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MISMATCH REPAIR PROTEIN EXPRESSION IN GASTRIC CANCER PATIENTS

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The doctoral thesis defense was held before the Hue University-level Thesis Defense Committee.

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The doctoral thesis can be found at:

- National library of Vietnam
- The library of Hue University
- The library of University of Medicine and Pharmacy, Hue University

INTRODUCTION

1. Rationale for study

Gastric cancer (GC) is one of the most common cancers in the world and even in Vietnam. Because it is frequently discovered at a late stage, this disease has a dismal prognosis. Recent data indicate that patient prognosis depends not only on the disease stage but also on the molecular and histopathological traits of the tumor. Interestingly, the American Cancer Genome Atlas and the Asian Cancer Research Group both view GC as a complex, heterogeneous disease and identify microsatellite instability (MSI) as a unique subgroup linked to its prognosis. The hallmark of MSI is a longer microsatellite, which results from a lack of the mismatch repair (MMR) protein. The clinical diagnosis of mismatch repair deficiency (dMMR) is based on MSI analysis by biomolecular assays or immunohistochemistry (IHC) techniques to assess the expression of MMR proteins. In GC, the prevalence of dMMR varies between countries and ranges from 8 to 25%. Although there have been reports of a correlation between dMMR status and pathologic and clinical variables, the findings are still unclear. Notably, several recent studies have shown that dMMR is not only a good predictor of survival but also may be able to forecast the effectiveness of immunotherapy and chemotherapy in locally advanced and metastatic GC cases.

According to research conducted in Vietnam, GC is a prevalent malignancy with a dismal prognosis, with a 25–35% 5-year survival rate following surgery in stage III, which is consistent with the global trend. Thus, there is a pressing need to advance research on prognostic indicators and forecast how well a treatment will work for this illness. Tumor biology, in particular, is becoming more and more interesting, and the MMR system plays a significant role.

Therefore, we conducted the research entitled: "*Mismatch repair protein expression in gastric cancer patients" with the two following objectives:*

1. To determine some clinical, paraclinical, treatment, and MMR protein expression in GC patients using the immunohistochemical technique.

2. To survey the relationship between MMR protein expression and some clinical and paraclinical factors and treatment response

2. Contribution of the thesis

Scientific values: This topic helps us answer the question of what the rate of dMMR in GC patients in the Central Highlands of Vietnam is and how this factor is related to specific clinical and paraclinical characteristics, as well as factors that can assist in predicting the expression of MMR proteins.

Practical value: Through this research, we can inform clinicians about the MMR status of GC patients, allowing them to actively participate in prognostic assessment and make the best treatment decisions for their patients.

3. Outline of the thesis

The thesis consists of 122 pages: the problem statement, 2 pages; the literature review, 32 pages; the research objects and methods, 18 pages; the research results, 32 pages; the discussion, 35 pages; the conclusion, 2 pages; the recommendation, 1 page. The thesis has 45 tables, 10 figures, 14 charts, and 142 references, of which 19 are in Vietnamese and 123 are in English.

Chapter 1
LITERATURE REVIEW

1.1. OVERVIEW OF GASTRIC CANCER

1.2. MICROSATELLITE INSTABILITY AND MISMATCH REPAIR SYSTEMS

1.3. IMMUNOHISTOCHEMISTRY

1.3.1. Principle

1.3.2. Immunohistochemical staining techniques

+ Direct enzyme immunoassay

+ Indirect enzyme immunoassay (bridging method)

1.2.3. The applications and value

1.4. MMR PROTEIN EXPRESSION AND GASTRIC CANCER

1.4.1. MMR protein expression

Previous research has revealed that the prevalence of dMMR is between 8 and 25%, with 8-17% in Asian countries and more than 20% in Western countries. The most prevalent pattern is MLH1 and PMS2 protein expression loss, which occurs in 50-90%, followed by an isolated loss of PMS2 expression of roughly 5-30%.

1.4.2. Correlation between MMR protein expression status and clinicopathological features of gastric cancer.

dMMR/MSI-H GC is frequently related to advanced age (>65 years), greater tumor size, female sex, intestinal type of Laurén, and distal stomach, and is more common in individuals with numerous GCs than in sporadic cases. The incidence of dMMR stage-dependent, with roughly 20% of individuals without regional lymph node metastases and less than 5% of patients having distant metastasis.

1.4.3. Prognostic role of dMMR in gastric cancer

Numerous studies have demonstrated that dMMR is a favorable predictive biomarker for GC. Furthermore, multivariate analysis revealed that dMMR is an independent survival predictor. Although dMMR has been demonstrated to be a significant prognostic factor in studies from Western countries, this finding remains controversial in Eastern countries due to variances in tumor biology and different responses to chemotherapy in patients with dMMR and pMMR GC in the two locations.

1.5. DOMESTIC AND FOREIGN STUDIES ON THE MMR PROTEIN EXPRESSION IN GASTRIC CANCER

1.5.1. DOMESTIC STUDIES

Le Thi Thu Nga investigated 67 patients with pT3 GC with regional lymph node metastases who had radical surgery and adjuvant chemotherapy with the XELOX regimen. The dMMR rate was 14.9%. The study found that dMMR was more frequent in women. The findings revealed that dMMR was a positive prognostic factor for GC patients, with a 3-year DFS rate of 58.3% in the pMMR group, significantly lower than in the dMMR group (100%).

1.5.2. FOREIGN STUDIES

1.5.2.1. MMR proteins expression status

According to research results, the incidence of dMMR in GC was low, ranging from 5-24%. The most common pattern was a simultaneous loss of MLH1 and PMS2 expression.

1.5.2.2. Studies on resectable GC patients

Zhang Q. (2018) studied 567 resectable GC patients, of whom 10.1% had dMMR. dMMR was common in elderly GC patients,

women, distal gastric tumors, Lauren intestinal type, and those with fewer lymph node metastases and nerve invasion. dMMR was an independent prognostic factor with a better prognosis than the remaining groups.

Guan W. (2021) surveyed 890 patients with all stages of GC (6.6% dMMR). The findings revealed that dMMR was linked with older GC patients, female gender, distal stomach, early stage, Lauren intestinal type, well-differentiated, and HER2 negative. The research revealed that dMMR GC had a better prognosis, with a considerably longer OS than the pMMR group (OS not reached vs. 53.9 months). However, this prognostic role was lost in multivariate analysis. Adjuvant chemotherapy did not affect OS or progression-free survival (PFS) in the dMMR group. Unresectable dMMR GC Patients responded poorly to chemotherapy.

Stolze T. (2023) retrospectively studied 223 resectable GC patients (10.3% dMMR) and showed that the dMMR group without perioperative chemotherapy had better survival than the group with chemotherapy with HR=0.36, p=0.03.

1.5.2.3. Studies on unresectable GC patients

In metastatic GC, dMMR status predicted poor chemotherapy response but excellent immunotherapy response.

- The role of dMMR in predicting chemotherapy response

Kubota (2020) analyzed the impact of molecular subgroups on the efficacy of chemotherapy and immune checkpoint inhibitor therapy in 410 metastatic GC patients and showed that the dMMR patients receiving first-line chemotherapy had a shorter OS with HR 1.97; p = 0.022. In contrast, Oh C.R. (2024) studied the role of

dMMR on the efficacy of first-line chemotherapy with fluoropyrimidine combined with platinum in 543 patients with recurrent and unresectable GC, of which 4.4% were dMMR, showing no difference in overall response rate, OS and PFS between the dMMR and pMMR subgroups, although the response rate of the dMMR subgroup was lower than that of the pMMR subgroup (27.3% vs. 34.3%). In addition, the dMMR subgroup tended to have a longer OS than the pMMR subgroup (17.9 vs. 12.2 months, $p = 0.183$).

Chapter 2

PARTICIPANTS AND METHODS

2.1. PARTICIPANTS

2.1.1. Participants

229 patients with histopathological diagnosis of GC at Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital from January 2021 to March 2024 were recruited.

2.1.2. Selection criteria

2.1.2.1. Selection criteria

- Confirmed diagnosis of primary gastric carcinoma by histopathological examination.
- Complete medical records

2.1.2.2. Exclusion criteria

- Recurrent or treated GC patients.

2.1.3. Sample size

Calculated using the sample size formula to estimate a population proportion. The minimum sample size estimate is 150 patients. We recruited 229 patients.

2.2. METHODS

2.2.1. Design of the study

Prospective, longitudinal, case series descriptive study.

2.2.2. Study Duration

From July 2021 to July 2024.

2.2.3. Data collection method

2.2.3.1. Data collection method

- Individual survey form for each patient.
- Patient medical records.

2.2.4. Research location

Department of Pathology, Hue University of Medicine and Pharmacy Hospital, Hue Central Hospital.

2.3. RESEARCH VARIABLES

2.3.1. General characteristics: Age, gender, body mass index (BMI), performance status (ECOG/WHO), chief complaint

2.3.2. Clinical characteristics

2.3.3. Paraclinical parameters: blood group, hemoglobin, albumin, tumor markers (CEA, CA-19.9, CA-72.4), and tumor macroscopic variables (image, location, and size).

2.3.4. Disease Staging Characteristics: Local invasion, regional lymph node metastasis, distant metastasis**.**

2.3.5. Pathological features: according to Lauren 1965 and WHO 2018, Modified Lauren classification and mucinous characteristics

2.3.6. MMR protein expression status

2.3.6.1. MMR protein expression status

Binary variable: including dMMR, pMMR

2.3.6.2. Each MMR protein expression status

MLH1, MSH2, MSH6, PMS2: negative or positive

2.3.6.3. Research methods

IHC staining with indirect enzyme immunoassay technique, Roche Ultra View DAB color detection kit on Ventana BenchMark GX, Serial number 816499.

2.3.7. Treatment characteristics

2.3.7.1. Therapy

Resectable GC : Radical surgery, indication for adjuvant chemotherapy, preoperative chemotherapy, adjuvant chemoradiotherapy, adjuvant chemotherapy

Unresectable GC: Palliative chemotherapy, palliative surgery.

2.3.7.2. Treatment Response:

For resectable GC (follow-up at least 1 year after surgery): Recurrence, site of recurrence, PFS. For unresectable GC: response rate to chemotherapy according to RECIST 1.1 criteria, OS.

2.4. STATISTICAL METHODS

- Data were processed using SPSS 21.0 software.
- Comparison test:

+ Using χ^2 test, comparisons were statistically significant with $p < 0.05$.

+ For variables with associations proven by χ^2 test, univariate logistic regression analysis was used to assess the likelihood of the variable occurunce.

- Variables changing over time were estimated using Kaplan-Meier, correlations were tested using Log-rank test.
- Using Cox regression model to determine prognostic factors for DFS

2.5. ETHICAL CONSIDERATIONS

The study was approved by the Ethics Committee in Biomedical Research of the University of Medicine and Pharmacy, Hue University (Approval number: H2021/441).

2.6. RESEARCH DIAGRAM

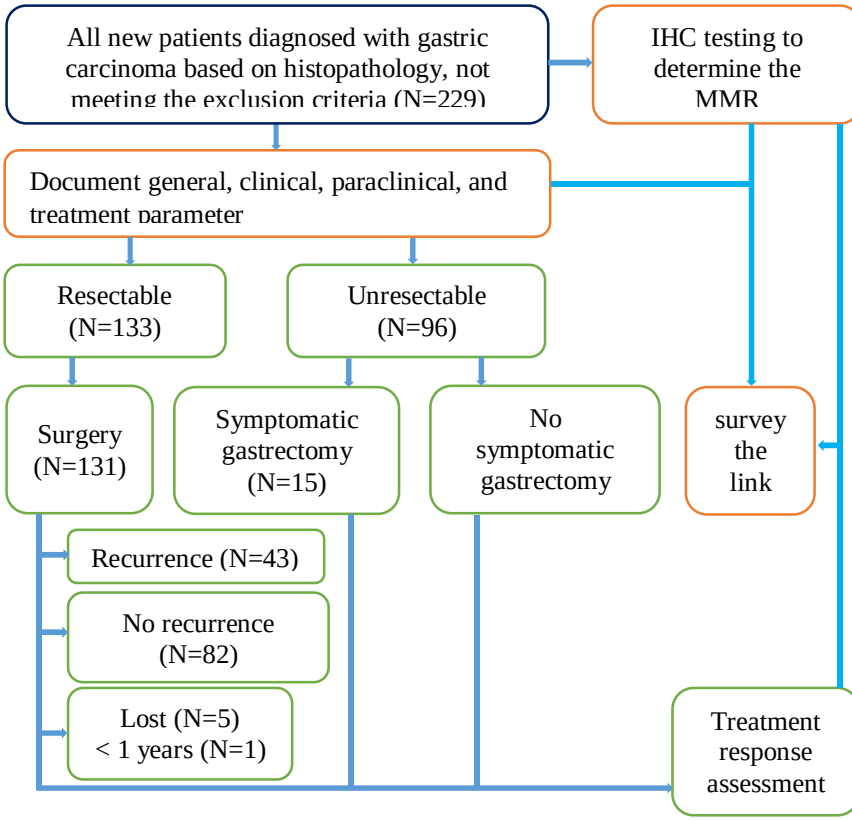

Figure 2.1. **Research diagram**

Chapter 3
RESULTS

3.1. CLINICAL AND PARACLINICAL CHARACTERISTICS AND MMR PROTEIN EXPRESSION

3.1.2. Clinical characteristics

Table 3.3. *Clinical characteristics (n=299)*

Đặc điểm lâm sàng	**n**	**%**
Epigastric pain	212	92,6
Weight lost	54	23,6
Vomitting, nausea	60	26,2
GI bleeding	50	21,8
Abdominal mass	12	5,2
Dysphagea	10	4,4
Ascites	6	2,6
Others	78	34,1

Comment: Epigastric pain is the most common clinical symptom with a rate of 92.6%.

3.1.3. Paraclinical characteristics

3.1.3.2. Macroscopic appearance (endoscopy + histopathology)

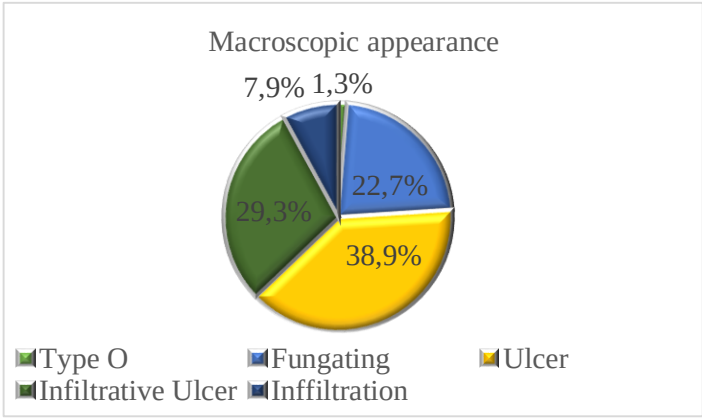

Figure 3.1. *Macroscopic appearance*

Comments: Nearly 99% of cases were images of advanced stage GC with ulcerative form being the most common at 38.9%, followed

by infiltrating ulcerative form 29.3% and fungating form 22.7%. Infiltrative form is the least common at 7.9%.

3.1.3.4. Tumor microscopic

Microscopic by Lauren

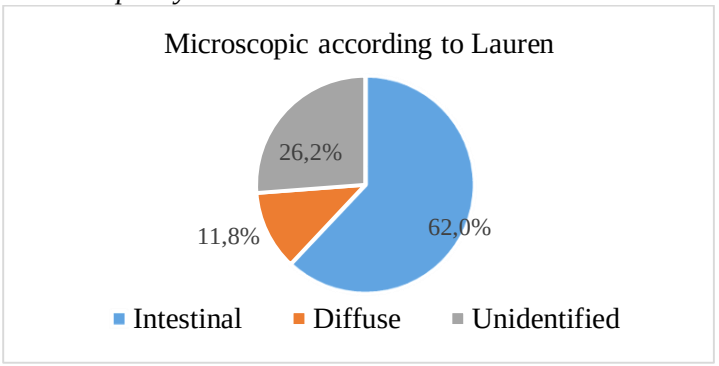

Figure 3.2. Microscopic characteristics according to Lauren

3.1.3.5. Staging characteristic

Table 3.8. *Staging characteristic*

Staging characteristic		**n**	**%**
Local invasion T n=224	Tis	2	0.9
	T1	19	8.5
	T2	35	15.6
	T3	62	27.7
	T4	106	47.3
Regional lymph node n=224	Present	140	62.5
	Absent	84	37.5
Distant metastasis n=229	Present	91	39.7
	Absent	138	60.3
Number of metastatic organs	One organ	34	37.4
	2 or more	57	62.6

Staging characteristic		n	%
n=91			
T, N, M Stage n=229	0	2	0.9
	I	37	16.2
	II	49	21.4
	III	50	21.8
	IV	91	39.7

Comments: The majority of tumors invaded T3 and T4 at a 75% rate. 62.5% of patients had regional lymph node metastasis, whereas 39.7% had distant metastases. Patients in stages 0, I, II, III, and IV were distributed in increasing proportions, at rates of 0.9%, 16.2%, 21.4%, 21.8%, and 39.7%, respectively.

3.1.4. Treatment characteristics

3.1.4.3. Treatment results in resectable gastric cancer

Table 3.12. *Treatment results in resectable gastric cancer*

Treatment results		n	%
Recurrence n=125	Present	43	34.4
	Absent	82	65.6
Recurrence duration n=43	<1 year	26	60.5
	1-2 years	16	37.2
	>2 years	1	2.3
Recurrence site n=43	Local	3	7.0
	Regional	1	2.3
	Distant metastasis	39	90.7

Comments: 34.4% of unresectable GC patients relapsed following radical surgery, with 60.5% relapsing within a year. The vast majority (90.7%) of recurrence patients developed distant metastatic.

3.1.5. MMR protein expression status

3.1.5.1. MMR protein expression status

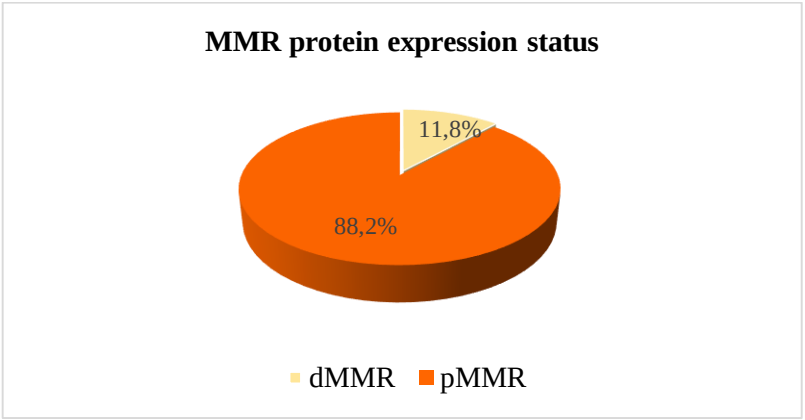

Figure 3.6. *MMR protein expression status*

Comments: There were 27 cases of dMMR among the 229 tissue samples examined, accounting for 11.8%.

3.1.5.4. Detailed model of dMMR cases

Table 3.16. *Detailed model of dMMR cases dMMR (n=27)*

MMR proteins	MLH1	PMS2	MSH2	MSH6	n=27	%
dMMR	-	-	+	+	13	48.1
	+	+	-	-	3	11.1
	+	+	+	-	1	3.7
	+	-	+	+	10	37.0
Total					27	100

Comments: The most prevalent dMMR pattern was a loss of both MLH1 and PMS2 expression, accounting for 48.1%, followed by a single loss of PMS2 expression of 37%. The simultaneous loss of MSH2 and MSH6 expression accounted for 11.1%. Single loss of MSH6 expression was the least prevalent, accounting for only 3.7%. There were no instances of losing all four proteins.

3.2. THE RELATIONSHIP BETWEEN MMR EXPRESSION AND SOME CLINICAL, PARACLINICAL FEATURES, AND TREATMENT RESPONSE

Table 3.32. *Univariate logistic regression model predicting dMMR status in subgroups with associated factors*

Characteristics		dMMR		p
		OR	KTC95%	
Distant metastasis	Absent	**4.4**	**1.5-13.0**	**0.009**
	Present	1	-	-
Stage	0, I	**4.8**	**1.3-17.3**	**0.018**
	II	**6.3**	**1.9-21.0**	**0.003**
	III	2.4	0.6-9.4	0.205
	IV	1	-	-
Lauren	Unidentified, diffuse	1	-	-
	Intestinal	**5.7**	**1.7-19.5**	**0.006**
WHO	Tubular (well, moderate differentiated), papillary	**5.3**	**1.2-23.3**	**0.029**
	Mucinous	3.3	0.5-20.9	0.212
	Signet ring cell, poorly adhesive, specific	0.8	0.1-9.9	0.905
	Tubular (poorly differentiated)	1	-	-
Grade	low	**4.5**	**1.6-12.3**	**0.004**
	high	1	-	-

Comments: dMMR was more common in stages 0, I, and II than in stages IV, with ORs of 4.8 (95% CI: 1.3-17.3; p=0.018) and 6.3 (95% CI: 1.9-21.0; p=0.003), respectively. dMMR was 4.4 times more likely in patients without distant metastasis than those with distant metastases. Tubular (well- and moderately differentiated) and papillary tumors were associated with a 5.3-fold higher incidence of dMMR than poorly differentiated tubular cancers. Low-grade GCs had a 4.5-fold higher likelihood of dMMR than high-grade GCs. dMMR was 5.7 times more prevalent in the Lauren intestinal subtype than in the unidentified, diffuse subtype (95% CI: 1.7-19.5).

3.2.5. Association between dMMR status and treatment response

3.2.5.1. Association between dMMR status and treatment response in resectable GC patients

Association between dMMR status and recurrence status

DFS stratified according to MMR status

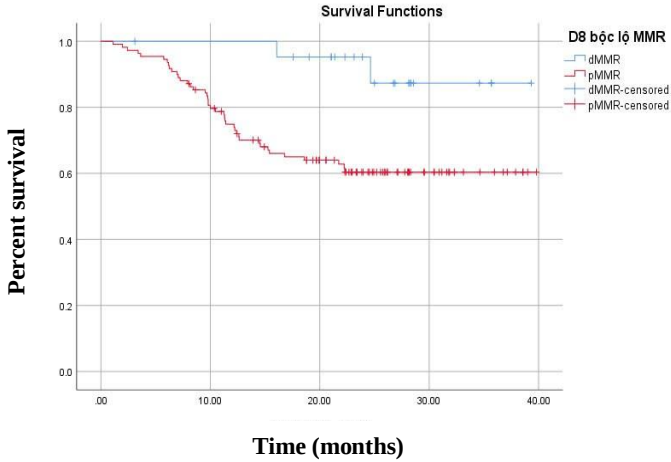

Figure 3.7. *DFS stratified according to MMR status*

Comments: The mean DFS of the study population was 29.80 (standard error 1.26) months (95% CI: 27.34-32.27). In which the dMMR group was 37.06 (standard error 1.52) months (95% CI: 34.09-40.03), longer than the pMMR group was 28.29 (standard error 1.43) months (95% CI: 25.49-31.09), this difference was statistically significant with p=0.012. The median DFS was not reached in both groups.

Cox regression model including some patient characteristics and MMR status predicted the likelihood of recurrence in resectable GC patients

Table 3.32. *The Cox regression model predicted recurrence risk in resectable GC patients based on general, clinical, paraclinical, and treatment characteristics.*

Characteristics		Crude HR (95%CI)	p	adjusted HR (95%CI)	p
Macroscopic apperance (Reference group: infiltration)					
	Type 0, fungating	0.25 (0.07-0.78)	0.017	0.15 (0.04-0.54)	**0.004**
	Ulcer	0.35 (0.13-0.93)	0.036	0.26 (0.08-0.81)	**0.021**
	Infiltrating Ulcer	0.20 (0.06-0.60)	0.004	0.16 (0.04-0.58)	**0.005**
Site (Reference group: non-cardia)					
	Cardia	3.22 (1.26-8.21)	0.014	4.14 (1.28-13.31)	**0.018**
Size (Reference group: ≤5 cm)					
	>5 cm	2.06 (1.10-3.86)	0.024	1.71 (0.84-3.48)	0.14
MMR status (Reference group: pMMR)					
	dMMR	0.18 (0.04-0.76)		0.09 (0.02-0.45)	**0.003**
Local invasion T (Reference group: Tis, T1, T2)					
	T3	6,11 (2.29-16.29)	0.00	4.96 (1.24-19.79)	**0.023**
	T4	6.55 (2.42-17.68)	0.00	4.37 (0.90-21.26)	0.068
Regional lymph node (Regional lymph node: absent)					
	Present	4.67 (2.35-9.30)	0.00	3.68 (1.18-11.47)	**0.025**
Stage (Reference group: Stage 0, I)					
	II	6.42 (1.47-28.08)	0.014	0.92 (0.11-7.67)	0.94
	III	18.4 (4.36-77.93)	0.000	1.09 (0.08-14.99)	0.95

Comments: Multivariate Cox regression analysis demonstrated that MMR status was an independent prognostic factor for DFS, alongside macroscopic appearance, tumor site, local invasion, and regional lymph node status. The analysis indicated that dMMR was a factor that significantly reduces the likelihood of recurrence in patients with resectable GC, with a HR= 0.09 (95% CI: 0.02-0.45; p=0.003).

Chapter 4
DISCUSSION

4.1. CLINICAL AND PARACLINICAL FEATURES AND EXPRESSION OF MMR PROTEIN EXPRESSION

4.1.2. Clinical features

GC symptoms are generally vague and nonspecific, resulting in many patients being diagnosed at an advanced stage. Epigastric pain is one of the most prevalent clinical complaints, and it is also the leading cause of hospitalization. Our study confirmed this finding, as we found that 92.6% of cases had epigastric discomfort, and 76.9% of participants were hospitalized due to this symptom.

4.1.3. Paraclinical features

4.1.3.2. Macroscopic apperance (based on endoscopy and pathology)

Ulcers and infiltrating ulcers were frequent macroscopic images in investigations. This finding aligns with our results, as ulcers and infiltrating ulcers were the two most common morphology in the study, with rates of 38.9% and 29.3%, respectively. Do Anh Tu also noted that ulcers represent a significant image, accounting for 64.2% of cases.

Microscopic according to Lauren classification

Domestic research by Phan Canh Duy (92.6%) and Nguyen Tai Tien (64.8%), as well as overseas studies by Zhang Q. (about 50%) and Karpińska-Kaczmarczyk K. (55.1%), showed a predominance of the intestinal subtype according to Lauren classification. Our findings were consistent with the authors' reports, which indicated that the intestinal subgroup was prevalent, accounting for 62%. These results contradicted the findings of Nappo F. in Italy, who found that the diffuse subtype

is prominent at 38.5% compared to the 30.2% intestinal type. This variation highlighted that the distribution of microscopic subgroups could differ by geographical region.

4.1.3.4. Stage features

Local invasion T

At the time of diagnosis, most tumors have invaded the layers of the stomach wall and metastasized to the lymph nodes. Phan Canh Duy's study showed that 83.3% of tumors had invaded the serosa. An J. in Korea reported this rate as 55.1%. Zang Q.'s study showed that over 50% of tumors were T3 or T4. Our study also noted that up to 75% of gastric tumors were at T3 or T4.

Regional lympho node

Lymph node metastasis is common in GC, even in the early stages. The lymph node metastasis rate in the Phan Van Cuong study was 69.1%, Nguyen Tai Tien was 62.2%, Nappo F. was 76.2%, and An J. (2020) was 91.9%. We also demonstrated a prominent rate of lymph node metastasis in the study group at 62.5%.

Stage

In this study, the proportion of patients in the local stage and stage I was low, with the corresponding rates of 0.9% and 16.2%. Meanwhile, the percentage of patients with stage IV was relatively high, 39.7%. GC is a rapidly progressing malignancy with a high potential for metastasis. In general, about 60% of GC patients were unresectable. According to Phan Van Cuong, 26.3% of cases had distant metastasis when first admitted to the hospital. This rate was 30.7% in the study by author Guan W.

4.1.4. Treatment features

4.1.4.3. Treatment results unresectable stage

Recurrence rate

Recurrence is the leading cause of death in GC patients. The recurrence rate varies significantly between regions and countries and ranges from 21.8% to 50% because most patients are in an advanced stage at diagnosis. Our study also showed 34.4% of recurrences. This rate was similar with previous investigations by Phan Canh Duy (Vietnam), Jiao X. (China), and Nappo F. (Italy), who found 31.4%, 22.7%, and 54.8%, respectively.

4.1.5. MMR protein expression

4.1.5.1. MMR protein expression

Our study analyzed 229 GC tissue samples, with 27 cases of dMMR, accounting for 11.8%. This conclusion was comparable with data from the same continent, such as Lee H. (2013) 10.9%, Zhang Q. (2018) 10.1%, Suzuki O. (2021) 11%, but lower than studies in the West such as Vos E. L. (2021) 15%, Marrelli D. (2016) 23.5%. Previous studies showed that the dMMR ratio was around 8-25%, while in Asian countries, it was 8-17%, and in Western countries, it was over 20%.

4.1.5.4. The detailed patterns of dMMR cases

The most prevalent pattern was the loss of MLH1 and PMS2 protein expression, which occurred in 50% to 90% in most studies. This is followed by a single loss of PMS2 expression of about 5-30%. MSH2 and MSH6 are usually expressed intact. Our study aligned with these findings, showing that the most prevalent patterns were the loss of MLH1 and PMS2, with a rate of 48.1%.

4.2. RELATIONSHIP BETWEEN MMR EXPRESSION AND SOME CLINICAL, PARACLINICAL FEATURES AND TREATMENT RESPONSE

The researchers discovered no link between MMR status and general or macroscopic features. The incidence of dMMR varied by cancer stage, with roughly 20% of individuals without regional lymph node metastases showing dMMR, compared to less than 5% of those with distant metastasis. Our results supported these observations, demonstrating that patients without distant metastasis were 4.4 times more likely to have dMMR than those with distant metastasis (95% CI: 1.5-13.0, p=0.009).

We also showed that dMMR GC was more common in stage II than in stage IV with OR=6.3 (95% CI: 1.9-21.0; p=0.003). Additionally, we found that dMMR was more common in stages 0 and I compared to stage IV, with an OR of 4.8 (95% CI: 1.3-17.3; p=0.018). Author An J. also reported that dMMR was more frequent in stages I and II. A pooled analysis by Polom K. indicated a correlation between dMMR status and TNM stages I and II at the time of diagnosis, yielding an OR of 1.77 (95% CI: 1.47-2.13; p<0.001). In contrast to most studies, we observed that the findings of Nappo F. and Zhao L. did not demonstrate any association between MMR status and disease stage.

The presence of dMMR in Lauren's intestinal subtype was found to be 5.7 times higher than in the unidentified and diffuse subtypes (95% CI: 1.7-19.5). Additionally, dMMR was 2.23 times more likely to occur in the intestinal subtype compared to the diffuse subtype, as shown in a meta-analysis involving over

18,000 GC patients. However, some studies, such as those by Fang W. and Giampieri R., reported no association between dMMR and tumor phenotype. Kaczmarczyk K. noted an association between the deficiency of MMR protein expression not only with Lauren's intestinal type, but also with the ductal and papillary structures according to the WHO classification.This finding aligned well with the results of our study. When comparing the poorly differentiated tubular adenocarcinoma group to well-differentiated/ moderately differentiated cases/the papillary adenocarcinoma group, we found that the latter was more likely to exhibit dMMR, with an odds ratio (OR) of 5.3 (95% CI: 1.2-23.3). Furthermore, author Yamamoto G. observed that moderately differentiated tubular GC had the highest rate of dMMR among the subgroups, with a rate of 43.3%.

Guan W. showed that dMMR was more prevalent in the low-grade group. This conclusion was consistent with our findings, which reveal that dMMR status was more common in the high-grade group than in the low-grade GC group (OR = 4.5; 95% CI: 1.6-12.3; p = 0.004). An J. also demonstrated that dMMR was more prevalent in the low-grade group. Karpińska-Kaczmarczyk K. and Nappo F. found that the grade of malignancy did not change MMR expression status.

4.2.5. Association of dMMR status with treatment response

4.2.5.1. Association of dMMR status with treatment response in resectable gastric cancer patients

Association between dMMR status and recurrence rate

Our results align with numerous studies indicating that dMMR was a favorable prognostic biomarker for GC. In our study, the median OS for the dMMR group was 37.06 months (standard error 1.52, 95%

CI: 34.09-40.03), which was longer compared to the pMMR group at 28.29 months (standard error 1.43, 95% CI: 25.49-31.09). The median OS for both groups had not been reached, and the difference between the two groups was statistically significant, with a p-value of 0.012. Our findings were consistent with those of many researchers, including Le Thi Thu Nga, Nappo F., Guan W., Vos E. L., Marrelli D. (2016), and Pietrantonio F. (2019).

Meta-analyses and case series studies have shown that patients with resectable GC who undergo radical surgery experienced a better OS and DFS than those with pMMR, regardless of whether they get adjuvant therapy. This remark was consistent with our study results, which showed that MMR status was an independent predictive factor for DFS. This conclusion was confirmed by a Cox regression model that incorporated general, clinical, and paraclinical traits as well as treatment details and MMR status in patients with resectable GC. The research found that patients with resectable dMMR GC had a 91% lower risk of recurrence than the pMMR group, with an HR of 0.09 (95% CI: 0.02-0.45; p = 0.003).

CONCLUSIONS

From January 2021 to March 2024, we conducted a survey of 229 gastric cancer patients diagnosed and treated at Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital and reached the following conclusions:

1. Some clinical and paraclinical characteristics, treatment details and MMR protein expression status

- Gastric cancer was more prevalent in men than in women. The average age was 64 ± 12.9 years. Epigastric discomfort was the most prominent clinical complaint (92.6%).

- Ulcerative type accounted for 38.9% of macroscopic images. Most of tumors were non-cardia, with more than half measuring ≤5cm. The most prevalent type was tubular adenocarcinoma (well and moderately differentiated) (51.1%). Intestinal type consisted of 62% of cases. Approximately 75% of initial cancers had T3 and T4 local invasion. Regional lymph node metastasis affected 62.5% of all patients. 39.7% of cases are diagnosed with distant metastases.

- The dMMR rate was 11.8% of the 229 tissue samples analyzed (62.9% of surgical tissue). The most common dMMR pattern was the simultaneous loss of MLH1 and PMS2 (48.1%). The single loss of PMS2 was 37%. Simultaneous loss of MSH2 and MSH6 accounted for 11.1%. Single loss of MSH6 was the least common, accounting for 3.7%.

- 98.5% of resectable patients underwent radical surgery, with a relapse rate of 34.4%. Among those who relapsed, 97.7% did so within two years post-surgery. For unresectable patients, 40.6% received symptomatic chemotherapy, while 52.1% underwent palliative surgery

2. The correlation between MMR protein expression and some clinical and paraclinical characteristics and treatment response

- There was a correlation between dMMR status and the following factors: early stage, well-differentiated and intermediate tubular/papillary adenocarcinoma, Lauren intestinal subtype, low-grade malignancy.

- In the resectable stage, dMMR was a favorable prognostic factor for gastric cancer patients, and was an independent prognostic factor for progression-free survival with HR= 0.09 (95% CI: (0.02-0.45), p=0.003)

- There was no statistically significant difference in overall survival between the dMMR and pMMR groups for unresectable patients, regardless of whether they received palliative chemotherapy or surgery. However, patients with dMMR exhibited a more prolonged overall survival.

SUGGESTIONS

As an independent prognostic factor for progression-free survival and poor response to adjuvant chemotherapy, MMR status should be analyzed before the Multidisciplinary Tumor Board to stratify patients and select appropriate treatment strategies.

SCIENTIFIC ARTICLES HAVE BEEN PUBLISHED RELATED TO THE DOCTORAL THESIS

International articles

1. Nguyen THC, Nguyen Tran BS, Nguyen TP, Ha TMT, Pham NC, Nguyen TGT, Hoang H, Dang Cong T. "Deficient Mismatch Repair Proteins in Gastric Mixed Neuroendocrine Non-Neuroendocrine Neoplasm: A Rare Case Report". Case Rep Oncol. 2023 Oct 17;16(1):1172-1182. doi: 10.1159/000533707. PMID: 37900850; PMCID: PMC10601832.

2. Nguyen THC, Nguyen TBS, Nguyen TP, Nguyen TGT, Phan MT, Le TH, Ha TT, Nguyen TTH, Ha TMT, Pham NC, Dang CT. "Mismatch repair deficiency and its relationship with histopathological features in gastric cancer patients". Nagoya J. Med. Sci. 2025 Feb, 87(1): 93-104. doi: 10.18999/nagjms.87.1.93: Q3 trong danh mục ISI.

Domestic articles

1. Nguyen Thi Hong Chuyen, Nguyen Thi Thu Giang, Nguyen Thi Linh, Nguyen Tran Bao Song, Nguyen Thanh Phuc, Le Thanh Huy, Ha Thanh Thanh, Nguyen Tran Thuc Huan, Pham Nguyen Cuong, Dang Cong Thuan. "The correlation between mismatch repair protein expression and the modified Lauren classification in gastric cancer patients". Hue journal of Medicine and Pharmacy, Special issue, 12-2023, pp. 226-232.

2. Nguyen Thị Hong Chuyen, Nguyen Thi Thu Giang, Nguyen Tran Bao Song, Ngo Quy Tran, Dang Cong Thuan (2024)."Prognostic value of mismatch repair protein expression in unresectable gastric cancer", Hue journal of Medicine and Pharmacy, 14(4), pp.53-58