Controversies and Challenging Therapeutic Modalities in Gastric Cancer

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Abstract Gastric cancer is still the fourth common neoplasm worldwide. Gastric ulcers, adenomatous polyps, and intestinal metaplasia have been associated with an increased relative risk. Tissue diagnosis and anatomic localization of the primary tumor are best obtained by upper gastrointestinal endoscopy. Despite new screening techniques peritoneal tumor spread and occult liver and lymph node metastases are only detected intra-operatively. Therapy is becoming more and more complex comprising surgical resection, investigational neoadjuvant, adjuvant or palliative chemotherapy, or supportive care. Complete surgical eradication of a tumor with resection of adjacent lymph nodes represents the best chance for long-term survival. The choice of operation depends upon the location of the tumor, the clinical stage, and the histologic type. Chemotherapy can provide symptom palliation, improve quality of life, and prolong survival in patients with advanced gastric cancer. Preoperative radiation therapy may allow for tumor downstaging and reduced probability of residual microscopic disease at surgery.

Keywords Gastric cancer · Therapeutic approach · Literature review

Introduction

According to GLOBOCAN (2002) and cancer incidence in five continents databases, gastric cancer is still the fourth common neoplasm worldwide behind cancer of lung, breast, and colon and rectum [1]. There were estimated 934,000 new cases per year in 2002 (8.6% of new cancer cases). Moreover, it is the second most common cause of death from cancer (700 deaths annually). Almost two-thirds of the cases occur in developing countries and 42% in China alone. The survival rate for stomach cancer fluctuates between 6% in sub-Saharan Africa and 52% in Japan, where, although it belongs to high risk areas, the mass screening by photofluoroscopy has been practiced since the 1960s.

Gastric ulcers, adenomatous polyps, and intestinal metaplasia have been associated with an increased risk of gastric cancer [2]. Lesions developing in patients considered to be at average risk involves an interplay of bacterial, host, and environmental facts. Dietary (nitroso compounds, high salt diet with low vegetables) and lifestyle factors (smoking and alcohol consumption) probably account for one-third–one-half of all gastric cancers. *Helicobacter pylori* (*H. pylori*) infection, especially certain genotypes (*vacA*s1-, *vacA*m1-, and *cagA*-positive) remains an important risk factor [3].

Diagnosis

Tissue diagnosis and anatomic localization of the primary gastric tumor are best obtained by upper gastrointestinal endoscopy. Although more invasive and costly, upper endoscopy is also more sensitive and specific for diagnosing a variety of gastric, esophageal, and duodenal lesions than alternative diagnostic strategies. The early use of upper

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endoscopy in patients presenting with gastrointestinal complaints may be associated with a higher rate of detection of early gastric cancer (EGC). The ability to perform biopsy during endoscopy adds to its clinical utility.

Early Gastric Cancer

The large-scale screening program in high-risk areas has led to the identification of EGC, also called superficial spreading carcinoma. As proposed by the Japanese Society of Gastroenterological Endoscopy in 1962, EGC is defined as adenocarcinoma limited to the gastric mucosa or submucosa regardless of whether regional lymph nodes are involved or not (T1Nx) [4]. This definition reflects an appreciation that EGC represents a subset of gastric neoplasms that presents a favourable prognosis compared to invasive gastric cancers that extend beyond the submucosa (T2–4Nx). Survival rates from 85% to over 90% 5 years after surgical resection of EGCs, and 77–90% at 10 years have been reported in Japan and the West.

The therapeutic approach of EGC is always gastrectomy (as it is described below). Subtotal as well as total gastrectomy is implemented depending upon the tumor location. A total gastrectomy is usually performed for lesions in the upper third of the stomach, and subtotal gastrectomy for lesions in the lower two-thirds [5]. Favourable outcomes with pylorus-preserving gastrectomy have also been reported in patients with EGC in the middle third of the stomach [6]. The role of adjuvant therapy, either with systemic chemotherapy, radiotherapy, or intraperitoneal chemotherapy, is not clearly established for EGC, especially for patients with node-negative disease.

Staging Laparoscopy in Gastric Cancer

The therapy of gastrointestinal tumors is becoming more and more complex comprising surgical resection, investigational neoadjuvant, adjuvant or palliative chemotherapy, or supportive care. The evaluation of tumor spread and exact staging are necessary for the decision of correct therapy. Despite new screening techniques, like trans-abdominal and endoscopic ultrasound (U/S), computed tomography (CT) scan, magnetic resonance imaging (MRI) and more recently positron emission tomography (PET) scan, peritoneal tumor spread and occult liver, and lymph node metastases are only detected intra-operatively in many patients [7].

Radiographically, occult metastatic disease can be identified, permitting biopsy of any suspicious lesions and avoiding unnecessary exploratory laparotomy [8]. At laparoscopy, peritoneal metastases are documented in 20–30% of Western

patients with gastric cancer with a negative CT, who would have been otherwise considered potentially resectable. Moreover, peritoneal cytology can be obtained to document a group of patients with high risk for peritoneal failure. At some institutions, patients without overt intraperitoneal metastases but positive peritoneal washings are referred for neoadjuvant therapy and then restaged to determine whether they are candidates for potentially curative surgery [9].

Surgical Treatment for Localized Disease

Complete surgical eradication of a gastric tumor with resection of adjacent lymph nodes represents the best chance for long-term survival. Since resection of the primary lesion also offers the most effective means of symptom palliation, abdominal exploration with curative intent should be undertaken unless there is unequivocal evidence of disseminated disease, a neoadjuvant approach is considered, or there are other contraindications to surgery. The choice of operation for gastric cancer depends upon the location of the tumor within the stomach, the clinical stage, and the histologic type. The major surgical considerations include the extent of luminal resection (total versus subtotal gastrectomy) and the extent of lymph node dissection.

Gastrectomy is the most widely used approach for therapy of invasive gastric cancer, although superficial cancers can sometimes be treated endoscopically. Total gastrectomy is usually performed for lesions in the proximal (upper third) of the stomach, while distal subtotal gastrectomy with resection of adjacent lymph nodes appears to be sufficient for lesions in the distal (lower two-thirds) of the stomach. However, patients with large midgastric lesions or infiltrative disease (e.g., linitis plastica) may require total gastrectomy. Recent trials show no added survival benefit for total compared to subtotal gastrectomy for patients with distal tumors [10].

One of the most controversial areas in the surgical management of gastric cancer is the optimal extent of lymph node dissection. Japanese surgeons routinely perform extended lymphadenectomy, a practice that some suggest at least partially accounts for the better survival rates in Asian compared to Western series. The term “extended lymphadenectomy” variably refers to either a D2 or a D3 lymph node dissection [10].

The draining lymph node basins for the stomach can be divided into 16 stations: stations 1–6 are perigastric, and the remaining 10 are located adjacent to major vessels, behind the pancreas, and along the aorta. A D1 lymphadenectomy refers to a limited dissection of only the perigastric lymph nodes. D2 lymphadenectomy is an extended lymph node dissection, entailing removal of nodes along the hepatic,

left gastric, celiac and splenic arteries, as well as those in the splenic hilum (stations 1–11). D3 dissection is a super-extended lymphadenectomy. The term has been used by some to describe a D2 lymphadenectomy plus the removal of nodes within the porta hepatis and periaortic regions (stations 1–16), while others use the term to denote a D2 lymphadenectomy plus periaortic nodal dissection (PAND) alone. Most Western surgeons classify disease in these regions as distant metastases and do not routinely remove nodes in these areas during a potentially curative gastrectomy [11, 12].

The arguments in favour of extended lymphadenectomy (e.g., D2 or D3 versus D1) are that removing a larger number of nodes more accurately stages disease extent and that failure to remove these nodes leaves behind disease in as many as one-third of patients, which would adversely affect survival. A consequence of more accurate staging is to minimize stage migration (the Okie phenomenon, as described by Will Rodgers). The resulting improvement in stage-specific survival may explain, in part, the better results in Asian patients. Moreover, it is a more effective and precise indicator for prognostic stratification of patients with lymph node positive gastric cancer [13].

There are two main arguments against the routine use of an extended lymphadenectomy: the higher associated morbidity and mortality (particularly if splenectomy is performed in order to achieve extended lymphadenectomy) and the lack of a survival benefit for extended lymphadenectomy in the majority of large randomized trials.

Chemotherapy

The majority of patients with esophageal or gastric cancer will require palliative treatment at some point in the course of their disease. Cytotoxic chemotherapy can provide symptom palliation, improve quality of life, and prolong survival in patients with advanced esophageal or gastric cancer.

First-Line Chemotherapy

Coincident with epidemiologic changes in histologic and anatomic distribution, the treatment of advanced gastric and esophageal cancers has converged, and the majority of patients with gastric, esophageal, or gastroesophageal junction cancers are treated similarly, regardless of histology. Despite a large number of randomized trials, there is no consensus as to the best agent or regimen. In general, combination chemotherapy regimens provide higher response rates in comparison with single agents, but this translates into only modestly longer durations of disease control and survival that are measured in weeks to a few months [14]. In randomized trials,

the epirubicin, cisplatin, infusional 5-FU (ECF) [15] and docetaxel, cisplatin, infusional 5-FU (DCF) combinations have emerged as standard regimens for first-line treatment [16–20]. A major problem with these regimens is the necessitation for central venous access and an ambulatory infusion pump. Data from the REAL-2 trial suggest that outcomes are comparable when capecitabine is substituted for infusional 5-FU, and when oxaliplatin is substituted for cisplatin in the ECF regimen. When both oxaliplatin and capecitabine are substituted in the ECF regimen, outcomes may be better than with ECF.

For these reasons, we suggest epirubicin, oxaliplatin, and capecitabine (EOX) rather than ECF or DCF for first-line treatment in most patients. However, this opinion is controversial, and others use ECF or DCF in these patients. While the use of capecitabine allows patients to avoid infusion pumps and a central venous catheter, the costs of capecitabine and oxaliplatin are significantly higher than with 5-FU and cisplatin, and toxicity is not necessarily less [21]. For elderly patients or those with a poor performance status, we suggest leucovorin-modulated 5-FU alone or single agent capecitabine. Other reasonable alternatives include single agent irinotecan, or low-dose weekly taxanes.

Despite recent advances in the treatment of disseminated disease, these patients still do poorly. The unfavourable survival raises the hypothesis of rapidly acquired pharmacological resistance through specific molecular pathways in gastric cancer. Therefore, new strategies are warranted in order to improve the median survival. These new therapies are divided into five different categories according to the pattern of acquired capabilities of the malignant cells elegantly described by Hanahan and Weinberg [22] including agents directed to interfere with the self-sufficiency in growth signals, such as epidermal growth factor receptor (EGFR) inhibitors [23]. Monoclonal antibodies (MAbs), like cetuximab and panitumumab, and the low molecular weight tyrosine kinase inhibitors (TKIs), like gefitinib are the most developed ones that have reached this clinical scenario [24]. In the same category belongs trastuzumab, a therapeutic anti-HER2 MAb. Patients with gastric cancer who are potential candidates for trastuzumab should have their tumors assayed for the presence of HER2 overexpression. We suggest the addition of trastuzumab to chemotherapy in patients with HER2-positive tumors (as defined by 3+ immunohistochemical staining or FISH positivity), as long as they do not have a contraindication to the drug. Another category comprises agents directed to inhibit the angiogenesis process like bevacizumab. This agent is a recombinant humanized anti-vascular endothelial growth factor (VEGF) MAb that is clinically being evaluated in many tumor types, like gastric cancer. Bevacizumab has demonstrated a survival advantage when added to

irinotecan-, oxaloplatin-, and 5-FU-based chemotherapy schedule in patients with gastric cancer [25, 26]. Third therapeutic alternative constitute agents directed to interfere with the limitless replicative potential, such as cell cycle inhibitors, like flavopiridol [27, 28]. This agent has been evaluated in combination with active chemotherapy drugs, like irinotecan and cisplatin in patients with advanced gastric cancer. Finally, newly investigated treatment options include agents directed to promote apoptosis, such as proteasome inhibitors, like bortezomib (PS-341) [29] and agents directed to inhibit the tissue invasion and the metastasis processes, such as matrix metalloproteinases inhibitors [30].

The high frequency with which gastric cancer spreads to the peritoneum has led several investigators to examine the utility of intraperitoneal (IP) chemotherapy for both the prevention and treatment of peritoneal carcinomatosis. These procedures are technically challenging, and expertise is limited to few centers worldwide [31–33].

Radiation Therapy

Preoperative Radiation Therapy

Preoperative radiation therapy offers theoretical advantage. Intact vasculature unperturbed by surgical manipulation may allow for better chemotherapy penetrability and greater radiosensitivity of aerated cells. Preoperative radiation delivery also allows for improved target identification and, thus, potentially smaller radiation fields, which could minimize treatment toxicity [34]. Preoperative radiation therapy may allow for tumor downstaging and reduced probability of residual microscopic disease at surgery. Finally, delivery of radiation therapy prior to surgery helps to ensure that patients receive all components of their multimodality treatment [35].

Postoperative Radiation Therapy

The impetus to evaluate chemoradiotherapy in the postoperative setting came from the demonstration of efficacy for unresectable or sub-totally resected gastric cancer [36, 37]. More recently, the Intergroup 0116 trial (INT 0116) established the role of radiation therapy in the postoperative setting for gastric cancer [38–40]. According to this trial, patients with stage IB–IV M0 adenocarcinoma of the stomach T3 and T4 with node positive disease follow adjuvant therapy including a 5-day course of daily 5-FU and leucovorin followed by 45 Gy radiation therapy delivered in 25 fractions with modified doses of 5-FU and leucovorin on the first four and last 3 days of radiation therapy. One month after completion of radiation therapy, two additional cycles of 5-FU and leucovorin were

delivered. At 3 years, statistically significant benefits in Disease Free Survival (DFS) (48% vs. 31%) and overall survival (50% vs. 41%) were noted among patients receiving adjuvant chemoradiotherapy. Given that no differences were noted in rates of distant metastatic disease, the overall survival benefit has been attributed to improvements in locoregional control, suggesting that chemotherapy is exerting its maximum effect as a radiosensitizer.

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