RESEARCH ARTICLE

Accuracy of Endoscopic Ultrasonography for Determination of Tumor Invasion Depth in Gastric Cancer

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Abstract

Background: Gastric cancer (GC) is one the common lethal cancers in Iran. Detection of GC in the early stages would assesses to improve the survival of patients. In this study, we attempt to evaluate the accuracy of EUS in detection depth of invasion of GC among Iranian Patients. Materials and Methods: This study is a retrospective study of patients with pathologically confirmed GC. They underwent EUS before initiating the treatment. The accuracy of EUS and agreement between the two methods was evaluated by comparing pre treatment EUS finding with post operative histopathological results. Results: The overall accuracy of EUS for T and N staging was 67.9% and 75.47, respectively. Underestimation and overestimation was seen in 22 (14.2%) and 40 (25.6%) respectively. The EUS was more accurate in large tumors and the tumors located in the middle and lower parts of the stomach. The EUS was more sensitive in T3 staging. The values of weighted Kappa from the T and N staging were 0.53 and 0.66, respectively. Conclusions: EUS is a useful modality for evaluating the depth of invasion of GC. The accuracy of EUS was higher if the tumor was located in the lower parts of the stomach and the size of the tumor was more than 3 cm. Therefore, judgments made upon other criteria evaluated in this study need to be reconsidered.

Keywords: Endoscopic ultrasonography - accuracy - gastric cancer - agreement - tumor staging

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Introduction

Gastric cancer (GC) is the second most common cause of cancer-related death in the world, with a wide variation in incidence rates across the global geography (Goh et al., 2014; Karimi et al., 2014). The incidence of GC in Iran is approximated at 7300 cases per year (Haidari et al., 2012; Massarrat and Stolte, 2014), is amongst the most common cancer in males, and it is reported to be the third most common cancer after breast and colorectal cancers in females. GC is also the first cause of cancer related death of both sexes in Iran (Kolahdoozan et al., 2010; Aghaei et al., 2013; Liu et al., 2013).

Despite many attempts, the treatment of gastric cancer remains challenging, primarily because most patients present in an advanced state of the disease(Piazuelo and Correa, 2013). Only complete resection with negative microscopic margins (R0 resection) of all gross findings provides a long-term survival benefit (Koessler et al., 2014).

Of recent, the detection of gastric cancer in its early stages along with the consequent minimal invasive treatment methods such as endoscopic mucosal resection or laparoscopic gastrectomy are gaining importance (Park et al., 2011; Kim, 2012). Based on the views of the Japanese Gastric Cancer Association (JGCA), early gastric cancer and stage 1A gastric cancer can be treated by means of endoscopy (Japanese Gastric Cancer, 1998). In this context, accurate preoperative determination of the GC stage is essential in the selection of an appropriate therapeutic mode. Previously, precise preoperative staging was not essential because the exact stage did not alter treatment plans (Garlipp et al., 2011). Endoscopic ultrasonography (EUS), which is considered to be the method of choice for locoregional staging, was commonly used for the differentiation of mucosal from submucosal lesions (Ganpathi et al., 2006; Jurgensen et al., 2013; Karimi et al., 2014). EUS actually is considered as one of the best diagnostic modalities for local and regional staging of gastric cancer (Kikuchi et al., 2011; Kim,

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2012; Jurgensen et al., 2013). The accuracy of EUS in the determination of T (scoring) is greater than 80%;although it could be influenced by endoscopic findings, location and size of tumors. In this view, there is controversy regarding the accuracy of EUS in anatomically defining of the extent of tumor invasion. Therefore the present study was conducted to evaluate the accuracy of EUS in determining the depth of GC invasion in comparison to surgical pathology results.

Materials and Methods

Design and patients

This study was conducted retrospectively at Firoozgar Hospital among patients who underwent EUS for the determination of local invasion of gastric tumors before surgical intervention, between 2009-2013

During this period the medical records of patients who referred to our center with a histopathologicaly confirmed diagnosis of gastric cancer and also underwent EUS for determining the depth of tumor invasion prior to treatment were studied. As a regular practice,once gastric cancer is diagnosed by histopathology, EUS and CT-scan are used to determine stages of tumore. The following patients were excluded from study for the following reasons:1) ambiguous pathological staging; 2) having received neoadjuvant chemotherapy or chemoradiotherapy; 3) having metastatic cancer or was considered as non operable gastric cancer.

Endoscopic ultrasonography exam

The instrument used for EUS exams was an ultrasound UM-3R, with a frequency of 20MHZ with a depth of 4 centimeters. The patients underwent conventional endoscopy before EUS evaluation to morphologically asses lesions and for obtaining biopsy. Local oropharyngeal anesthesis was administered with lidocain (5%) for all. Intravenous midazolam and petedin were used for sedation, under the supervision of an anesthesiologist.

The EUS was performed by an experienced gastroenterologist with a track record of more than 1000 EUS per year. For the EUS procedure, as the scope was advanced toward the tumor, the stomach wall was examined as follow; mucosa was defined as a hyperecho in the first layer,hypoecho in the second layer,. hyperchoic layer in the third layer, the hypoechoic zone in the forth layer, and the fifth layer included hyperechoic layer corresponds to the subserrosa and serosa. The extent of invasion was assessed according to the infiltration of tumor into each layer.

Surgical procedures

Surgical intervention was based on the Japanese Gastric Cancer Association (JGCA) classification. Tumor location were classified according to the longitudinal axis of the stomach as three zones: upper, middle and lower third. Total gastrectomy with Roux en Y reconstruction was considered for tumors in the upper third of the stomach. In cases of subtotal gastrectomy, this orBilroth reconstructions were performed appropriately. The surgical specimens were then referred for histopathologic evaluation.

Histopathology evaluation:

The histopathological exams of surgically resected tissues were performed on 2-5 millimeter thick sections. The specimens were stained with Hematoxyline and Eosin (HandE).The size of tumors were reported as ≤3 and >3 centimeters. Histopathological findings were classified according to the World Health Organization (WHO). Undifferentiated types were defined as poorly differentiated adenocarcinoma, signet ring cell adenocarcinoma and mucinous adenocarcinoma.

Statistic analysis

The accuracy and sensitivity of EUS in the staging of gastric cancer were assessed using histopathological staging of surgically resected specimens as the gold standard. Data was analyzed using STATA software, version 12 (StataCorp, Texas, USA). Univariate analysis was performed by chi-square and the weighted Kappa test was used to evaluate the consistency between the EUS and histopathological staging of gastric cancer.

Ethics

The ethics committee of Firoozgar hospital approved this study in accordance to the declaration of Helsinki.

Results

Patients characteristics

A number of 106 patients were enrolled in this study. The mean age of patients was 63.3±11.9, of them 48 (45.8) were female. The average size of tumors was more than three centimeters 63 (59.4%). With consideration to the location of lesions, the main part of tumors was located in the middle third 63 (59.4%), and also 15 (14.1%) and 28 (26.4%) for upper and lower third of stomach, respectively. The main macroscopic type of tumors was non-depressed 89(84.0%).

Regarding T staging during EUS, T1, T2, T3 and T4 were observed in 8 (7.55%), 32 (39.1%), 52 (49.0%) and 14 (13.2%), respectively.

Surgical and pathological results

Surgical intervention of GC comprised of total gastrectomy and subtotal gastrectomy. In this regard 49 (46.2%) subjects underwent total gastrectomy. None of them benefitted from endoscopic resection. The pathology results indicated that an undifferentiated type was seen in 72 (67.9%) cases. According to the T staging, T1, T2, T3 and T4 were seen in 13 (12.2%), 27 (25.4%), 41 (38.6%), and 25 (23.5%), respectively.

Comparison of EUS findings with pathological results

In 67.92 % of patients, the EUS T staging concurred with their pathological staging. Underestimation and overestimation were seen in 13 (12.2%) and 13 (12.2%), respectively. The sensitivity/PPV for EUS staging for stages T1, T2, T3 and T4 was 36.6%/ 50.0 %, 72.4%/65.6%, 80.4%/63.4% and 48.0%/85.71%, respectively. Also the overall accuracy for T staging by EUS was 67.9% (Table

Table 1. T and N Staging: Histopathology and Endoscopic Ultrasound (EUS)

		Histopathologic staging					Sensitivity (%)	PPV* (%)	Overall accuracy (%)
EUS T staging		T1	T2	T3	T4	Total			
	T1	4	4	0	0	8	36.36	50	67.92
	T2	5	21	6	0	32	72.41	65.62	
	T3	2	4	33	13	52	80.48	63.46	
	T4	0	0	2	12	14	48	85.71	
	Total	11	29	41	25	106			
EUS N staging		N0	N1	N2	N3	Total			
	N0	15	5	2	0	22	62.5	68.18	75.47
	N1	6	28	4	2	40	77.77	70	
	N2	3	1	22	0	26	75.86	84.61	
	N3	0	2	1	15	18	88.23	83.33	
	Total	24	36	29	17	106			

*Positive predictive value

Table 2. Analysis of the Degree of Consistency between Endoscopic Ultrasound (EUS)and Histopathology (the Value of Weighted Kappa)

Staging	Observed agreement (%)	Expected agreement (%)	Kappa	SE*
T staging	67.92	30.7	0.53	0.05
N staging	75.47	26.95	0.66	0.05

*Standard error

Table 3. EUS Accuracy for Tumor Depth

	Correct (N)	Incorrect (N)	Accuracy (%)
Tumor location			
Upper Third	5	10	33.3
Middle Third	41	22	65
Lower Third	18	10	64.3
Morphology			
Depressed	3	14	17.6
Non-Depressed	58	31	65.1
Tumor size			
≤3 cm	32	31	50.8
>3 cm	30	13	69.8
Histology			
Differentiated	27	16	62.7
Undifferentiated	37	26	58.7

1). The sensitivity/PPV for EUS staging for stages N0, N1, N2 and N3 was 62.5%/68.1%, 77.7%/70.0%, 75.8%/84.6% and 88.2%/83.3%, respectively. Also the overall accuracy for N staging by EUS was 75.4% (Table 1).

Based on the EUS and histopathology staging, consistency in the endoscopic T staging and N staging was evaluated. The observed agreement for T and N staging were 67.9 and 75.4, respectively. Also the values of weighted Kappa for T and N staging were 0.53 and 0.66, respectively (Table 2).

With consideration to the tumor size, in those with a tumor size of more than 3 cm; 69.8% of EUS staging concurred to the corresponding pathologic findings. But this concurrence was 50.8% for tumors less than 3 cm in size. This concurrence was more prominent in T1 and T2 staging. Regarding the location of tumors; there was greater accuracy in the middle and lower part of the stomach (Table 3).

Discussion

For over a decade, EUS was considered a very high accuracy modality for T staging in GC (Lee et al., 2005; De Angelis et al., 2013). Some previous reports have illustrated the superiority in the accuracy of EUS compared to conventional CT scanning or MRI, in the detection of tumor invasion in gastric cancer (Mandai and Yasuda, 2012; De Angelis et al., 2013). It is also reported that in gastric cancer, the invasion level correlates with lymph node metastasis; therefore differentiations between T staging levels have become of greater significance (Mouri et al., 2009; Yoshino et al., 2012). EUS has the capability of illustrating the stomach wall layers comprehensively and thus can evaluate the level of tumor infiltration more accurately.

In the present study we have found that the accuracy of EUS concerning T staging and nodular involvement in comparison to post surgery histopathology studies are about 68% and 75.4% respectively (Tables 2,3) ; comparable with other studies (Puli et al., 2008). Based on previous reports, the accuracy of EUS in T staging could reached to 93% with a lower rate of over or underestimation. In 1991 Botet et al reported a 92% accuracy of EUS with its corresponding pathological findings (Botet and Lightdale, 1992). After which many studies were carried out to determine the accuracy of EUS in comparison to pathology findings (Botet and Lightdale, 1995; Opacic and Rustemovic, 2003; Wang et al., 2014). In this context , a meta analysis by Puli et al reported that the sensitivity and specificity of EUS in gastric cancer staging was more than 80% and 90% respectively (Puli et al., 2008). In addition, another meta analysis by Mocellin revealed that the sensitivity and specificity of EUS reached 86% and 91%(Mocellin et al., 2011). However, other studies have not shown the same results and while reporting figures in the range of 60-90% (Bohle et al., 2011).

The accuracy of EUS in T staging, depends on the depth of tumor and the changing of stomach layer anatomy. Furthermore, previous studies revealed that depressed, ulcerative and undifferentiated gastric cancers are associated with a lower accuracy in EUS staging. It is noteworthy that all types of infiltration have been taken into account in our study, but our results were not

compatible with other reports (Bohle et al., 2011; Mocellin et al., 2011; Kutup et al., 2012; Mandai and Yasuda, 2012; De Angelis et al., 2013). A definite explanation cannot be offered by the authors in this regard; but attributions could be made to the limited number of patients and also the stage of diagnosis of GC. In addition, in the present study the location and size of tumors are associated with accuracy of EUS staging, where in cases with tumors located in the middle and lower part of the stomach, the EUS accuracy was higher than other parts. The accuracy was the lowest in those with tumors in the upper parts. These findings are comparable with previous reports. These findings may be due to the difference in the thickness of stomach layers, presence of fibrosis or blood vessels surrounding the tumor that making EUS evaluation difficult. Along with these issues, we have to also consider the limited number of cases.

In the present study, a weighted kappa, which assigns less weight to agreement as categories are further apart, was calculated. The EUS T staging and the pathological T staging demonstrated moderate consistency (Kappa=0.53, Moderate agreement=0.41-0.60) (Viera and Garrett, 2005). Also the EUS N staging and the pathological N staging demonstrated substantial agreement (Kappa=0.66, substantial agreement=0.61-0.80) (Viera and Garrett, 2005). Although in our study, the factors affecting EUS accuracy were the location and size of tumor, we were not able to demonstrate a significant association between them. This result is comparable with other studies as reported by Tsuzuki, kim and Park (Park et al., 2011; Tsuzuki et al., 2011; Kim et al., 2014). In comparison with previous reports, the macroscopic morphology of lesions were not associated with EUS accuracy; this could be related to the low number of depressed lesions (Lee et al., 2012; Mandai and Yasuda, 2012; De Angelis et al., 2013). In addition, the issue regarding the pathological type of lesions still remains a challenging item and was not associated with the accuracy of EUS staging in our study. For the clarification of this matter a multicentre study with more cases is required. Furthermore, when considering the limitations of this study, firstly, the numbers of participants were not enough in all stages of GC, and secondly, the greater part of our participants had large gastric tumors, providing us with a limited number of patients with small tumors, making comparison between should be considered carefully.

As a conclusion, in gastric cancer, it is vital to carefully detect the disease stage before initiation of treatment and consequently select the modality of treatment such as being surgery or endoscopic resection. In this study, we endeavored to compare preoperative EUS staging results with post surgery histopathology findings. Based on our findings the accuracy of EUS concerning the tumors that was located in the middle part of the stomach and the size of the tumor was more than 3 cm is higher.

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