RESEARCH ARTICLE

Clinicopathological and p53 Gene Alteration Comparison between Young and Older Patients with Gastric Cancer

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Abstract

Background: Differences in clinicopathological characteristics of gastric cancer (GC) between young and older patients are controversial and a matter of debate. Determining the statistical significance of clinicopathological information with respect to age might provide clues for better management and treatment of GC. Materials and Methods: A total of 103 Indian GC patients were enrolled for study and specimens were classified according to the AJCC-TNM system. Patients were grouped into two age-wise categories, young patients (<40 years; n=13) and older patients (≥40 years, n=90). The clinicopathological features of both groups were retrospectively examined and compared. p53 alterations were analyzed by polymerase chain reaction-single strand conformational polymorphism and immunohistochemistry methods at gene and protein levels respectively. The cases were considered p53 over-expressed if it was present in more than 25% of the tumor cells and p53 alterations was correlated with the clinicopathological characteristics of the patients as well as etiological factors for GC in both groups. Results: We found significant association of young patients with cancer stage (p=0.01), and very strong association with histology grade (p=0.064) and poorly differentiated (p=0.051) state of GC. However, neither young nor elderly patients showed associations with location, gender, etiological factors and p53 expression and alteration. Overall the male-to-female ratio of GC patients was 3.12 and the value was higher in the young (5.5) than in the older group (2.91). Conclusions: Clinicopathological features of GC like cancer stage, cell differentiation and histological grades were significantly different among young and old age cohorts. We observed a male predominance among the young group that decreased significantly with advancing age. More awareness of GC onset is required to detect cancer at an early stage for successful treatment.

Keywords: Gastric cancer - p53 - comparative study - young age - old patients - India

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Introduction

Gastric cancer is one of the most common gastrointestinal malignancies worldwide and every year ~1 million new cases of GC are diagnosed and 740,000 die of this disease worldwide (Parkin et al., 2005; Santoro et al., 2007; Ferlay et al., 2013; Guggenheim et al., 2013; Karim et al., 2013). Although recent developments in medical screening has decreased the incidence of advanced GC, still GC in youngsters remains a serious problem as routine screening in many countries including India does not usually include people <40 years of age. GC is difficult to diagnose in young people and is asymptomatic even in the advanced stages of the disease (IARC, 2001; Isobe et al., 2013). At National Cancer Registry Programme, cancer incidence data are available for metropolitan and rural area of India since 1982. Similar to most parts of the world, all urban registries in India have a uniform male:female ratio of around 2 (Sipponen et al., 2002; Lim et al., 2003). Stomach remained as the leading site of cancer in males in Chennai and Bangalore and it is next to cervix and breast cancer among women (Rao and Ganesh, 1998).

Gastric cancer is considered to be disease of elderly and prevalence increases with age (Anderson et al., 2010). GC patients younger than 40 years are rare; approximately 2-16.2% of GC occurs in patients younger than 40 years old (Santoro et al., 2007; Kuling et al., 2008; Dhobi et al., 2013), and only 1.1-3.3% of cases occur in patients younger than 30 years of age (Lim et al., 2003). The preponderance of evidence showed that there are differences in the clinicopathological features and molecular mechanism of gastric carcinoma between young and older patients (Quispe et al., 2000; Lim et al., 2003; Hajmanoocheri et al., 2013a; 2013b). Few reports have suggested that younger patients are frequently diagnosed with advanced tumor stages and that GC has a poorer prognosis in young in comparison to older patients (Smith et al., 2009; Saito et al., 2012; Dhobi et al., 2013). However, the reported data concerning this matter are still controversial (Yokota et al., 1999; Medina-Franco et al., 2000; Piso et al., 2002; Nguyen et al., 2013).

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This study was conducted to elucidate differences in the clinicopathological variables among different age group (young vs old) GC patients.

Materials and Methods

The complete medical record of all patients (n=103) with histological confirmed diagnosis of primary GC at *i*) Roy's & Trivedi's Diagnostics, Kolkata, West Bengal; *ii*) Govt. Medical College, Srinagar, Jammu & Kashmir; and *iii*) All India Institute of Medical Sciences and Dharamshila Cancer Sansthan, New Delhi were reviewed. Patients were divided into two major groups according to their age; young group (n=13, median age 37 years) included patients <40 years of age, and older group (n=90, median age 63 years) included patients ≥40 years of age.

Clinicopathological characteristics

Gastric carcinoma was classified into intestinal, diffused and mixed types according to Lauren's histological criteria (Lauren, 1965). Complete assessment of resected or endoscopic specimens including clinical, radiological, operative information and pathological examinations were used to find tumor site. TNM system endorsed by the International Union Against Cancer (UICC) was used for staging (Sobin et al., 2002). The demography, clinicopathological features, TNM tumor stage and other related data from both groups were reviewed and analyzed. A comparison of results between the patients in the young and older group was performed and summarized in Table 1 and 2.

Statistical analysis

Clinicopathological parameters were analyzed by chi-square test and Fisher's exact test. Statistical analysis was performed using SPSS software and $p<0.05$ were considered statistically significant.

Table 1. Demographic Characteristics and Presenting Symptoms for Young and Old Patients with Gastric Adenocarcinoma

Characteristics		<40 (n=13) N %	≥40 (n=90) N %	p value
Gender	Male	11 (85)	67 (74)	0.424
	Female	2 (15)	23 (26)	
Abdominal pain	Yes	10 (77)	66 (73)	0.782
	No	3 (23)	24 (27)	
Weight loss and/or anemia	Yes	9 (69)	61 (68)	0.916
	No	4 (31)	29 (32)	
Dyspepsia	Yes	6 (46)	46 (51)	0.737
	No	7 (54)	44 (49)	
Nausea, Vomiting	Yes	7 (54)	47 (52)	0.473
	No	4 (46)	43 (48)	
Anorexia	Yes	4 (31)	23 (26)	0.444
	No	7 (69)	67 (74)	
Dysphagia	Yes	5 (38)	21 (23)	0.24
	No	8 (62)	69 (77)	
Abdominal mass	Yes	2 (15)	29 (32)	0.215
	No	11(85)	61 (68)	
Gastrointestinal bleeding	Yes	1 (8)	17 (19)	0.32
	No	12 (92)	73 (81)	
Obstruction	Yes	1 (8)	9 (10)	0.792
	No	12 (92)	81 (90)	
Perforation	Yes	1 (8)	2 (2)	0.272
	No	12 (92)	88 (98)	

Table 2. p53 Expression and Clinicopathological Characteristics of the Patients with Gastric Adenocarcinoma by Age Group

Characteristics		<40 (n=13)	≥40 (n=90)	N	p value
Stage	I	3	29	31	0.01
	II	1	37	38	
	III	9	18	27	
	IV	-	6	6	
Cell differentiation					
Well differentiated		1	10	11	0.051
Moderately differentiated		2	37	39	
Poorly differentiated		10	43	53	
Histology	Intestinal	2	43	45	0.064
	Diffused	9	40	49	
	Undifferentiated/Mixed	2	7	9	
Tumor Site	Cardiac	2	19	21	0.87
	Fundus	2	14	16	
	Body	4	19	23	
	Antrum	5	38	43	
P53 expression	Positive	2	35	37	0.098
	Negative	11	55	66	
P53 alteration (SSCP)	Positive	1	17	18	0.32
	Negative	12	73	85	

Table 3. Differences in the Age Definition and Prognosis of young Patients with Gastric Cancer: Reported Series

Manuscript publication	Total no of patients	No. of young patients (%)	Age limit (years)	Prognosis of young in comparison to older patients
Theuer et al., 1996	203	30 (15.0)	<41	Poorer
Li et al., 1999	6098	312 (5.1)	<35	Poorer
Eguchi et al., 1999	1654	86 (5.2)	<40	Better
Quijano et al., 1999	80	11 (13.7)	≤35	Poorer
Yokota et al., 1999	923	34 (3.7)	<50	Similar
Lo et al., 1999	1,642	61 (3.7)	≤39	Similar
Medina et al., 2000	235	38 (16.2)	≤40	Similar
Quispe et al., 2000	--	92	≤31	Better
Loea et al., 2000	2000	92 (4.6)	≤40	Similar
Piso et al., 2002	643	38 (5.9)	<40	Better
Lim et al., 2003	4123	135 (3.3)	≤30	Poorer

Results

This study includes 103 Indian patients with GC collected from different part of India. A total of 13 (12.6%) patients were below 40 years (younger group) and 90 patients were 40 years or above (older group) (Figure 1). We found overall male-to-female ratio of 3.1:1 and it was higher in young (5.5:1) than in older group (2.9:1) of patients. The demographic characteristics and the presenting symptoms of the young and older patients are summarized in Table 1. Epigastric pain, bloating and heartburn were the most common presenting symptom in both groups (77% in young group and 73% in older group) followed by weight loss and/ or anemia. Most of the cases were symptomatic. The distributions of the presenting symptoms in both groups were similar.

Among young patients of gastric carcinoma, we found very strong association with stage III (p=0.01), histology grade (p=0.064) and poorly differentiated cases (p=0.051). However, neither young nor old group had shown such

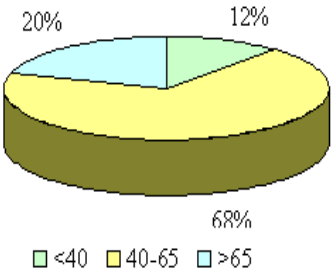

Figure 1. Prevalence of Gastric Cancer in Different Age Group: Young (<40 years) and Old (40-65 years and >65 years)

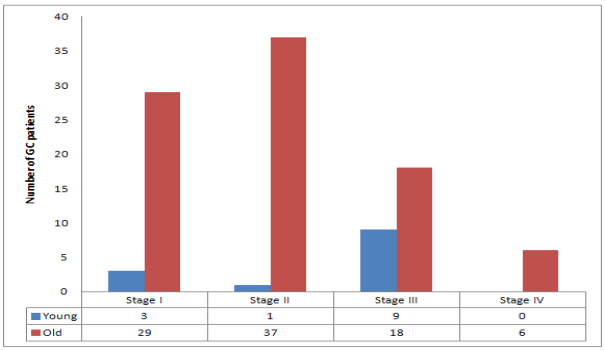

Figure 2. Tumor Stage of Gastric Cancer in Relation to Age: 73% of Old Patients were Diagnosed and Detected Earlier Stage of I or II While 69% of Young Patients were Detected in Advance Stage of III or IV

association with gender, cell differentiation, location, etiological factors, or p53 alterations (Table 2).

The mean delay in months between the initial symptoms and the diagnosis of gastric adenocarcinoma for the young group (10.1±0.9) was significantly different from that for the older group (6.3±0.4). At presentation, percentage of stage I or II cancer in older group (73%) were significantly higher than that in younger group (31%), while 69% of young patients were detected in advance stage III (Figure 2).

Discussion

It is still controversial whether GC in young patients differs from that in older patients (Table 3). Several studies have reported that the clinicopathological features and biological characteristics of GC in young individuals including significant predominance of male sex, proximal location, infiltrated, diffused growth, delayed diagnosis, rapid disease progression, frequent lymph node metastasis, and a poorer prognosis (Quispe et al., 2000; Lim et al 2003; Smith et al., 2009; Anderson et al., 2010; Saito et al., 2012; Dhobi et al., 2013; Nguyen et al., 2013), while other studies did not find any significant differences in clinicopathological characteristics between young and older patients of GC (Medina-Franco et al., 2000).

Incidence, the frequency of early-onset GC in our study was 12.6% (13/103), which is in accordance with earlier reports of 2-15% in young patients under 40 years (Medina-Franco et al., 2000; Piso et al., 2002; Al-Refaie et al., 2010; Seker et al., 2013).

Gender, we found male-to-female ratio as 5.5:1 in young, 2.9:1 in older group and 3.1:1 in overall GC patients that were much higher than standard ratio of 2:1 (Sipponen et al., 2002). In contrast to other reports (Quispe et al., 2000; Lim et al., 2003; Isobe et al., 2013), we observed a male predominance among the young group and this male-to-female ratio decreased significantly in older group. On the other hand, a few studies have suggested that the incidence of GC in men and women was almost the same in both groups (Yokota et al., 1999; Crew et al., 2006; Chung et al., 2014; Seker et al., 2013).

Presentation, both young and old patients have almost similar symptoms, but owing to its relatively uncommon presentation in young age group, the diagnosis may be delayed or less likely to be accurately made preoperatively (Medina-Franco et al., 2000). Epigastric pain is reported in significantly higher percentage in young patients. Few reports have indicated that the tendency to omit endoscopy in dyspeptic patients younger than 45 years might be leading to an increased rate of delayed GC diagnosis (Boldys et al., 2003). Boldys et al. (2003) suggested that age and symptoms could not determine the need for endoscopy, at least in area of high prevalence of GC.

Tumor site, we found distal location specifically antrum as the most frequent site for GC in both young and old group and is consistent with other reports (Liu et al., 2004). However, few studies have reported that cancers are located in proximal (Koea et al., 2000; Lim et al., 2003) or middle (Nakamura et al., 1999) parts of the stomach.

Gross patterns, depressed lesions were found more common than polypoidal gross pattern in young patients in the present study similar to earlier reports (Choi et al., 1996; Nakamura et al., 1999; Yokota et al., 1999; Lim et al., 2003) but no statistical significance could be found. Nakamura et al., reported that only 2 out of 60 patients with polypoid lesions whereas Choi et al., did not find a single case of polypoid lesion (Choi et al., 1996; Nakamuara et al., 1999).

Histology, in agreement with the reported literature (Piso et al., 2002; Lim et al., 2003; Seker et al., 2013) most of the GC cases in young patients were of the diffuse type. Similarly, a high rate of poorly differentiated tumors were found in young patients compared to older patients as reported before (Nakamura et al., 1999; Koea et al., 2000) but this was not statistically significant (p=0.064).

Tumor stage, most of young patients were from stage III, few were from stage II and none were found under stage IV. In both the groups, young and older patients, GC was diagnosed at a later stage and is in agreement with other reports (Koea et al., 2000; Lim et al., 2003; Simsa et al., 2004).

Treatment, in current study the treatment type and resection rate of GC was not related to the age of patients and finding was in accordance with other report (Piso et al., 2002; Simsa et al., 2004).

Molecular biology, although there were no concrete data of molecular biology in this study, some commentaries are described below for the sake of completeness of the discussion. We had shown significant association of p53 expression and alterations with histological grades and gender earlier but non-significant with age of GC patients (Karim et al., 2009; 2013; Sadeghi et al., 2013).

Alteration of p53 gene has been reported controversial with any age group. Haruma et al. (2000) have shown that p53 overexpression were more common in young patient than in older patients. They have also suggested that p53 and cyclin-E may act independent of *H pylori* or adjunctive manner for gastric carcinogenesis. On the other hand Rugge et al. (2000) reported that p53 mutations are uncommon in early onset of GC.

Before ending the discussion, we would like to highlight some of the limitations in present study: *i*) "older and younger patients" that was defined in this study as >40 years for old and up to 40 years for younger might seem inappropriate but we followed it because most of the study on GC dealing with this kind of comparison employ the cut-off line of 40 years old (Table 3) and there is no thumb rule to decide the cut-off point for the age; *ii*) The number of young patients of GC is very low as compared to older patients and because of small number of young patients there is chance of biasness present.

In conclusion, some significant differences were found among clinicopathological features like cancer stage, histological grade and cell differentiation of GC of young and older patients. The incidence of gastric cancer in men were higher than those in women in all age groups, we found male predominance among the young group that decreased significantly with advancing age. Epigastric pain, weight loss and anemia were most common symptom in patients. More awareness of gastric cancer onset is required to detect cancer at early stage to treat it successfully. Patient education, health promotion, open access endoscopy and improvement of the diagnostic techniques may be the best way of improving the prognosis of GC.

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