

This study highlights the detection of the expression of the MMR gene using IHC and its clinicopathological association. H&E Images and data charts are as follows.

Image 1: Well-differentiated adenocarcinomas (H&E 20X)

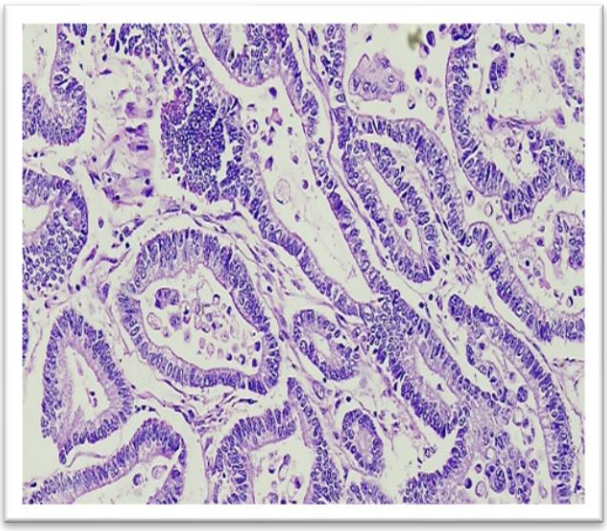

Image 2: Moderately differentiated adenocarcinomas (H&E 20X)

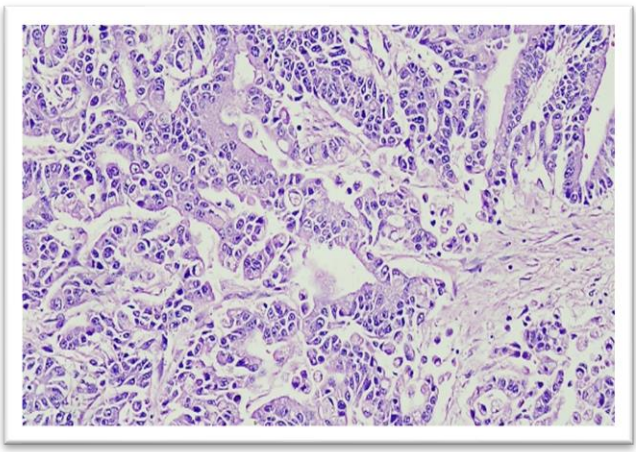

Image 3: Poorly differentiated adenocarcinomas (H&E 20X)

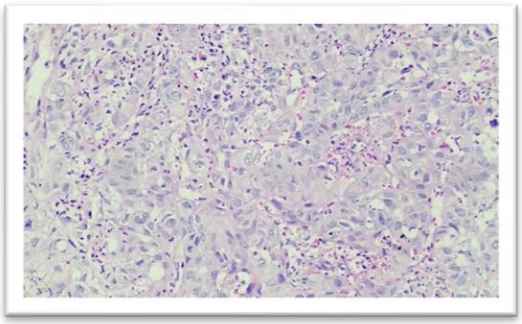

Table No. 1: Correlation between age, gender, tumour type and its histological subtype with MSI status.

Table No. 1		MSI status			Total	p value
		MSIH	MSIL	MSS		
Age group	<50 years	8	2	10	15	0.501
	>50 years	19	7	6	32	
Total		27	9	11	47	
Gender	female	13	2	6	21	0.301
	male	14	7	5	26	
Total		27	9	11	47	
Degree of differentiation	Moderately	20	6	4	30	0.123
	Poorly	6	1	5	12	
	well	1	2	2	5	
Total		27	9	11	47	
Histological subtype	Intestinal	5	0	6	11	0.01
	Diffuse	14	3	3	20	
	Mixed	8	6	2	16	
Total		27	9	11	47	

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Table no.2: Correlation between age, sex, degree of differentiation, tumour location, and histological features with MMR gene expression patterns.

Table No. 2		MLH1		MSH2		MSH6		PMS2	
		Intact	Loss	Intact	Loss	Intact	Loss	Intact	Loss
Age group	<50 years	08	07	08	07	08	07	11	04
	>50 years	23	09	19	13	13	19	24	08
	P value	0.211		0.69		0.41		0.90	
Gender	Male	16	10	14	12	11	15	23	03
	Female	15	06	13	08	10	11	12	09
	P value	0.47		0.57		0.71		0.014	
Degree of differentiation in upper GI adenocarcinoma	Moderately differentiated	18	12	15	15	12	18	21	09
	Well-differentiated	04	01	04	01	03	02	04	01
	Poorly differentiated	09	03	08	04	06	06	10	02
	p value	0.50		0.34		0.64		0.64	
Site of tumour	Periampullary region	13	06	09	10	10	09	11	08
	Stomach	11	07	10	08	10	10	14	04
	Gastroesophageal junction	03	03	04	02	01	05	06	00
	Oesophagus	04	00	04	00	02	02	04	00
Histological subtype	Intestinal type	12	08	12	08	10	10	14	06
	Diffuse type	09	02	08	03	06	05	09	02
	Mixed type	10	06	07	09	05	11	12	00
	p value	0.44		0.31		0.40		0.76	

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References:

1. Duan Y, Xu D. Microsatellite instability and immunotherapy in gastric cancer: a narrative review. Precis Cancer Med. 2023 Jun;6:14–14.
2. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer. JAMA Oncol. 2018 May 10;4(5):e180013.
3. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. New England Journal of Medicine. 2015 Jun 25;372(26):2509–20.
4. Shokal U, Sharma PC. Implication of microsatellite instability in human gastric cancers. Indian J Med Res. 2012 May;135(5):599–613.
5. van Velzen MJM, Derks S, van Grieken NCT, Haj Mohammad N, van Laarhoven HWM. MSI as a predictive factor for treatment outcome of gastroesophageal adenocarcinoma. Cancer Treat Rev. 2020 Jun;86:102024.
6. Na W, Lee IJ, Koh I, Kwon M, Song YS, Lee SH. Cancer-specific functional profiling in microsatellite-unstable (MSI) colon and endometrial cancers using combined differentially expressed genes and biclustering analysis. Medicine. 2023 May 12;102(19):e33647.
7. Umar A, Boland CR, Terdiman JP, Syngal S, Chapelle A d. l., Ruschoff J, et al. Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability. JNCI Journal of the National Cancer Institute. 2004 Feb 18;96(4):261–8.
8. Ito T, Suzuki O, Kamae N, Tamaru JI, Arai T, Yamaguchi T, et al. Comprehensive analysis of DNA mismatch repair-deficient gastric cancer in a Japanese hospital-based population. Jpn J Clin Oncol. 2021 Jun 1;51(6):886–94.
9. ZHU L, LI Z, WANG Y, ZHANG C, LIU Y, QU X. Microsatellite instability and survival in gastric cancer: A systematic review and meta-analysis. Mol Clin Oncol. 2015 May;3(3):699–705.
10. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202–9.