

## REVIEW

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# A Review of Gastric Cancer Research in Malaysia

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## Abstract

Incidence rates of gastric cancer in Malaysia has declined by 48% among males and 31% among females in the latest reporting period of 13 years. Malays used to have age-standardized-rates only a fifth of those in Chinese and Indians, but the incidence among them is slightly rising even as the rates drop in the other races. Besides ethnicity, a low level of education, high intake of salted fish and vegetables, *H pylori* infection and smoking are risk factors. Consumption of fresh fruit and vegetable is protective. Variation in the strains of *H pylori* infection affect gastric cancer risk, with hspEAsia isolates among Chinese appearing linked to a high incidence than with hpAsia2 or hpEurope strains among Indians and Malays. It was reported in the 1980s that only about 3% of patients presented with early gastric cancer, but more encouraging rates reaching 27% with Stage 1 and 2 disease have been reported in the twenty-first century from leading centres. More tumours occur in the distal stomach except in Kelantan, where the incidence is low and main site is the cardia. Prompt endoscopy is advocated and open access, with direct referrals, to such services using a weighted scoring system should be more utilized. In view of the high rate of late disease laparoscopic staging unnecessary laparotomy needs to be avoided. Late presentation of gastric cancer however, is still predominant and the mortality to incidence ratio is relatively high. Besides seeking to reduce risk factors and achieve early detection, implementation of improved care for patients with late disease must be promoted in Malaysia.

**Keywords:** Gastric cancer- Malaysia

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## Introduction

Malaysia is a country with a moderate risk for gastric cancer (GCa). It remains a major cause of mortality and morbidity although there is evidence it is on the decline. Several hundred Malaysians develop and die from the disease each year (Azizah et al., 2016). Even though we have reports from our National Cancer Registry we do not have a national data base to monitor cancer the patient characteristics and outcomes of our GCa patients. Following the method of similar recent reviews of major disease in Malaysia, a literature search of articles as detailed in the paper Bibliography of clinical research in Malaysia: methods and brief results, using the MESH terms, Stomach Neoplasms, covering the years 2,000 till 2016 was undertaken. (Teng and Zuhariah, 2014)

69 articles were identified. In brief, clinical research publications containing data on Malaysia for the period Jan 2000 - July 2017 were included (last search date 13 August 2017). Conference proceedings and conference abstracts, relevant theses/dissertation, books/book chapters, reports and clinical practice guidelines were included.

### Section 1: Review Of The Literature

#### Epidemiology

As in the rest of the world, the rates of stomach, or

gastric, cancer is declining in Malaysia (Goh, 2007). The latest report of the Penang Cancer registry in the Malaysian National Cancer Registry Report (2007-2011) Azizah et al., (2016) shows the Age Standardized Rate(ASR) for gastric cancer(GCa) in Penang is 6.9 for males and 4.7 for females. This compares to an incidence among males between 1994-1998 (Rokiah M et al., 2003) of 13.3 and for females of 6.8, a decline of 48 and 31 percent respectively over 13 years.

There are ethnic differences. As with the leading cancers such as breast, colorectal, lung, cervix and nasopharyngeal Chinese have the highest incidence of GCa. Malays had rates 4-5 times lower than Chinese and Indians, but that gap is closing (Table1) as the incidence among Malays rise and that among the other races decline. Males have higher rates than females (Lim et al., 2008). They had nearly twice the incidence of GCa compared to females in all races but the difference may be decreasing as the overall incidence declines (Azizah et al., 2016). The disease occurs mainly in individuals above the age of 50 years.

In the context of Asia, South-east has a GCa incidence (8.2 for men and 4.1 for women per 100,000) less than a third that of East Asia, where the incidence is highest in the world, according to GLOBOCAN 2012 estimates (Ng et al., 2015). The Mortality to Incidence Rate (MIR) for

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GCa is among the highest for any cancer in South-east Asia (0.88), and holds true for Malaysia.

There are also regional differences within Malaysia (although the National Cancer Registry report of 2007 has reports by states, the data appears unsafe) (Azizah et al., 2016). Malays in Kelantan have been reported to have half the rate of stomach cancer of Malays in Penang. (NorSaleha, 2006) They may have the lowest rates of stomach cancer in the world (Lim, 2009).

#### *Risk Factors*

Goh et al., (2007) conducted a case-control study of 87 cases of GCa (and 174 controls) diagnosed histologically by endoscopy at the University Hospital, Kuala Lumpur. Besides race, the independent risk factors for GCA were; low level of education [odds ratio (OR) 9.8], high intake of salted fish and vegetables (OR 5.2), *H. pylori* infection (OR 2.5) and smoking (OR 2.5). On the other hand a high intake of fresh fruits and vegetables was an independent protective factor (OR 0.15). As in the rest of the world, the advent of the refrigerator, which has moved the diet of the population away from preserved foods, has probably done more to reduce the incidence of stomach cancer than any other factor. The study was unable to confirm that high chilli intake was protective for GCa. Chilli intake, however, was significant on univariate analysis. Curcumin, an ingredient of turmeric powder used in curries, has been shown to be protective for GCA (Nagabhusan and Bhide, 1992) whereas capsaicin, the chemical that produces the burning sensation, may have a beneficial effect at low dose but the opposite at high doses (Pabalan et al., 2014).

In a study of 50 patients, Karim and Pallesen (2003) found that 10% were associated with the Epstein Barr virus, in line with findings elsewhere.

#### *Ethnicity*

Being Chinese had the highest independent risk for GCa (OR 10.23) according to Goh et al., (2007). What the genetic or environmental factors behind this is not clear. Ethnicity has another curious effect in that, although having *H. pylori* is risk factor for GCa, Indians, who have a high prevalence of *H. pylori*, appear relatively protected. Among *H. pylori* positive subjects, only 23.3% of Indians had GCa, compared to 60.5% of Chinese and 82.3% of Malays (Goh et al., 2007). This has also been observed in India and been labelled the "Indian enigma" (Quek and Goh, 2008).

#### *Helicobacter Pylori*

Goh (2009) noted that 43% of GCa patients had *H. pylori* between 1989-1990 compared to 37% between 1999-2000 based on urease test biopsies. Infection rates of *H. pylori* among all patients endoscoped declined from 52% to 30% in the same period. However, the prevalence of *H. pylori* based on serology among 87 patients with GCa was 79%. It was found to be higher among Indians (82%) than Chinese (79%) and Malays. (75%) (Goh et al., 2007).

In a study of 234 patients with endoscopic antral gastritis in Kelantan, where the prevalence of *H. pylori* is exceptionally low, Yeh et al., (2009) found histological chronic antral atrophic gastritis in 42.3%, intestinal

metaplasia in 7.7% and *H. pylori* infection in 6.8%. *H. pylori* infection was still the only variable factor associated with intestinal metaplasia and dysplasia. They believed this supported the notion 'No *H. pylori*, no GCa', even though *H. pylori* is not the only risk factor necessary.

The low prevalence of *H. pylori* in Kelantan, may be a key factor for the low incidence of GCa there (Uyub et al., 1994). The diversity of *H. pylori* strains found in the region, may partially explain the "Indian enigma" (Goh, 2009). Populations with hspEAsia of *H. pylori* isolates, such as Chinese in Malaysia, exhibit a high incidence of GCa while the incidence is low in populations with a high proportion of hspIndia, hpAsia2 or hpEurope strains, such as Indians and Malays. (Tay et al., 2009; Breurec et al., 2011; Gunaletchumy et al., 2014)

#### *Clinical Features*

##### *Staging*

Jasmi et al., (1996a) noted that between 1984 and 1989, only 3.1% of their GCa patients at HUKM presented with early gastric cancer, but proportion rose to 11.9% (5.1% stage 1, 6.8% stage 2) between 1990-1995. The total number seen had also increased from 97 in the first and 117 in the second period.

Kandasami et al., (2003) on the other hand in a retrospective search of cancers in Ipoh Hospital between 1988-1998 found Stage 1 gastric cancer in only 3.6% (9/250) of their patients, Stage 2 in another 3.6% (9/25), Stage 3 in 11.2% (28/250) and more than 80% (204/250) had stage 4 disease.

Of the 404 incident cases of GCa in the Penang Cancer Registry between 2004-2008, 182 had the stage of cancer reported. 13.7% were Stage 1, 13.7% were stage 2, 31.9% were stage 3 and 40.7% were in stage 4. Caution is warranted regards the accuracy of these percentages as reporting of stage could have been selective. (Azizah et al., 2010) 70 cases of gastric resections with curative intent had surgery in UMMC between 2005 till 2010. 9(13%) were Stage 1, 10(14%) in Stage 2, 32(46%) were Stage 3 and 19 (27%) were in Stage 4. (Durairaj, 2012)

##### *Pathology*

##### *Location of tumour*

In Kuala Lumpur, Goh et al., (2007) found that 15(17%) were proximal, 66/87(76%) of GCAs were located distally in the stomach, and 9(7%) involved the stomach totally. In Penang, Gurjeet (2004) noted that, 9/32 (28%) gastric carcinomas were located in the cardia or gastro-oesophageal junction while 23/32(72%) were non-cardia. Durairaj (2012) recorded that 11/70(16%) were proximal, 26/70(37%) were middle and 33/70(47%) were distally located in the stomach in his series of resected GCa between 2005 till 2010.

In an earlier series from 1988 to 1998, Kandasami et al., (2003) in Ipoh, found that in 155/250 (62%) of the patients the cancer was located at the gastric antrum, 23/250(9%) involved the body and antrum, 33/250(13%) involved the body, and in 39/250 (15%) of the patients, the disease located at the cardia and fundus of the stomach. The predominance of distal tumours appears to correlate

to an earlier series reported in 1976 from the University Hospital where 53% of GCa was located in the antrum, 28% in the body, 17% in the cardia and fundus and 3% involved the entire stomach (Bahari et al., 1976).

On the other hand, in sharp contrast in Kelantan 14/23 (61%) were cardia-located tumours.(Gurjeet et al., 2004).

### Histology

Most GCa are adenocarcinomas. Kalavathy (1993) retrieved and studied gastrectomy specimen from 79 cases in UMMC between 1986 and 1991. 42(53%) were the intestinal type by Laurén's classification and 37(47%) were diffuse type with no other type seen. There no age no gender difference in the distribution. In Goh et al.,'s series (2007), 59(68%) belonged to the intestinal type, according to Laurén's classification, and 28(32%) were the diffuse type. Similarly, in Penang 23(72%) were intestinal type, 8(25%) diffuse and 1(3%) mixed type. The ratio was also similar in Kelantan with 16(70%), 5(22%) and 29%) cases respectively.(Gurjeet et al., 2004) There does not appear to be any evidence *H pylori* infection is linked to the intestinal type of GCa. Durairaj (2012), on the other hand found 31/70(44%) of a series who had surgery with curative intent had intestinal type, compared to 39/70(56%) with diffuse type and noted a better survival for those with intestinal type.

Durairaj (2012) did not find Bormann's grading significantly associated with survival.

Jasmi et al., (1996b) have reported a series of 7 cases of leiomyosarcoma of the stomach at UKM between 1989 and 1995. All but one were males. The mean age was 56 years Three were Malays. 3 Chinese and 1 Indian. The tumours were large and exophytic ranging in size from 8-20cm. Two had liver metastases wrong diagnosed as originating from the pancreas. Three patients were alive after surgery ranging from 6 months to 6 years.

Inflammatory myofibroblastic tumour (IMT) is a rare cancer of the stomach, which has been reported in Malaysia in a boy of 13 years. Local recurrence was detected 3 years later with invasion into the pancreas and hilum of the spleen. Wide resection of the stomach, distal pancreatectomy and splenectomy achieved recurrence-free for two years (Hamidah et al., 2007). Gastrointestinal stromal tumours (GIST) are derived from the gastrointestinal mesenchyma, in the gastrointestinal tract and can also occur in the stomach. Siam and Siow have described a 29-year-old Iban man with GIST in the stomach who presented with intussusception (Siam and Siow, 2008). More than half (53%) of GIST tumours have been noted in the stomach in a Malaysian report (Kkrishnappa et al., 2016)

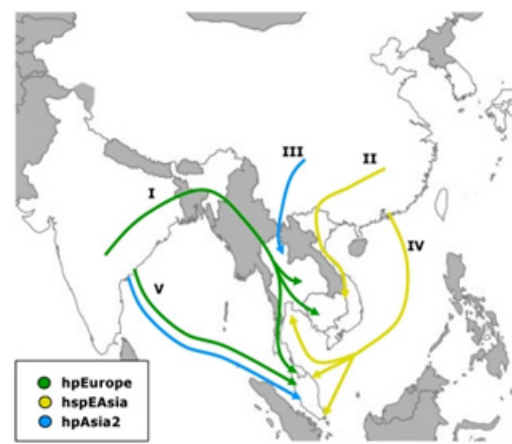


Figure 1. Human Migration into South-East Asia According to *H. pylori* Strain Evidence.(from Breurec et al., 2011)

### Biomarkers

Cheah and Ramachandran (1994) noted that GCa cells from patients in Kuala Lumpur (n=79) produced more sulphomucins compared to normal controls.

GCa cells, like other cells, exhibit cluster of differentiation (CD) antigens which characterize the response of the immune system to these cells. *H pylori* infection has been shown to induce the expression of certain CD antigens. Sukri et.al. (2016) have found that CD 5, CD40, CD 71, and CD 39 (antigens perpetuating tolerance of immune cells) were upregulated more than twofold in GCa cells from six patient in HUKM compared to normal mucosa, while CD279 (antigen essential in T cell apoptosis) was upregulated in normal gastric mucosa cells taken from these patients at least 10cm from the tumour site.

Methylation of the Deleted in Colorectal Cancer (DCC) gene has been observed in the course of gastric carcinogenesis and disappeared in advanced gastric carcinoma (Hibi et al., 2010). The rs10502974 SNP which was located within the intronic region of DCC gene was the single nucleotide polymorphism(SNP) most significantly associated with *H. pylori* infection (p=0.00549) among Malays in Kelantan (Maran et al., 2013a).

The XRCC1 gene, mapped to human chromosome 19q13.2-13.3, is recognized as a gene related to DNA repair. Three common SNPs, (Arg194Trp), (Arg280His) and (Arg399Gln) are associated with gastrointestinal cancer risk. Halim et.al. noted an increased risk for GCA among 250 patients in Sabah, with OR of 1.89 for those with the (Arg194Trp) SNP and OR of 2.94 for the(Arg399Gln) SNP. The frequency of 194Trp allele was higher than reported in Egypt and Mexico but was lower than those reported in Eastern Asia including Han Chinese

Table 1. Age Standardised Incidence of Gastric Cancer (GCa) in Penang among Various Ethnic Groups

	Males			Females		
	Malays	Chinese	Indians	Malays	Chinese	Indians
1994-1998	3.0	17.7	20.3	2.2	8.5	11.5
1999-2003	3.2	12.3	9.4	1.8	7.8	10.8
2004-2008	4.1	10.4	7.5	2.0	6.4	7.0

gastrointestinal cancer populations. The 399Gln allele frequency was found higher when compared to Egyptian, Han Chinese, Japanese, Korean and Western Mexican populations but was lower than in the Thai population gastrointestinal cancer population. (Halim et al., 2016)

Rajadurai (2017) has found human epidermal growth factor receptor2 (HER2) overexpression, a biomarker of breast cancer, in advanced GCa and gastroesophageal junction cancer. HER2 overexpression was evident in nearly 24.6% (56/288) of the Malaysian, and significantly more among males and diffuse-type tumors.

#### *In H pylori related GCA*

##### *Factors in the bacteria*

By comparing the *H. pylori* genome of 21 Malaysian and 6 other Asian *H. pylori* strains, Gunaletchumy et al. (2014) found the presence of outer membrane protein GC26\_66 (type 1), hypothetical ATPase protein GC26\_69, hypothetical protein GC26\_73 and hypothetical protein GC26\_33 were shown to be risk factors for gastric cancer development. In addition, outer membrane GC26\_77 may have a protective effect against peptic ulcer disease.

CagA+*H. pylori* infection is known to have a propensity of developing GCa. The CagA protein possesses EPIYA motifs which are key to the function of the protein in phenotypic changes of the bacteria. The EPIYA motifs have been divided into four classes, designated EPIYA-A to -D. Schmidt et al., (2009) founds genes encoding EPIYA-A in 97.6% and EPIYA-B in 100% of *H. pylori* isolated from patients in UMMC, Kuala Lumpur and Changi, Singapore. However, 93.0% of isolates from Indian patients with functional dyspepsia encoded EPIYA-C while 91.8% of such Chinese patients encoded EPIYA-D. 61.5% of Malay patients with functional dyspepsia and *H. pylori* infection had isolates with EPIYA-C and 38.5% EPIYA-D. Only *H. pylori* isolates from distal GCa patients who were Chinese were studied and 81.7% of them encoded for EPIYA-D. These findings may explain the "Indian Enigma".

##### *Factors in the patient*

Schmidt et al., (2011) studied gene polymorphisms (SNPs) related to immune and cancer-related pathways for association with *H. pylori* infection in 422 patients undergoing endoscopy in Malaysia (UMMC) and Singapore and found significant association among Chinese, between SNPs (i) PTGS2-1195G (rs689466) and an increased risk of GCa on adjusting for *H. pylori* status (OR 1.53, and (ii) IL1B-1473C (rs1143623) and a decreased risk of GCa (OR 0.64). (iii) EBBR2+1963G (rs1801200) was associated with low *H. pylori* infection (OR 0.48).

Chronic inflammation of the gastric mucosa, a consequence of *H. pylori* infection, is a risk factor for GCa. A number of nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are involved in the inflammatory pathway. Castano-Rodriguez et al., (2014a) investigated the role of genetic polymorphisms and expression of genes involved in the NLR signaling pathway in *H. pylori* infection and GCa among 310 ethnic Chinese in Malaysia and Singapore (87 non-cardia

GCA cases and 223 controls with functional dyspepsia). CARD8 (rs11672725), NLRP3 (rs10754558), NLRP3 (rs4612666), NLRP (12-rs199475867) and NLRX1 (rs10790286) showed significant associations with GCa. On multivariate analysis, only CARD8 (rs11672725) remained a risk factor (OR 4.80).

Autophagy plays a pivotal role in *H. pylori* infection and inflammation. Defects in autophagy may lead to *H. pylori*-related GCa. In the same cohort of Chinese studied by Castano-Rodriguez et al., (2015) ATG16L1 (rs2241880) increased the risk of GCa (OR 2.38) and *H. pylori* infection (OR: 1.49) while IRGM (rs4958847) decreased GCa risk (OR 0.26).

Toll-like receptors (TLRs), an important part of the innate immune system, may also play a role in *H. pylori*-related GCa. Also studied in that cohort, after multivariate analysis, TLR4 (rs11536889) remained a risk factor for GCa (OR: 3.58). Six other polymorphisms [TLR2 (rs3804100), TLR2 (-196 to -174del), MD-2 (rs11465996), MD- (rs16938755), LBP (rs2232578) and TIRAP (rs7932766)] increased the risk of GCa in combination with *H. pylori* infection in these Chinese individuals. On the other hand TLR4 (rs10759932) decreased the risk of *H. pylori* infection (OR: 0.59). (Castaño-Rodríguez et al., 2014b). Ram et al., (2015) have found that TLR1 (rs4833095) and TLR-10 (rs10004195) linked with increased levels of leptin, leptin receptor, pro-inflammatory cytokines and low levels of ghrelin associated with *H. pylori* infection, were also associated with GCa.

Among Kelantan Malays with *H. pylori* infection and gastric precancerous lesions identified during endoscopy, SNPs rs9315542 (UFM1 gene), rs6878265 (THBS4 gene), rs1042194 (CYP2C19 gene) and rs10505799 (MGST1 gene) were significantly associated with atrophic gastritis, complete intestinal metaplasia, incomplete metaplasia with foci of dysplasia and dysplasia, respectively. There was a higher chance of a subject having the allele compared to controls for rs9315542 (0.4 vs 0.06), rs6878265 (0.6 vs 0.01), rs1042194 (0.6 vs 0.01) and rs10505799 (0.5 vs 0.02). (Maran et al., 2013b)

#### *Management*

##### *Diagnosis*

Because indications for upper gastrointestinal endoscopy varies, the rate GCa is detected can vary, from 1.4% (16/1119) for patients endoscopy for dyspepsia (Kudva and Thein-Htut, 1988), to 3.4% (7/208) at a new endoscopy service (Paramarajah, 1985). Goh et al., (2009) reported a rate of 2.8% and 2.0% from the same hospital between 1989-1990 and 1999-2000 respectively.

Prompt endoscopy has been advocated for the earlier diagnosis of gastric cancer in East Asia (Chen et al., 2015).

However, it has been argued that the prompt endoscopy advocated for East Asia where the incidence is much higher, may not be applicable to Malaysia (Mahadeva and Goh, 2015). Mahadeva et al., (2008) have proposed that testing for *H. pylori* and treating would be a more cost-effective strategy for Malaysia. Besides the Urea Breath Test and the biopsy urease test, a stool antigen test has been found to be highly sensitive and specific.

(Osman et al., 2014)

However, in order to facilitate early diagnosis, Tata et al., (2014) have devised, an open access endoscopy service using a weighted scoring system consisting of demographic data (age, race and sex) as well as symptoms (melena, anemia, vomiting, weight loss, epigastric mass/fullness, dysphagia, early satiety and dyspepsia).

#### *Presentation*

Unfortunately GCa cause no specific symptoms especially in the early stage. Loss of weight and appetite, early satiety, anaemia and a palpable mass appear too late.

Kandasami et al., (2003) found 82% of their patients were found to have Stage 4 GCa, not surprisingly curative surgery was performed to only 16% of the patients. An alarming 33.2% of the patients did not even receive palliative surgery. At the initial assessment or at time of surgery the disease was too advanced for any form of surgical procedures. In 18 patients (7.2%) the abdomen was opened and closed at surgery and in another 109(43.6%) some palliative procedure was done.

Reviewing 86 patients with stomach cancer in Seremban between 2004 and 2008, Tata et al., (2013) found that the mean duration from the first appearance of cancer symptoms to diagnosis at endoscopy was 32.4 weeks. The main reasons for the long delay were self-medication, empirical treatment for dyspepsia and delay in high risk patients obtaining an appointment for an endoscopy procedure.

In unusual cases, GCa has presented in a 27-year old woman with perforation of the stomach at 16 weeks of gestation in her third pregnancy (Jasmi et al., 2000) and with pulmonary lymphangitic carcinomatosis in three women, two of whom were young (Liam et al., 1989). Inferior vena cava obstruction has also been reported as the presenting feature in a 56-year old woman in Malaysia with stage 4 GCa (Patel, 2015).

#### *Assessment*

Treatment strategy in GCa depends heavily on the stage of disease and staging assessment is mandatory.

In the context of the low rate of resectable stomach cancers in Malaysia (Kandasami et al., 2003), Mahadevan et al., (2010) have evaluated the role of laparoscopic staging in an effort to reduce unwarranted open laparotomy in patients with GCA. Computed tomography (CT) scan often under-stage disease and endoscopic ultrasound is not widely available in Malaysia. After excluding patients with obvious metastatic disease, they enrolled 40 patients for laparoscopic staging. Laparoscopic staging detected 90.3% of T3 tumours compared with 58% detected by CT. On the other hand the sensitivity of laparoscopic staging in detecting nodal disease (70%) was not much higher than CT (62.5%). Laparoscopy detected peritoneal metastases in 7 out of the 40 cases (17.5%) none of which were noted on CT scan, avoiding unnecessary laparotomy in these patients (Kandasami, 2012). Siow et al., (2017) have investigated and advocated the placement of a T-tube feeding jejunostomy at the same laparoscopy staging procedure.

#### *Outcome*

In his series 70 patients with GCa undergoing resection with curative intent, Durairaj (2012) noted the mean size of tumour was 59.6mm and 28.6% had surgical margins involved. No patients underwent neoadjuvant therapy but 24(34%) had adjuvant chemotherapy including 4 with concurrent radiotherapy. There were 16 patients with post-operative complications and 5 post-operative deaths. The overall survival was 71% at 1 year and 46% at 3 years. Tumour size and location, Lauren's intestinal type and differentiation of tumour, surgical margins, lymphovascular invasion and stage of cancer were the tumour factors associated with survival.

#### *Section 2: Relevance of Findings for clinical practice*

It is heartening to note that the burden of GCA is declining. Nevertheless, it still remains a major cause of morbidity and mortality in Malaysia. With its high Mortality to Incidence rate, several hundred Malaysians are estimated to die from GCA each year. The effort that needs to be made to improve survival for those who will get the disease is to achieve early detection. In this regard, open access upper GI endoscopy among those identified with high risk using a scoring system should be more widely applied, especially in areas where the incidence of GCA appears to be higher, such as the states of Sabah, Sarawak, Penang, Johore and Negeri Sembilan.

The eradication of *H. pylori*, avoidance of smoking, pickled vegetables and salted/smoked foods which have already been responsible for a declining incidence of GCA should not be overlooked.

#### *Section 3: Future Research Direction*

We have to take note and manage the reality that most of our patients will continue to present with late disease. In this regard determining the most appropriate chemotherapy with or without radiotherapy in the face of our resources is most appropriate for palliation should be investigated. Feeding regimes, supportive care and other ancillary services that best meet the needs of patients in their different settings need to be determined. As treatment strategies become more specific to disease stage, the training of surgical and supportive staff to meet such needs should also be addressed. How best to position tertiary hospitals to cater for our population in Malaysia also warrants study.

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