



**PROPHYLACTIC TOTAL GASTRECTOMY (PTG) FOR  
HEREDITARY DIFFUSE GASTRIC CANCER (HDGC):  
CASE REPORT OF A GERMAN FAMILY- TREATMENT OPTION,  
RISKS AND COMPLICATIONS**

**Khalid Al-Shareef\***

Department of Surgery, Rotkreuzklinikum München, Academic Teaching Hospital, of the Technical University of Munich, Germany.

Corresponding Author:- **Khalid Al-Shareef**  
E-mail: [drkhash93@hotmail.com](mailto:drkhash93@hotmail.com)

<p><b>Article Info</b> <i>Received 15/02/2015</i> <i>Revised 27/02/2015</i> <i>Accepted 07/03/2015</i></p> <p><b>Key words:</b> Prophylactic total gastrectomy, Hereditary diffuse gastric cancer and Curative surgery.</p>	<p><b>ABSTRACT</b> Hereditary diffuse gastric cancer (HDGC) is a familial cancer syndrome specifically associated with germline mutations in the gene CDH1 located at 16q22.1, which encodes the cell–cell adhesion molecule, E-cadherin. Diagnosis is often difficult, as there is currently no good screening test for DGC, especially endoscopy. , it is nowadays commonly recommended, that prophylactic total gastrectomy (PTG) is the standard management of choice for germline E-cadherin gene mutation carriers. Four sisters aged between 54 and 58 years presented in our outpatients department with the genetic determined CDH1 gene mutation for further consultation. The genetic analysis was performed because their mother died at the age of 77 from gastric cancer, and their brother had already died from gastric cancer. Recommendations were prophylactic gastrectomy and all patients should undergo investigation for lobular breast cancer (LBC) (Mamogram MRI,U\S, tumor marker CA15.3) and a Colonoscopy was recommended every 3-5 years from 40 years old age. Pre-operatively, no contraindications for the operations or evidences of other tumor localization so, patients were scheduled for the operations. Post-operatively, patients were discharged in good condition and histopathology resected stomach with regional lymph nodes of small and large were Tumor-free for all patients. Conclusively, hereditary gastric cancer is a rare disease. A reliable method for the detection of early stages or precursors of gastric cancer is not yet available. Curative surgery (PTG) can be performed at an early stage with a low rate of serious complications.</p>
---	---

**INTRODUCTION**

Hereditary diffuse gastric cancer (HDGC) is a familial cancer syndrome specifically associated with germline mutations in the gene CDH1 located at 16q22.1, which encodes the cell–cell adhesion molecule, E-cadherin [1]. HDGC is characterized by autosomal dominance and high penetrance and a high cumulative risk for advanced gastric cancer [2]. Mainly appearing as a poorly differentiated adenocarcinoma that infiltrates the stomach wall in most cases causing thickening of the wall (linitis plastica) without forming a distinct tumor masses [3].The

life time risk of diffuse gastric cancer (DGC) of 60–80%, with a mean age of onset of 37 years. [4] As in most hereditary cancer syndromes, multiple organ sites may be commonly affected by cancer, in HDGC women have a 39%-52% risk for lobular breast cancer (LBC) as well [5, 6]. In general, a lack of shared genetic risks for most breast and GI cancers was suggested through a recent study of 13,023 genes in 11 breast and 11 colon cancer cell lines in which the only commonly mutated gene between these two cancer types is p53 [7]. This likely reflects underlying



differences in the biology of these diseases, however also highlights the unique nature of germline mutations in the CDH1 gene which are strongly associated with specific histologically defined subtypes of breast and GI cancer, namely LBC and DGC which are both part of the HDGC syndrome [8].

Indications for inherited gastric cancer are: (a) a young age at diagnosis, (b) familial clustering of gastric cancer, and (c) gastric cancer and the presence of a second primary cancer in the same patient. In families with clustering of gastric cancer cases, the diffuse type is the most frequent, but not the only, presenting histological type. Familial occurrence of intestinal gastric cancer is rare, but several cases have been reported [9–11]. Hereditary DGC (HDGC) is characterized clinically by the presence of two or more documented cases of diffuse gastric cancer in first- or second-degree relatives with at least one case diagnosed prior to the age 50 years OR three or more documented cases of diffuse gastric cancer in first- or second-degree relatives, regardless of age of onset [12].

Diagnosis is often difficult, as there is currently no good screening test for DGC, especially endoscopy has no a low sensitivity. The disease starts in the mucosal layer, below the preserved surface epithelium, and only becomes visible when infiltrating the mucosal layer when disease is already progressing. The efficacy of endoscopic surveillance by current methods is largely ineffective [13]. Genetic disposition/determination can be detected in 100% of those patients. Therefore in case of the above named risk factors a genetic examination should be performed.

As described above the genetic mutation of the CDH1 gene has a 80% risk of occurring gastric cancer. Many case series about treatment option for those patients have been published in the recent years. Hebbard *et al* retrospectively studied consecutive patients undergoing PTG for HDGC. All patients were confirmed to have a truncating mutation of the CDH1 gene. Twenty-three patients underwent. Major complications were found in 4/23 patients (17%), with no mortality. Two of 23 patients (9%) had positive mucosal biopsies on preoperative EGD. Twenty-two of 23 patients (96%) had evidence of diffuse/signet-ring carcinoma on final standardized pathological evaluation. Therefore, 21/23 (91%) were not picked up by preoperative EGD screening [14]. Mastoraki *et al* evaluated the results of surgical treatment for HDGC with special reference to the extent of its histological spread and to analyze the recent literature in order to provide an update on the current concepts of prophylactic gastrectomy for disease prevention. They concluded that prophylactic gastrectomy has provided many members of affected families with relief from GC with minimal implications [15].

Based on that, it is nowadays commonly recommended, that prophylactic total gastrectomy (PTG) is the standard management of choice for germline E-cadherin gene mutation carriers. In our clinic a family with a high penetrance of the CDH1 gene mutation presented

for further treatment options. We now describe our approach, including risks and complications resulting from the treatment.

### Case report

Four sisters aged between 54 and 58 years presented at our outpatients department with the genetic determined CDH1 gene mutation for further consultation. The genetic analysis was performed because their mother died at the age of 77 from gastric cancer, and their brother had already died from gastric cancer. The further family history revealed at least 6 in the mother family having died/suffering from gastric cancer. Their mother had four half-siblings, two sisters and two brothers, a one sister died of stomach cancer and another is suffering from Parkinson's disease. Their brother died at the age of 32 from a stomach carcinoma, another died of tumor disease, the half-brother of their mother also died of stomach cancer. Similarly, the son of their brother, the brother's daughter was diagnosed with a gastric carcinoma. No cancer history was detected in their father and his family (Figure 2)

In the family, a genetic analysis was performed in a humangenetic center in Munich. The molecular genetic analysis revealed the pathogenic mutation c.1746\_1747dupG;p (Leu583Alafs\*) in six sisters. Four sisters were positive and two were negative. The cases were extensively discussed in our interdisciplinary tumor conference of the red cross Hospital in Munich. The interdisciplinary board according to the named literature recommended prophylactic gastrectomy. These recommendations and further treatment options and risks were discussed also broadly with the family.

Further recommendations were prophylactic gastrectomy and all patients should undergo investigation for lobular breast cancer (LBC) (Mamogram MRI,U\S, tumor marker CA15.3) and a Colonoscopy was recommended every 3-5 years from 40 years old age. After performing the preoperative diagnosis, no contraindications for the operations or evidences of other tumor localization, so patients were scheduled for the operations.

Here we describe intra-operative findings and postoperative course of the 4 patients. One patient was nauseated but no pain, no vomiting, on examination there was mild epigastric tender, laboratory investigation was normal, CT scan with contrast done there was no leak only collection treated by CT guided draining, and doing well discharge in good condition histopathology resected stomach with regional lymph nodes of small and large was Tumor-free for all patients.

### DISCUSSION AND CONCLUSION

Gastric cancer (GC) is one of the most frequent cancers in the world. Being the fourth most common malignancy and the second leading cause of cancer associated death worldwide [16]. The majority of cases are



sporadic and familial clustering is observed in about 10% of the patients and 3% show autosomal dominance and high penetrance [17]. Hereditary diffuse gastric cancer (HDGC) is an autosomal-dominant, inherited cancer syndrome in which affected individuals develop diffuse-type gastric cancer at a young age. It is associated with truncating mutation of the E-cadherin gene, named CDH1.

Because of a lack of specific signs or due to its sometime quiet presentation, this condition is frequently diagnosed only at an advanced stage [18]. Histologically, GC has been classified by Lauren as either diffuse or intestinal. The intestinal type pathology is linked to environmental factors and advanced age, whereas the diffuse type occurs in younger patients and is related to multifocal signet ring cell infiltrates. Overall rates of gastric cancer have declined significantly over the last 50 years, this is partially caused by the decrease of *H. pylori* prevalence. The relationship between *H. pylori* and the diffuse type of gastric cancer is less clear. For this type of gastric cancer, no other exogenic risk factors are known and its incidence has not decreased which suggests that genetic factors play a more important role in diffuse gastric cancer [19]. All the gastric cancers with CDH1 mutations have shown invasive, poorly differentiated, DGC and display signet ring cells. As the neoplasm is relatively rare, a limited number of tumor samples are available for study. (HDGC) was initially described in three Maori families from New Zealand and is characterized as an autosomal dominant cancer susceptibility syndrome largely attributable to germline mutations and deletions in the gene encoding E-cadherin, CDH1 [20]. However, it is known that CDH1 acts as a tumor suppressor gene, with mutation of CDH1 and loss of functional E-cadherin leading to tumorigenesis [21]. Loss of E-cadherin is also observed in sporadic cancers, including LBC, ovarian cancer, endometrial cancer and colorectal tumour [22]. Genetic testing is now commercially available, and more than 70 distinct mutations have been recognized across diverse ethnic backgrounds to date, CDH1 is the only gene implicated in HDGC. referral to genetics testing currently is recommended for:

Families with two or more cases of DGC, with at least one case of DGC diagnosed before the age of 50 years;

- Families with three or more cases of DGC, diagnosed at any age;
- Isolated individuals diagnosed with DGC before the age of 35 years;
- Isolated individuals with personal history of both DGC and LBC;
- Families with one member with DGC and another with either LBC or signet-ring cell colon cancer.
- Genetic testing for CDH1 mutations is also recommended for families with multiple cases of LBC.
- Isolated patients with pathologic features strongly suggestive of HDGC should also be tested [23].

Although it has been proposed that individuals carrying a CDH1 cancer predisposing mutation should

undergo routine surveillance for GC, endoscopic diagnosis may prove difficult as early foci of HDGC are typically subtle and underlie normal mucosa [24]. Chromoendoscopy permits direct inspection and biopsy of suspicious areas despite the fact that DGC tend to spread in the submucosa rather than appear as exophytic mass [25]. Major difficulties include the prompt identification of submucosal lesions as well as sampling bias in amacroscopically normal gastric mucosa.

Like in other familial cancer syndromes, genetic counseling should take place before testing. A team that includes a geneticist, gastroenterologist, surgeon and oncologist should discuss the possible outcomes of testing and the management options associated with each.

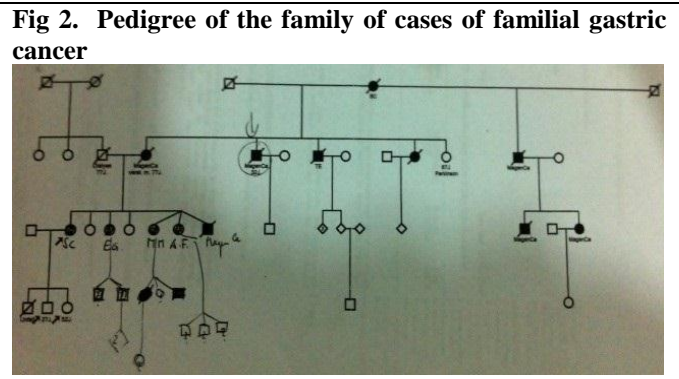
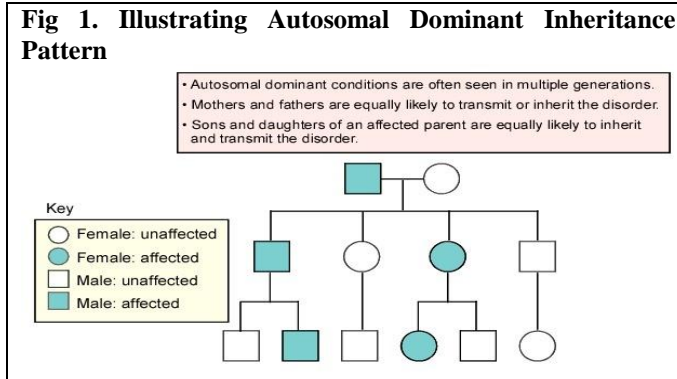
Despite its clear genetic origin, optimal management of HDGC family members has been controversial. Early genetic screening is mandatory, with prompt intervention for affected individuals [26]. Because of high cancer penetrance, poor outcomes, prophylactic total gastrectomy should be recommended in each case of asymptomatic CDH1 mutation carrier who elects to eliminate the risk of developing lethal GC. Recently GC has emerged as the one in which therapeutic intervention at the time of diagnosis in a symptomatic patient is still accompanied by the worst and nearly universally fatal outcome. In published series of CDH1 mutation carriers who underwent prophylactic gastrectomy, nearly all specimens contained multiple foci of diffuse signet ring cell cancer. The pathology of the stomachs of 6 asymptomatic family members with an inherited CDH1 mutation who underwent prophylactic gastrectomy. Foci of DGC have been observed on final pathology even in patients with extensive negative preoperative screening, including high-resolution CT, PET scans, chromoendoscopy-guided biopsies, and endoscopic ultrasonography [27] in Canada, there was a retrospective study for 23 patients undergoing PTG for HDGC. Two of 23 patients (9%) had positive mucosal biopsies on preoperative EGD. Therefore, 21/23 (91%) were not picked up by preoperative EGD screening. Twenty-two of 23 patients (96%) had evidence of diffuse/signet-ring carcinoma on final standardized pathological evaluation. DGC identified in asymptomatic CDH1 carriers typically is in an early stage and can be resected completely by prophylactic gastrectomy, and surgery can be considered curative [28]. The entire stomach must be removed, because HDGC arising in the residual stomach after subtotal gastrectomy has been reported. The distal margin should be at least 1.0 cm below the pyloric region to ensure resection through duodenal mucosa. Before performing the reconstruction, a frozen section procedure of the proximal margin is warranted to confirm that no gastric cardia mucosa is left behind and allowing direct re resection. because any residual gastric mucosa may be at risk for present or subsequent (pre)malignant lesions [29]. If no invasive cancer is diagnosed preoperatively, an extensive lymphadenectomy with higher risk of complications is



considered to be unnecessary as the metastatic risk of intramucosal carcinomas is exceedingly low [30].

Apart from complications associated with all elective GI surgical resections, such as bleeding, infection, and anaesthetic misadventures, the most significant complication anastomosis leak. Randomised controlled trials depicted that the incidence of an anastomotic leak, stenosis, morbidity and length of hospitalisation are not statistically different when a stapled versus a hand-sewn anastomosis is performed [31]. Overall mortality in 14 controlled randomised trials of gastric pouch reconstruction after total gastrectomy less than 4% [32]. Other mechanical or metabolic consequences of the operation include decrease in vitamin B12 and protein

absorption, bacterial overgrowth due to loss of parietal and chief cells of the stomach, reflux, dumping and weight loss. to overcome these problems large number of reconstructive procedures warranted to establish intestinal continuity after PTG. many technical variations for interposition have been reported and none appear more prevalent than the traditional Roux-en-Y esophago-jejuno-stomy with pouch in eliminating the above mentioned quality of life issues [33]. Laparoscopic total gastrectomy with Roux-en-Y reconstruction has been initiated recently and can fulfill this requirement and, given the improved post-operative recovery and decreased morbidity, appears well suited for the asymptomatic, cancer susceptible patients detected in HDGC families.



**Table 1. Description of intra-operative findings and postoperative course of the four patients**

Parameters	female XX years	female XX years	FemaleXX Years	female XX years
Operation time	3-5 hours	3-5 hours	3-5 hours	3-5 hours
Intra-operative Complications	non	non	non	non
Blood loss	nil	nil	nil	nil
drainage	+	+	+	+
Post-operative Course	good	good	good	good
Complications	non	non	non	Epigastric collection treated conservatively
Hospital stay	9-11	9-11	9-11	9-16
Histological findings	Negative	Negative	Negative	Negative

However, only surgical teams experienced in advanced laparoscopy should attempt this procedure. To our knowledge there are no previous reports of Deutsche families with HDGC. All patients were admitted to the

hospital one day before surgery and underwent PTG (D1: Removal of the entire stomach, complete omentectomy, and all N1 lymph nodes (safe standard). Proximal and distal gastric mucosal margins were examined intra



operatively to ensure complete removal of all gastric mucosa. These results were confirmed postoperatively by pathologist. (Figure 3) Reconstruction by Longmire's with a pouch because prospective randomized trials show a significantly better quality of life, a higher body weight and a better glucose regulation in patients with a curative operation and good life expectancy, if the duodenal passage is preserved also jejunal pouch offers a better reservoir, less reflux and a better nutritional passage [34]. Postoperative all patients treated by fast track protocol, length of stay in hospital (range 9–12 days), all discharged in good health status.

Conclusively, hereditary gastric cancer is a rare disease. A reliable method for the detection of early stages

or precursors of gastric cancer is not yet available. For these reasons, gastric surveillance in high risk families should be performed in specialized centers and preferably within a research setting. The provided criteria for referral to genetics services, for diagnostic classification, for DNA analyses and for surveillance may aid in optimizing medical care for individuals at high risk for developing gastric cancer. Treatment strategy represents the culmination of a successful collaboration between molecular biologists, geneticists, oncologists, gastroenterologists, and surgeons. A previously lethal disease is now detected by molecular techniques, allowing curative surgery at an early stage; PTG can be performed with a low rate of serious complications.

## REFERENCES

1. Guilford PJ, Hopkins JB, Grady WM, Markowitz SD, Willis J, Lynch H *et al.* (1999). E-cadherin germline mutations define an inherited cancer syndrome dominated by diffuse gastric cancer. *Hum. Mutat*, 14(3), 249–255.
2. Caldas C, Carneiro F, Lynch HT, Yokota J, Wiesner GL, Powell SM *et al.* (1999). Familial gastric cancer: overview and guidelines for management. *J Med Genet*, 36, 873–880.
3. Barber ME, Save V, Carneiro F, Dwerryhouse S, Lao-Sirieix P, Hardwick RH *et al.*, (2008). Histopathological and molecular analysis of gastrectomy specimens from hereditary diffuse gastric cancer patients has implications for endoscopic surveillance of individuals at risk. *J Pathol*, 216, 286–294.
4. Hebbard PC, Macmillan A, Huntsman D, Kaurah P, Carneiro F, Wen X *et al.* (2009). Prophylactic total gastrectomy (PTG) for hereditary diffuse gastric cancer (HDGC): the Newfoundland experience with 23 patients. *Ann Surg Oncol*, 16(7), 1890–1895.
5. Kaurah P, MacMillan A., Boyd N, Senz J, De Luca A, Chun N *et al.*, (2007). Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. *JAMA*, 297, 2360–2372.
6. Pharoah PD, Guilford P, Caldas C. (2001). International Gastric Cancer Linkage Consortium. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology*, 121, 1348–1353.
7. Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD *et al.*, (2006). The consensus coding sequences of human breast and colorectal cancers. *Science*, 311, 268–274.
8. Kasmintan A. Schrader, Serena Masciari and David G. (2008). Huntsman Hereditary diffuse gastric cancer: association with lobular breast cancer. *Fam cancer*, 7(1):73-82
9. Gonzalez CA, Sala N, Capella G. (2002). Genetic susceptibility and gastric cancer risk. *Int J Cancer*, 91, 249–260.
10. Hemminki K, Li X, Czene K. (2004). Familial risk of cancer: data for clinical counseling and cancer genetics. *Int J Cancer*, 94, 109–114.
11. Lynch HT, Grady W, Suriano G, Huntsman D. (2005). Gastric cancer: new genetic developments. *J Surg Oncol*, 90, 114–133.
12. Fitzgerald RC, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V *et al.*, (2010). Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet*, 47(7), 436–444.
13. Newman EA, Mulholland MW. (2006). Prophylactic gastrectomy for hereditary diffuse gastric cancer syndrome. *Journal of the American College of Surgeons*, 202(4), 612–617.
14. Hebbard PC, MacMillan A, Huntsman D, Kaurah B, Carneiro F, Wen X *et al.*, (2009). Prophylactic total gastrectomy (PTG) for hereditary diffuse gastric cancer (HDGC): The Newfoundland experience with 23 Patients. *Ann Surg Oncol*, 16, 1890–1895.
15. Mastoraki A, Danias N, Arkadopoulos N, Sakorafas G, Vasiliou P. (2011). Prophylactic total gastrectomy for hereditary diffuse gastric cancer. Review of the literature. *Vasilios Smyrniotis Surgical Oncology*, 20, 223–226.
16. Cisco RM, Ford JM, Norton JA. (2008). Hereditary diffuse gastric cancer: implications of genetic testing for screening and prophylactic surgery. *Cancer*, 113(7), 1850–1856.
17. Pandalai PK, Lauwers GY, Chung DC, Patel D, Yoon SS. (2011). Prophylactic total gastrectomy for individuals with germline CDH1 mutation. *Surgery*, 149(3), 347–355.
18. Ziogas D, Roukos DH. (2009). CDH1 testing: can it predict the prophylactic or therapeutic nature of total gastrectomy in hereditary diffuse gastric cancer? *Ann Surg Oncol*, 16(10), 2678–2681.
19. Kluij I, Sijmons RH, Hoogerbrugge N, Plukker JT, de Jong D, van Krieken JH. (2012). Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance. *Fam Cancer*, 11(3), 363–369.



20. Guilford PI, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P *et al.*, (1998). E-cadherin germline mutations in familial gastric cancer. *Nature*, 392(6674), 402-405.
21. Norton JA, Ham CM, Van Dam J, Jeffrey RB, Longacre TA, Huntsman DG *et al.*, (2007). CDH1 truncating mutations in the E-cadherin gene: an indication for total gastrectomy to treat hereditary diffuse gastric cancer. *Ann Surg*, 245(6), 873-879.
22. Cisco RM, Norton JA. (2008). Hereditary diffuse gastric cancer: surgery, surveillance and unanswered questions. *Future Oncol*, 4(4), 553-559.
23. Huntsman DG, Carneiro F, Lewis FR, MacLeod PM, Hayashi A, Monaghan KG. (2001). Early gastric cancer in young, asymptomatic carriers of germ-line E-cadherin mutations. *N Engl J Med*, 344(25), 1904-1909.
24. Fitzgerald RC, Caldas C. (2004). Clinical implications of E-cadherin associated hereditary diffuse gastric cancer. *Gut*, 53(6), 775-778.
25. Fennerty MB. (1999). Tissue staining (chromoscopy) of the gastrointestinal tract. *Can J Gastroenterol*, 13(5), 423-429.
26. Lynch HT. (2001). Family information service and hereditary cancer. *Cancer*, 91, 625-628.
27. Cisco RM, Ford JM, Norton JA. (2008). Hereditary diffuse gastric cancer: implications of genetic testing for screening and prophylactic surgery. *Cancer*, 113(7), 1850-1856.
28. Hebbard PC1, Macmillan A, Huntsman D, Kaurah P, Carneiro F, Wen X *et al.*, (2009). Prophylactic total gastrectomy (PTG) for hereditary diffuse gastric cancer (HDGC): the Newfoundland experience with 23 patients. *Ann Surg Oncol*, 16(7), 1890-1895.
29. Kluijdt I, Siemerink EJ, Ausems MG, van Os TA, de Jong D, Simões-Correia J *et al.* (2012). CDH1 hereditary diffuse gastric cancer syndrome: clinical variations and implications for counseling. *Int J Cancer*, 131(2), 367-76.
30. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJH. (2011). Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol*, 11, 439-449.
31. Lynch HT1, Grady W, Suriano G, Huntsman D. (2005). Gastric cancer: new genetic developments. *J Surg Onco*, 90(3), 114-33.
32. Lehnert T, Buhl K. (2004). Techniques of reconstruction after total gastrectomy for cancer. *Br J Surg*, 91, 528-539.
33. Bozzetti F1, Bonfanti G, Castellani R, Maffioli L, Rubino A, Diazzi G *et al.*, (1996). Comparing reconstruction with Roux-en-Y to a pouch following total gastrectomy. *J Am Coll Surg*, 183(3), 243-248.
34. <http://www.ncbi.nlm.nih.gov/pubmed/10378365>"Zeitschrift für Gastroenterologie.

