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Expression of PI3K-AKT-mTOR signaling pathway in gastric cancer

Abstract

Background: The PI3K/AKT/m TOR pathway is activated in gastric cancer (GC). This pathway may be an appropriate target for GC therapy. Such therapy may involve inhibiting cell proliferation, enhancing apoptosis, and restoring the sensitivity of cancer cells to chemotherapy.

Aim: To study the expression of the PI3K/AKT/mTOR pathway in Egyptian patients with GC.

Methods: Enrolled Patients were divided into 2 groups, group 1 included 23 patients with lymph node metastatic (LNM) gastric cancer (GC) and group 2 included 10 patients with non-metastatic GC. Liver and renal biochemical tests, CBC, H. pylori testing, CEA, CA19-9 & metastatic radiological work up were done. Upper Gastrointestinal endoscopy was done to diagnose the site, size and morphology of GC and to take biopsy from the suspicious lesion, adjacent mucosa and all parts of the stomach. Enrolled patients had received surgical resection when appropriate. The harvested tumor tissue was processed for histopathology as well as Immunohistochemical staining (IHC) for detection of expression of PI3K/AKT/mTOR. IHC score for the expression of mTOR, AKT & PI3K (ranging from 0 to 12) was calculated as follows: Grade of stain intensity × Grade of coloration rate. A score ≥4 was considered positive.

Results: The mTOR expression was positive in 54.5%, AKT expression was positive in 72.7% & PI3K expression was positive in 36.4% of cases. There was significantly higher expression of AKT in metastatic (87%) than non-metastatic GC (40%), p=0.010. AKT expression was significantly higher in LNM GC (median score was 12) than non-metastatic GC (median score was 2.5), p=0.028. AKT score at cutoff value of more than 3 was a statistically significant discriminator between LNM and non-metastatic GC, AUC=0.743, p=.014, sensitivity, 87% & specificity, 60%.

Conclusion: The mTOR expression was positive in 54.5%, AKT expression was positive in 72.7% & PI3K expression was positive in 36.4% of GC cases. AKT expression score may discriminate between LN metastatic and non-metastatic gastric cancer

Keywords: mammalian target of rapamycin (mTOR), AK strain transforming (AKT), phosphatidyl-inositol 3 kinase (PI3K), gastric cancer (GC), Egypt

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Abbreviations: AJCC, american joint committee on cancer and international union against cancer; ALT, alanine transaminase; AST, aspartate transaminase; AUCs, area under the curve; CA 19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; CBC, complete blood count; CI, confidence interval; MPCT, multi-phasic computed tomography; DM, diabetes mellitus; ELISA, enzyme-linked immunoassay; GC, gastric cancer; GSK3 beta, glycogen synthase kinase-3beta; H&E, hematoxylin and eosin; H. pylori, helicobacter pylori; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; IHC, immunohistochemistry; IQR, interquartile range; IRB, institutional review board; LNM, lymph node metastasis; MPCT=multi-phasic computed tomography; mTOR, mammalian target of rapamycin; AKT, AK strain transforming ; PI3Ks, Phosphoinositide 3-kinases; PKB, protein kinase B; ROC, receiver operating characteristic curve; SD, standard deviation; SLE=systemic lupus erythematosis; SPSS, statistical package for the social sciences; pTNM=pathologic tumor node metastasis; Vac A, vacuolating cytotoxin A& WHO, World health

Introduction

Gastric cancer (GC) remains an important cancer worldwide and is responsible for over one million new cases in 2020 and an estimated 769;000 deaths. It ranks fifth for cancer incidence and fourth for cancer mortality globally. It is 2-fold higher in men than in women. Incidence rates are highest in Eastern Asia (Japan and Mongolia) and Eastern Europe; whereas rates in Northern America and Northern Europe are generally low and equivalent to those seen across the African regions.[1] In Egypt; GC ranks 10th for cancer incidence in both sexes and 9th for cancer mortality. It represents 2.5% of all cancers and 3% of all cancer mortality.[2] Molecular characterization of GC has revealed high rates of recurrent genetic mutations in members of the phosphatidyl inositol 3 kinase/AK strain transforming /mammalian target of rapamycin pathway (PI3K/AKT/mTOR pathway) which is an important promoter of cell growth; metabolism; survival; metastasis; and resistance to chemotherapy.[3] The PI3K/AKT/mTOR pathway is activated in tumor tissues from patients with advanced GC compared with that in non-tumorus gastric mucosa.[4] This pathway may be an appropriate target for GC therapy. Such therapy may involve inhibiting cell proliferation; enhancing apoptosis; and restoring the sensitivity of cancer cells to chemotherapy.

Aim of the work

To assess the expression of the PI3K/AKT/mTOR pathway in Egyptian patients with metastatic and non-metastatic GC.

Patients: This is a two centers based descriptive cross sectional study; convenient sampling; that was conducted at Hepatology and Gastroenterology Unit; Specialized Medical Hospital and Oncology Hospital of Mansoura University; after approval of Medical Ethics and Research Committee of Faculty of Medicine; Mansoura University ;during the period from May 2019 to May 2020. Institutional research board (IRB) code number was MD.18.05.38. A written informed consent of participation in the study was obtained from the enrolled patients after explaining the aim of the work and the procedures of this research. Also; the confidentiality of enrolled patients information and their right not to participate in the study were respected.

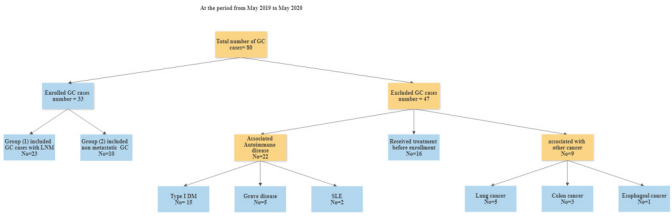
Inclusion criteria

Patients aged more than 18 years, of both genders with gastric cancer (GC).

Exclusion criteria: Patients with other known cancers; GC patients who received GC related treatment before enrollment & patients with known autoimmune disease.

Out of 80 patients with GC; 33 cases fulfilled the inclusion criteria and were enrolled in the study. Enrolled patients were divided into two groups; group I which included 23 patients with Multi-phasic abdominal computed tomography (MPCT) proved regional lymph node metastatic GC and group II which included 10 patients with non metastatic GC (Flowchart of the study).

Flowchart of the study



GC, gastric cancer; LNM, Lymph node metastasis; DM, Diabetes Mellitus; SLE, Systemic lupus erythematosis

Methods

All the enrolled patients were subjected to full medical history; clinical examination; laboratory investigation; radiological investigation & upper gastrointestinal endoscopy.

Laboratory investigations included CBC; ALT; AST; serum Albumin; total bilirubin; direct bilirubin; serum creatinine; HBs Ag; total HBc Ab and HCV Ab by third generation ELISA test; ESR; CRP; LDH;CEA & CA19-9.Radiological investigations included MPCT of chest; abdomen and pelvis as well as bone scan. Upper Gastrointestinal endoscopy was done to diagnose the site; size and morphology of GC and to take biopsy from the suspicious lesion ; adjacent mucosa and all parts of the stomach ; using standard biopsy forceps & Pentax Video Upper Gi Scope; Eg_2790i- Germany. The morphology of the lesions was described according to Borrmann classification which includes four subtypes: Type I: nodular polypoid tumor; Type II: bowl-shaped ulcer with easily identified elevated margins; Type III: infiltrating ulcerative tumor with poorly defined margins; and Type IV: poorly demarcated; infiltrative and diffuse tumor infiltration of the gastric wall (linitis plastica).[5] Enrolled patients had received surgical resection when appropriate. The harvested tumor tissue was processed for histopathology as well as Immunohistochemical staining (IHC) for detection of expression of PI3K/AKT/mTOR pathway. Postoperative pathologic TNM staging (pTNM) based on the 8th edition of the American Joint Cancer Committee (AJCC) & Union for International Cancer Control (UICC) was done.[6]

Histopathological evaluation: The harvested tumor tissue was fixed in 10% formalin solution and embedded in paraffin and stained with Haematoxylin and Eosin (H&E) for subsequent analyses. All tissue specimens were examined by an experienced pathologist and classified according to the Japanese classification into differentiated GC which is either well or moderately differentiated; undifferentiated GC which has signet ring differentiation & mixed GC.[7]

Immunohistochemical staining

Immunohistochemical staining for mTOR , AKT and PI3K was done on retrieved paraffin blocks using rabbit polyclonal antibodies.

Evaluation

The results were blindly evaluated by the pathologist. mTOR positive staining was yellow or brownish and was seen mostly in the cytoplasm of tumor cells and surrounding epithelial cells. Some mTOR-positive staining was also observed on the cell membrane and in intercellular substances. AKT-positive staining was yellow or brownish and was located in the nucleus or cytoplasm of the tumor cells. PI3K-positive sections showed yellow or brownish staining distributed in the cytoplasm of tumor cells and/or epithelial cells around the tumor and; in some cases; in the nuclei. The results were graded on a scale from 0 to 4 by using a semi quantitative method according to the literature. Five fields (center; left; right; up; and down) of each section were selected under high magnification for cell counting; and the percentage of stain-positive cells in the same type of cells was recorded as the coloration rate. Grading according to the coloration rate was as follows: grade 0: stain-positive tumor cells equals 0%; grade 1: stain-positive tumor cells < 10%; grade 2: stain positive tumor cells 10%–50%; grade 3: stain-positive tumor cells 51%–80%; and grade 4: stain-positive tumor cells > 80%.Grading according to stain intensity was as follows: grade 0: no stain; grade 1: light yellow; grade 2: brownish-yellow; and grade 3: brown. The score; ranging from 0 to 12; was calculated as follows: score, grade in stain intensity × grade in coloration rate. A score ≥4 was considered to be positive.

Sample size: A total of convenient sample of 30 cases was used because of the limited condition and high cost of the materials used. Convenience sampling is a specific type of non-probability sampling method that relies on data collection from population members who are conveniently available to participate in study.

Statistical analysis: Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows; Version 26.0.Armonk; NY: IBM Corp).Qualitative data were expressed as absolute frequency (N) and relative frequency (%; percentage).Quantitative data were initially tested for normality using Shapiro-Wilk's test with data being normally distributed if $p>0.05$. Presence of significant outliers (extreme values) was tested for by inspecting box plots. Quantitative data were expressed as mean ± standard deviation (SD) if normally distributed or median and interquartile range (IQR); or range if not. IQR is the difference between 75th percentile and 25th percentile; while range is the difference between maximum and minimum values.

Receiver Operating Characteristic (ROC) curve analysis: The cutoff point of a test to discriminate diseased cases from non-diseased cases was evaluated using ROC curve analysis. Comparisons of AUCs was done by using MedCalc Statistical Software version 18.9.1

Results

Results: Table 1 shows that the median age of the patients was 64years, 66.7% of them were males, 33.3% were females. Current smoking was present in 42.4% of the cases. H-Pylori infection was documented in 48.5%. Suspicious dietary habits were reported in 63.6% of the cases .This study showed that 30.3% of the cases had positive HCV serology. Diabetic Mellitus was present in 24.2% of the patients. The present study found that non cardia GC was more common than GC affecting the cardia (81.8% versus 18.2% respectively) & the most common affected site was the antrum (51.5%) followed by the corpus (36.3%). In this study, the median tumor size was 6 cm (IQR= 3.5-8.2 cm) & lymph node metastasis (LNM) was present in 69,6% of the cases. The most common morphological types of GC were Borrmann type I (photo1) and type III (infiltrating ulcerative tumor), occurred equally in 36.3% of cases for each. As regards the histopathology of the studied tumors, 54.5% were differentiated adenocarcinoma, 36.3% were undifferentiated adenocarcinoma, and 9.1% were mixed type (photo3). The pTNM stages of studied tumors was as follows; stage 1a (T1N0M0) represented 21.2%, stage1b (T2N0M0) represented 3.0%, stage 2a (T3N0M0) represented 6.1%.These stages represented the non-metastatic GC.Stage1b (T1N1M0) represented 39.4 %, stage 2b (T2N2M0) represented 21.2% and stage 2b (T1N3a M0) represented 9.1%. These stages represent the LNM GC.As regard tumor markers of GC, the median serum level of CEA was 3µg/L (IQR=1.6-12.5) and it did not show significant difference between LNM GC & non metastatic GC. The median serum level of CA 19-9 was 17 U/ml (IQR =3.4-63.5) and it did not show significant difference between metastatic & non metastatic GC. Table 2 shows a fair agreement of MPCT of the abdomen and upper GI endoscopy for localization of GC (Kappa=0.255, p ≤.001). Tables 3–5 and photo (3) show the IHC staining of the PI3K/AKT/m TOR pathway in the studied GC cases. Expression of m TOR was positive in 54.5% of GC patients, without significant difference between LNM GC (median score was 8) and LNM non-metastatic GC (median score was 3), p = 0.105. AKT expression was positive in 72.7% of GC with significantly higher AKT score in LNM GC (median score was 12) than non-metastatic GC (median score was 2.5), p = 0.028.There was significantly higher AKT score positivity in LNM GC (87%) than non-metastatic GC (40%), p=0.01. Figure 1 shows that AKT score > 3 can discriminate between LNM GC and non-metastatic GC with sensitivity of 87% and specificity of 60%, AUC=0.743 & p = 0.014. The PI3K expression was positive in 36.4% of GC with insignificant higher score in LNM GC (median score was 2) than non-metastatic GC (median score was 1.5), p=0.144. Positive PI3K score was insignificantly higher in LNM GC (47.8%) than non-metastatic GC (10%), p = 0.054. There was statistically significant negative correlation between PI3K score and presence of diabetes (r = -0.358 & p=0.041).

Table 1 Characteristics of the studied cases (N = 33)

Variable	N (%)
Age in years, median (range)	64 (52.5-70)
Sex (Male/Female)	22 (66.7%)/11 (33.3%)
Suspicious dietary habits	21 (63.6%)
Current smoking	14 (42.4%)
Positive family history of cancer stomach	10 (30.3%)
H. pylori infection	16 (48.5%)
Positive anti-HCV Ab	10 (30.3%)
Diabetes Mellitus	8(24.2%)
Endoscopic location of GC	
- Cardia	6 (18.2%)
- Non cardia Antrum Corpus Fundus	27 (81.8%) 17 (51.5%) 12 (36.3%) 2 (6%)
Tumor size in cm : Median (IQR)	6 (3.5-8.2)
Endoscopic morphology of GC	
-Borrmann type I	12 (36.36%)
-Borrmann type II	9 (27.2%)
-Borrmann type III	12 (36.36%)
Histopathology -Differentiated adeno-carcarinoma -Undifferentiated adeno-carcinoma -Mixed	 18(54.5%) 12(36.3%) 3(9.1%)
pTNM classification	
-Stage 1a (T1N0M0)	7(21.2%)
-Stage 1b (T1N1M0)	13(39.4%)
-Stage 1b (T2N0M0)	1(3.0%)
-Stage 2a (T3N0M0)	2(6.1%)
-Stage 2b (T2N2M0)	7(21.2%)
-Stage 2b(T1N3aM0)	3(9.1%)
Tumor marker : Median (IQR)	
CA 19-9 (U/ml)	17 (3.4-63.5)
CEA (µg/L)	3 (1.6-12.5)

H. pylori= Helicobacter pylori, HCV-Ab = Hepatitis C virus antibody, IQR= Interquartile range, GC= Gastric cancer, pTNM=pathologic Tumor, Node, Metastasis, CA 19-9= Cancer antigen 19-9& CEA= Carcinoembryonic antigen.

Table 2 Agreement of endoscopic and MPCT localization of G

Kappa	P value	Endoscopy	MPCT	Site
0.255	<0.0011	6 (18.2%)	7 (21.2%)	Cardia
		2 (6.1%)	0 (0%)	Fundic
		0 (0%)	4(12.2%)	corporal
		11(33.3%)	7(21.2%)	Antral
		2 (6.1%)	0 (0%)	Pyloric
		4 (12.2%)	3 (9.1%)	Greater curvature
		2 (6.1%)	3 (9.1%)	Lesser curvature
		6 (18.2%)	2 (6.1%)	Antral & corporal
		0 (0%)	7 (21.2%)	Antral & pyloric

MPCT=multi-phasic computed tomography & GC= Gastric cancer

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Table 3 Results of Immunohistochemistry staining

Marker	Stain intensity		Coloration rate		Score	Positivity
	Grade	N (%)	Grade	N (%)	Median(IQR)	N (%)
mTOR	1 2 3	16 (48.5%) 8 (24.2%) 9 (27.3%)	1 2 3 4	5 (15.2%) 6 (18.2%) 8 (24.2%) 14 (42.4%)	6 (2 – 9)	18 (54.5%)
AKT	0 1 2 3	1 (3%) 9 (27.3%) 8 (24.2%) 15 (45.5%)	0 1 2 3 4	1 (3%) 3 (9.1%) 7 (21.2%) 5 (15.2%) 17 (51.5%)	6 (2.5 – 12)	24 (72.7%)
PI3K	0 1 2 3	1 (3%) 19 (57.6%) 8 (24.2%) 5 (15.2%)	0 1 2 3 4	1 (3%) 15 (45.5%) 3 (9.1%) 5 (15.2%) 9 (27.3%)	2 (1 – 6)	12 (36.4%)

mTOR= mammalian target of rapamycin, AKT= Phosphorylated AK strain transforming & PI3Ks= Phosphoinositide 3-kinases

Table 4 Immunohistochemistry staining in LNM GC versus non metastatic GC.

Marker score	LNM GC	Non metastatic GC	P value
m TOR score	8 (2-12)	3 (1-6.5)	0.105
AKT score	12 (4-12)	2.5 (1.0-7.5)	0.028
PI3K score	2 (1-8)	1.5 (1.0-3.0)	0.144
Positivity of Marker score:-			
Positive m TOR score (≥4)	13 (56.5%)	5 (50%)	1.000
Positive AKT score (≥4)	20 (87%)	4 (40%)	0.010
Positive PI3K score (≥4)	11 (47.8%)	1 (10%)	0.054

LNM= Lymph node metastasis, GC= Gastric cancer, mTOR= mammalian target of rapamycin, AKT= AK strain transforming & PI3Ks= Phosphoinositide 3-kinases

Table 5 Performance of biomarkers in discriminating between LNM GC & non-metastatic GC

Biomarker	Cutoff value	AUC	P value	Sensitivity	Specificity
m TOR score	>6	0.680	0.081	56.5%	80%
AKT score	>3	0.743	0.014	87%	60%
PI3K score	>3	0.663	0.092	47.8%	90%

LNM= Lymph node metastasis, GC= Gastric cancer , mTOR= mammalian target of rapamycin, AKT= AK strain transforming & PI3Ks= Phosphoinositide 3-kinases

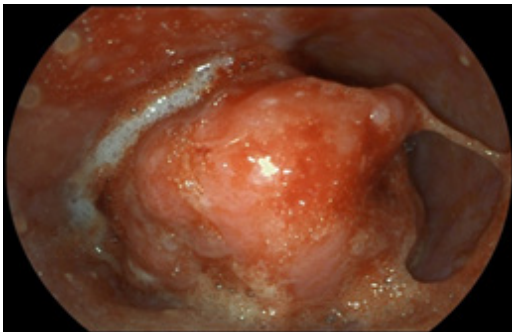

Figure 1 Borrmann type I: nodular polypoid GC.

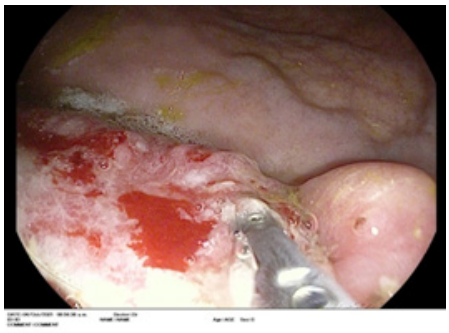

Figure 2 Borrmann type II: bowl-shaped ulcer.

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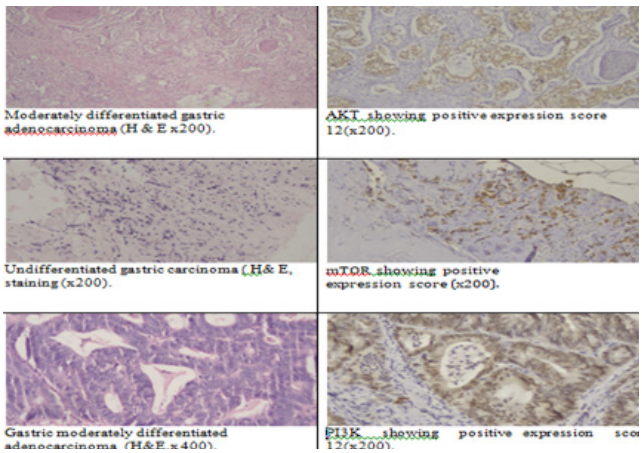

Figure 3 Histopathology & IHC of GC.

IHC, Immunohistochemistry; GC, gastric cancer; H&E, Hematoxylin and Eosin; AKT= AK strain transforming; mTOR= mammalian target of rapamycin; PI3Ks= Phosphoinositide 3-kinases

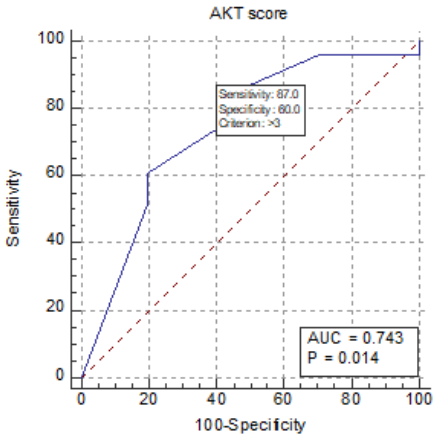

Figure 4 ROC curve of AKT score in discriminating between LNM GC and non-metastatic GC. At cut off value of AKT score > 3, the sensitivity is 87%, specificity is 60%, AUC=0.743 & p=0.014

AKT, AK strain transforming; AUCs, Area under the curve; ROC, Receiver Operating Characteristic curve

Discussion

The present study showed that GC was more common in males than females; which is consistent with Globocan 2020 registry. Also; Bray et al reported that GC is more prevalent in males .9 In developed countries, gastric cancer is 2.2 times more likely to be diagnosed in males than females. In developing countries, this ratio is 1.83. This may be explained by the protective effect of estrogen in females and the male predominance of H pylori infection; which is a known risk factor for GC. The median age of the patients was 64 years, which is consistent with that reported by Bray et al. who reported that most cases occurred after the age of 60 year.9 Also, Eusebi et al. reported that GC is a rare event before the age of 50 years.10 This current study showed that current smoking was present in 42.4% of the cases. This is consistent with that of Nishino et al who found that current smoking significantly increased the risk of gastric cancer in men and women.11 H-Pylori infection was documented in 48.5% of the GC cases of this study. Chao et al found that HP infection can affect the degree of malignancy and invasiveness of GC and is related to its location.12 Nakayama et al., reported that H. pylori VacA activates the PI3K/Akt signaling pathway, resulting in phosphorylation and inhibition of GSK3 beta, and subsequent translocation of beta-catenin to the nucleus which affect the transcriptional activity.13 There is reported interaction between smoking and Cag A positive H. pylori infection in the pathogenesis of GC. Smokers have a suppressed innate immune system, a potential mechanism through which smoking could contribute to a more severe H. pylori infection and thus a higher risk of developing GC. In the present study, suspicious dietary habits like intake of reheated and salted food were reported in 63.6% of cases of GC. This finding is in agreement with Salvador I et al., who reported that the consumption of reheated foods at least 3 times per week and adding salt to more than 50% of foods are risk factors for GC and metaplasia.14 This study showed that 30.3% of the cases had positive HCV serology. Chronic HCV infection can induce the development of both hepatic and extra-hepatic malignancies because of the persistent inflammation.1Fiorino et al found that HCV infection-induced chronic inflammation may lead to progressive rearrangement of gastric tissue structure and thus promote the cancerous transformation .16 Chen et al reported that HCV infection was a risk factor for the development of GC.17 Diabetic Mellitus was present in 24.2% of patients of this study. Glucose per se may affect the development of cancer via β-catenin acetylation with increased Wnt signaling which is a characteristic of GC.18 The present study found that non cardia GC was more common than GC affecting the cardia & the most common affected site was the antrum followed by the corpus. Kang et al found that the most frequent site of GC was the lower part of the stomach (the antrum & pylorus).19 Also, Martínez et al. found that GC was most commonly localized in the antrum followed by body .20 This finding may be explained by the higher affection of the antrum by H pylori infection. This study showed a fair agreement of MPCT of the abdomen and upper GI endoscopy in localization of GC. This finding is in agreement with Gai et al who found that the sensitivity & specificity of preoperative evaluation of GC by CT were 68% & 96% respectively .21 In this study, the median tumour size was 6 cm & lymph node metastasis (LNM) was present in more than two thirds of the cases. This finding is in agreement with that of Pokala et al who concluded that tumor size is one of the independent predictors of lymph node metastasis in early GC.22. Also, Chen et al have concluded that tumor diameter≥3 cm is one of the independent risk factor of LNM in GC.23 The present study showed that Borrmann type I (polypoid mass) and type III (ulcerated mass) were the most common morphological types of GC. This finding agrees with that of Ray-Offor and Obiorah who reported that Borrmann Type I was the predominant morphology in GC.24 The results of this study showed that mTOR expression was present in 54.5% of GC. This agrees with Guo et al who found that the overall rate of mTOR expression in GC patients was 60.8%.25 Li et al study showed positive correlations between mTOR expression in GC and pathological parameters such as invasion depth, differentiation and LNM .26.The results of this study showed that AKT expression was 72% and it was significantly higher in GC with LNM than in non-metastatic disease. Also; AKT score & AKT score positivity were statistically significant predictor of LNM .This is in agreement with Ye et al who reported AKT positivity in 82.2% GC tissues; with higher expression in GC tissues than the non-cancerous tissues.27 This finding also agrees with Petrini et al. who found that patients with overexpression of AKT in GC had a poor prognosis, suggesting that AKT can be used as prognostic marker for GC.28 Also, Grille et al. reported that AkT activation in cancer cells facilitates tissue invasion and metastasis .29 The present study showed that there was significant positive correlation between AKT score and mTOR score. This can be explained by the fact that AKT requires mTOR to achieve its full activation. Murayama et al. suggested

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that inhibition of mTOR is essential for preventing the progression of tumours with highly activated AKT /mTOR signaling.30 The results of this study also showed that there was significant negative correlation between PI3K score and presence of diabetes. Hong et al reported that oncogenic activation of PI3K/AKT signaling at least partially promotes cellular glucose uptake.31 As regard tumor markers of GC, the serum level of both CEA & CA 19-9 did not show significant difference between LNM GC & non metastatic GC. This finding agrees with that of Gwak et al., who reported that CEA did not show statistically significant relationship with nodal involvement, depth of invasion or tumor stage.32 Limitations of the present study were the limited number of GC patients and the lack of patients with distant metastasis. It is recommended to undergo the future studies on higher number of GC patients and to include patients with all GC stages.

Conclusion

AKT expression was positive in 72.7%; m TOR expression was positive in 54.5% and PI3K expression was positive in 36.4% in Egyptian patients with GC. AKT score was a statistically significant discriminator between regional lymph node metastatic GC and non-metastatic GC.

Acknowledgments

None.

Conflicts of interest

No conflicts of interest

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None.

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