

## Gastric cancer: Where is the place for the surgeon, the oncologist and the endoscopist today?

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Received: March 28, 2010 Revised: December 28, 2010

Accepted: January 4, 2011

Published online: January 15, 2011

### Abstract

Gastric cancer remains a major health issue and a leading cause of death worldwide. While the incidence is decreasing in western countries, there has been a shift to more proximal cancers of the diffuse type, which are usually more aggressive and associated with a worse prognosis. Radical surgery still offers the only chance of long term survival, but surgery has reached a plateau of effectiveness and more aggressive approaches like "ultraradical" lymphadenectomy have not improved prognosis. There are three options to improve the situation: Earlier detection, neoadjuvant chemotherapy and adjuvant therapy. Whilst systematic gastroscopic screening makes sense in countries with a high incidence of gastric cancer, in other regions targeted investigation of risk groups including first-degree relatives of cancer patients, patients with a chronic corpus-dominant gastritis or with defined genetic abnormalities may help to detect cancer at an earlier stage. Neoadjuvant chemotherapy has meanwhile proved to significantly improve the prognosis not only in patients with a locally advanced cancer who cannot be resected for cure but also in those who are potentially amenable to curative resection. In the largest randomised study so far reported, perioperative chemotherapy raised overall survival after 5 years from 23% to 36%. The role of adjuvant chemotherapy has been discussed for over 30 years. Meta-analyses

demonstrate a small but significant effect which, however, seems to be restricted to Asian patients. In a large US-study, adjuvant radiochemotherapy appeared to significantly improve outcomes. However, less than 50% of the study patients underwent a systematic lymphadenectomy and so the results of the therapy group were not better to those of "only resected" patients in two large European studies. Thus, the indication of adjuvant (radio-)chemotherapy in gastric cancer currently remains uncertain. Endoscopists have found a therapeutic role through endoscopic resection of early cancers, introduced mainly by Japanese authors. With the development of high resolution endoscopy, endosonography and adequate equipment, the endoscopic curative resection of T1a-tumors (restricted to the mucosal layer) has been established.

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**Key words:** Gastric cancer; Surgeon; Oncologist; Endoscopist

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Menges M. Gastric cancer: Where is the place for the surgeon, the oncologist and the endoscopist today? *World J Gastrointest Oncol* 2011; 3(1): 10-13 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v3/i1/10.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v3.i1.10>

Gastric cancer remains a major health issue and a leading cause of death worldwide. While we observe a steady decrease in the United States and Europe, the incidence of gastric cancer remains high in Central and South America and is highest in countries of the Far East including Japan, Korea and China where up to 100 cases per 100 000 inhabitants are reported<sup>[1]</sup>. Particularly in countries with a

declining incidence, there is a shift from distal to proximal gastric cancers and adenocarcinomas of the gastroesophageal junction, usually of the diffuse histological type<sup>[2]</sup>. The incidence of adenocarcinomas of the distal esophagus and the esophagogastric junction is, along with that of hepatocellular carcinoma, increasing at a faster pace than that of any other malignancy in western countries. These proximal tumors tend to present at a more advanced stage, with a more aggressive histology and are associated with a worse prognosis<sup>[3-7]</sup>. Nevertheless, they are locally treated in the same way and classified as “gastric cancer” in ongoing studies, as it is done in this editorial.

Radical surgery still offers the only chance of cure for gastric cancers invading the muscular layer ( $> T1$ ). Nonetheless only half of patients qualify for that option at the time of diagnosis and many of those who have been resected for cure will face recurrent disease. Despite continuous efforts in the field, the results of surgery have reached a plateau of effectiveness. Even with extended surgery including systematic lymphadenectomy, only about half of patients achieve a microscopically tumor-free resection. In the German Gastric Cancer Study which enrolled 1999 patients, the R-0-resection rate was only 41.1% in UICC stage III<sup>[8]</sup>. “Ultraradical” (Extended) lymphadenectomy of more than the D2-compartment resulted in more R-0-resections, but also had a significantly higher perioperative morbidity and mortality<sup>[9,10]</sup>.

So, how can this dilemma be addressed? In my opinion there are three options: (1) Earlier detection; (2) neoadjuvant therapy; and (3) postoperative adjuvant therapy.

First of all, disease should be detected earlier. At least in the western countries, we still face the problem that about two thirds of patients are being diagnosed in an advanced stage (UICC III and IV), where a systemic spread of tumor cells has to be anticipated<sup>[11,12]</sup>. In countries like Japan, systematic gastroscopic mass screenings of the whole workforce of companies have raised the detection rate of early cancers to 50% of all detected cancers<sup>[13]</sup>. Defined risk groups include first-grade relatives of gastric cancer patients and individuals with a chronic corpus-dominant *Helicobacter pylori*-associated gastritis, especially those with intestinal metaplasia and atrophy. In future, defined genetic abnormalities (E-cadherin-mutations<sup>[14]</sup>, patients with a HNPCC-syndrome) may also help to detect gastric cancer earlier in countries with a lower incidence.

At the same time, endoscopists have to be trained to be even more attentive and sensitive to the smallest lesions. Fortunately, the recent developments of HDTV-capable endoscopes and other technical developments (narrow band imaging, endo-microscopy, staining) substantially contribute to a better detection of early neoplasms.

Secondly, we already know that outcome can be improved by neoadjuvant systemic therapy. In principle, pre- and a post-operative as well as a combined approach are possible. Preoperative-neoadjuvant-therapy aims at the “downsizing” and possibly even “downstaging” of locally

advanced tumors, which may render the tumor resectable (R-0). Moreover, the systemic chemotherapy will diminish tumor cells which have already spread but are not detectable at the time of diagnosis. Since 1989, there have been seven phase-II-studies on 289 patients who were not amenable to curative resection (UICC stages IVb and IV). Tumor stage was mostly defined by surgical staging during laparotomy. After neoadjuvant chemotherapy an average R-0-resection rate of about 40% (18%-52%) was reached and the overall survival was significantly raised in those who underwent R0 resection (overview in<sup>[15]</sup>). Understandably, there are no phase-IV-studies in non-resectable patients as controls cannot be justified from an ethical point of view. However, the concept has proved to be very useful even in patients with potentially curable disease. Two recent large phase-IV-studies have demonstrated a substantial benefit of neoadjuvant chemotherapy. In patients with potentially R-0-resectable gastric cancers (mainly UICC stages II b and IVa) neoadjuvant treatment resulted in an overall increase in R-0-resection rate, disease-free and overall survival. In the MAGIC-trial, which enrolled 503 patients (74% with gastric cancer), the 5-year-survival rate of the chemotherapy plus surgery group was 36% as compared to 23% in the “surgery only” group<sup>[16]</sup>. Whether the scheduled postoperative chemotherapy (three cycles of ECF) played a major role has to be questioned since only 40% of patients actually received it. Moreover, a simpler chemotherapy regime, such as 5-Fluorouracil combined with Cis-Platinum, seems to lead to results equivalent to the ECF-protocol<sup>[17]</sup>.

Thirdly, surgical results might be improved by postoperative, adjuvant therapy. This has been a subject of debate for decades with over 800 publications since the 1970s. Until the late 1990s, it was widely accepted that adjuvant chemotherapy has no role in gastric cancer patients. Opinion has slightly changed since. Four meta-analyses since 1999<sup>[18-21]</sup> all demonstrated a small but significant benefit in contrast to the first meta-analysis<sup>[22]</sup>. In their meta-analysis on 21 randomized studies, Janunger and colleagues pointed out that the survival benefit of adjuvant chemotherapy is restricted to studies on Asian patients and further large well designed multicenter European studies enrolling only caucasian patients did again not show a significant benefit<sup>[23-25]</sup>. Whether this is mainly due to the different agents used (in Japan for instance fluoropyrimidine derivatives like S-1 and Uracil/Tegafur) or to genetically determined differences in response to therapy remains to be determined.

Postoperative radiochemotherapy on a large scale came into the debate with the US intergroup study of MacDonald and colleagues at the beginning of this decade<sup>[26]</sup>. The authors demonstrated a significant superiority of postoperative radiochemotherapy over surgery alone in terms of time to progression and overall survival. However, this study had several weak points, the most important of which is the fact that less than 50% of the patients received a systematic lymphadenectomy. The results of the chemotherapy arm were similar to those after systematic lymphadenectomy alone in both of the large European

surgical studies<sup>[27,28]</sup>. Thus, proof of the benefits of adjuvant radiochemotherapy in patients having undergone systematic lymphadenectomy remains to be established.

Where is the place for the endoscopist?

Endoscopic resection of early tumors of the stomach has a long tradition in countries like Japan and Korea. However, this did not spread worldwide until the development of endosonography which enabled the endoscopist to delineate the different layers of the gastric wall curative endoscopic resection. Until recent years there was a consensus that well differentiated tumors that are restricted to the mucosal layer and extend over less than 20 mm qualify for an endoscopic resection. With the development of endoscopic submucosal dissection, propagated by Japanese authors, together with "high-definition" endosonography that allows for differentiation of the mucosal from the submucosal layer, the border of a reasonable (and successful) endoscopic resection has been shifted to tumors invading the first submucosal layer and to any horizontal extension. Furthermore, as a result of interdisciplinary efforts involving visceral surgery and gastroenterology, a combined endoscopic and (laparoscopic) surgical approach, may in future make even more deeply infiltrating tumors curatively respectable, thereby reducing gastrectomy.

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S- Editor Wang JL L- Editor Hughes D E- Editor Ma WH