Study of the MDM2 status in patients with gastric and colorectal carcinomas and its correlation with prognostic factors

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ABSTRACT

Background: Gastric and colorectal cancers are the second and the fourth most common cancers in Iran, respectively. The presence of Murine Double Minute 2 (MDM2) has been identified in many cancers and its relationship with prognosis is under investigation. This study aimed to assess the status of MDM2 and its relationship with prognostic factors in gastric and colorectal carcinoma.

Materials and Methods: This study was performed on 99 paraffin blocks of gastric and colorectal cancers, during the years 2001 to 2007 from Mostafa Khomeini Hospital, Tehran, Iran. Tissue sections were prepared, stained with Hematoxylin and Eosin and immunohistochemistry to evaluate for MDM2 expression. The type of tumor, lymph node involvement and tumor grade was determined. Results: Of the 99 cases, 34.3% and 65.7% cases were diagnosed with gastric and colorectal adenocarcinoma, respectively. The average tumor size was 5.5 cm. MDM2 expression level was 82.4% and 90.8% in gastric and colorectal adenocarcinoma, respectively. No statistical difference was found between MDM2 expression and various prognostic factors; however, significant correlation was observed between gastric \( P = 0.03 \) and colorectal \( P = 0.03 \) tumor size and the percentage of MDM2 immunoreactivity.

Conclusion: Considering the role of MDM2 in cell growth and its positive correlation with tumor size (an established prognostic factor), it can be indirectly concluded that MDM2 is also important in prognosis. However, additional investigation is needed.

KEY WORDS: Colorectal cancer, gastric cancer, prognosis, MDM2

INTRODUCTION

According to available statistics, gastric and colorectal cancers are two of the five most common cancers in Iran.\(^1,2\) By examining prognostic factors, novel strategies can be developed in diagnosis and treatment. Among the most important factors affecting prognosis of gastric and colorectal cancers are depth of invasion, lymphovascular invasion and distant metastases.\(^3\) In addition, biomarkers have become increasingly important in prognosis. By regulating cell growth and death, Murine Double Minute 2 (MDM2) is one of these biomarkers. MDM2 is one of the known four genes of MDM,\(^4\) located on the extrachromosomal nuclear bodies called Double minute.\(^5\) The MDM2 gene, with 90kDa molecular weight and 491 amino acids, is located at 12q14.3-q15.\(^6,7\) Studies have shown that MDM2 leads to P53 inhibition, and its presence has been proven in various tumors.\(^8,9\) Several studies have been conducted on the prognostic value of MDM2. For instance, MDM2 contributes to poor prognosis through enhancement of gene expression in glioma.\(^10\)
and 3-µm sections were cut. After tissue sectioning, one slide was stained by the conventional Hematoxylin and Eosin method to identify tumor and nodal metastases, and another slide was stained using an immunohistochemical antibody to MDM2 according to manufacturer instructions (Novacastra, UK). All specimens were studied in terms of tumor grade, depth of invasion, nodal metastases and MDM2 expression. With regard to the grade of malignancy, specimens were classified into well, moderately and poorly differentiated.

The presence or absence of MDM2 was then determined by light microscopy in patients with colorectal and gastric cancer [Figure 1]. We counted positive cells in 1000 tumor cells in hypercellular areas and calculated positive cells percent, where greater than 10% was considered as positive.[12] Data were analyzed by SPSS17 statistical software using Spearman, Mann-Whitney and Chi-square tests.

**RESULTS AND FINDINGS**

This study was performed on 99 cases with a mean age of 60.81 ± 14.09 years. The youngest and the oldest participants were 23 and 91 years old, respectively. 34.3% of the specimens were gastric and the rest were colorectal adenocarcinoma. The diffuse type consisted of 3 cases of gastric adenocarcinoma. 20.6% of patients with gastric cancer were females and 79.4% were males. While in colorectal adenocarcinoma 47.7% were females and 52.3% were males.

Average tumor size was 5.15 ± 2.34 cm in these patients, with a range of 2 and 14.5 cm.

Pathological characteristics, including tumor depth, grade of tumor differentiation and lymph node involvement were evaluated. In terms of tumor depth, 88% of gastric and 86.2% of colorectal adenocarcinomas had full thickness involvement.

In terms of the grade of differentiation, gastric tumors were most frequently moderately differentiated (41.2%) and colorectal tumors were well differentiated (67.7%).

50.5% of cases were found to have no lymph node involvement; 41.2 in gastric and 55.4 in colorectal tumors. Regarding tumor size (T) and lymph node status (N), stage N0 was seen in 49.5% and T3 in 86.9%.

The frequency of MDM2 expression was 87.9% in all specimens; 82.4% in gastric adenocarcinoma (83.9% intestinal and 66.7% diffuse type) and 90.8% in colorectal adenocarcinoma.

The mean percentage of stained cells was 63.7 ± 26.83 in these specimens, with a range of 0-99%. The average percentage of stained gastric adenocarcinoma cells was 60.18 ± 27.035 (62.43 ± 26.538 in intestinal and 37.67 ± 25.423 in diffuse types) and it was 63.49 ± 26.769 for colorectal adenocarcinoma.

**DISCUSSION**

The present study was conducted on 99 patients with gastric

![Figure 1: Positive immunohistochemical staining of the tumor cells for MDM2 (Immunoperoxidase × 400).](image-url)
and colorectal adenocarcinoma, in which MDM2 expression was positive in 87.9% of specimens.

The mean MDM2 staining percentage was 63.7%, which correlated to tumor size and lymph node status. A review of Iran’s database revealed no research investigating the association between MDM2 and gastrointestinal cancers; however there are overseas reports.

Block et al. performed a cross-sectional study on 45 cases with early gastric adenocarcinoma (i.e., tumors below 2 cm), and investigated P53 and MDM2 status. MDM2 was not observed in P53-positive or P53-negative tumors. They concluded that P53 inactivation by MDM2 does not play a role in the early stages of gastric adenocarcinoma. Considering that our study confirmed the relationship between gastric tumor size and increased percentage of MDM2 staining, it can be concluded that MDM2 should be positive in later stages of the tumor growth. It should be noted that in our study the tumors were more than 2 cm in size.

In a case-control study, Broll et al. examined 12 samples of healthy colorectal tissue with 60 cases of colorectal adenocarcinoma in terms of MDM2 expression. They reported a significant relationship between lymph node involvement and MDM2 nuclear expression. This relationship was not meaningful in our study. Such a discrepancy may be due to ethnic differences or variations in tumor size.

Casper et al. studied gastric adenocarcinoma for MDM2 expression and did not find a remarkable correlation between MDM2 expression and patients' survival or nodal involvement. In our study, patient survival was not directly assessed, but lymphatic involvement was evaluated as in the Casper study. We also obtained similar results. No significant relationship was observed in the number of lymph nodes either. A direct correlation was found between N (based on TNM system) and staining percentage. This relationship was not correlated with short-term survival of patients with positive MDM2. Survival should be confirmed in these studies.

In a study on colorectal adenocarcinoma and adjacent normal tissue and adenoma, Abdolfattah et al. reported 30% MDM2 expression in adenoma, 25% in adenocarcinoma and 3.8% in normal tissue. This was accompanied by a lack of P53 expression in both adenoma and adenocarcinoma. MDM2 expression showed no significant relationship between grade and lymphatic involvement, which is consistent with the present study.

Ohmiya et al. investigated SNP (309) and P53 by PCR. They concluded that the overall risk of gastric cancer increases with increasing SNP (309), especially of intestinal type. They reached the conclusion that SNP (309) is an independent marker for poor survival. In the Ohmiya study, SNP (309) and not MDM2 protein expression was evaluated. Nonetheless, SNP (309) is known to enhance MDM2 expression in other studies. Therefore, it can be postulated that MDM2 expression is correlated with poor survival. This finding is in accordance with our study, since tumor size and N goes up with increasing MDM2 expression, which in turn can contribute to the poorer prognosis.

CONCLUSIONS

With regard to the role of MDM2 in cell growth, its positive relationship with tumor size and the effective role of tumor size in prognosis, it can be indirectly concluded that MDM2 is also important in tumor prognosis. However, additional investigation is needed.

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REFERENCES


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