Perspectives in the Treatment of Incurable Gastric Cancer

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1. Introduction

Gastric cancer is the second most frequent malignancy in the Western world [1]. The prognosis remains poor despite of advances in diagnostic techniques and therapeutic management: approximately 800,000 new cases and 620,000 cancer-related deaths are reported worldwide per year [2]. More than 50% of gastric cancer patients and approximately 40% of esophageal cancer patients either die from a primary unresectable tumor or from tumor recurrence after radical treatment within five years [3]. The main reasons for this are the late onset of predominantly unspecific symptoms and the aggressive biological behavior [4]. Palliative chemotherapy, best supportive care and the interdisciplinary management of severe tumor-related complications (tumor bleeding, tumor perforation, complete obstruction, treatment-refractory pain) are well accepted treatment options whereas non-curative resections of the primary tumor as well as resection of secondary tumor lesions are controversially discussed [5]. However, there is growing evidence that non-curative tumor resections can prolong the remaining life time with acceptable perioperative morbidity [6-8]. Furthermore, the quality of life can be improved by reducing the incidence of severe tumor-related complications [9].

2. General aspects of incurable gastric cancer

Patients who do not undergo surgical or cytoreductive treatment die within three (stage 4) to six months (stage 3) [10,11].

The only option for cure is radical surgical treatment, recently more and more in combination with neoadjuvant and adjuvant chemotherapy [12,13]. With advanced tumor stage survival of resected patients dramatically declines: at UICC stage 1 the 5-year-survival rate of patients with R0 resection is 95%, whereas at stage 2 it ranges from 35% to 65%, depending on the presence of positive lymph nodes and the number of dissected lymph nodes [14,15]. In the rare cases where curative resection is achieved, the 10-year-survival rate ranges from 3% for stage 3b to 5% for stage 4 (according to UICC classification from 2002)[16]. Following the standardized treatment for locally confined gastric cancer the main determining factor for survival is the extent of lymph node involvement although the impact of extended surgical lymph node removal is still under discussion [17].

Unfortunately, the majority of patients with gastric cancer is diagnosed at an advanced stage of the disease and may not be suitable for treatment with curative intent [18]. But which
alternatives can be offered to those patients? Especially patients with an incurable stage of the disease have to face the fact that they will die from their tumor within short time. Furthermore, 50% of those patients will develop severe tumor related complications necessitating invasive endoscopic, radiological or surgical treatment [19]. There are two important aspects of individuality in incurable gastric cancer patients: the individuality of the patients and the individuality of the tumor. The decision as to whether aggressive palliative treatment should be used rather than best supportive care or no treatment at all at patients’ request depends on the personal expectation of the individual patient [20]. The response to that treatment on the other hand is crucially influenced by the molecular biology and the pathological behavior of the tumor [21,22]. Considering these circumstances, it becomes clear that the currently available tumor classification systems are limited with respect to the decision making process [3].

In fact, palliative strategies are much less standardized than curative treatment. A multitude of protocols has been introduced to improve and prolong the remaining life span of palliatively treated patients [23]. Recently first steps towards molecular-based target-specific therapy using trastuzumab and bevacizumab have been undertaken. The importance of surgery for palliative treatment is controversially discussed for more than 40 years [6,7,9,24-26]. Numerous authors reported about prolonged survival, improvement of quality of life and symptom relief and, therefore, supported palliative gastric resection [6,9,26]. Other investigators presented limited retrospective data and recommended gastric resection only in cases of otherwise not controllable complications, such as tumor bleeding or organ perforation [5,27].

Currently two basic palliative treatment strategies can be defined: a canonical palliative treatment strategy including palliative chemotherapy, best supportive care and invasive treatment for severe life-threatening tumor related complications versus cytoreductive (neoadjuvant) chemotherapy plus non-curative tumor resection.

3. Canonical palliative treatment strategy

The widely as beneficial accepted palliative chemotherapy and best supportive care is aimed to improve overall survival and to improve or at least to stabilize the quality of life [5]. Long term survival can be observed in few unusual cases but is not originally an aspired treatment outcome.

Overall, it is generally accepted that patients with incurable gastric cancer who are treated with chemotherapy live longer than those who receive best supportive care only. Several studies indicate that patients who underwent chemotherapy have longer overall survival (11 versus 4 months) and a longer time to progression (6-8 versus 2-3 months) as compared to those patients whose received best supportive care only [28].

The variety of available chemotherapy protocols that have been published during the last 30 years is very wide. Most chemotherapy protocols contain one or a combination of several of the following drugs: antimetabolites (5-Fluorouracil), platinum-containing analoga (cisplatin, oxaliplatin), topoisomerase-1-inhibitors (anthracyclins: epirubicin, doxorubicin), topoisomerase-2-inhibitors (irinothecan), tubulin depolymerisation inhibitors (taxans: paclitaxel, docetaxel) and mitomycin. All abovementioned agents are targeted to somehow disrupt the natural mechanisms of DNA synthesis or of the cell division process. Therefore, these agents manifest their effect not only on tumor cells but also on any other cells within the organism that undergo cell division to maintain the biological tissue and organ integrity.
The most frequently used agent is 5-fluorouracil and its oral analogon capecitabine. It has been described to elucidate an overall response of 20% when administered as a single agent treatment. Wagner and co-workers, compared 13 studies with a total of 1914 patients to evaluate the impact of a combination versus a single agent chemotherapy. Patients with a combination therapy had longer median survival (8.3 vs 6.7 months), longer progression free survival (5.6 vs 3.6 months) and a higher overall response rate (35% vs 18%). Based on these data, most oncologists in western countries do not treat their patients with a single-agent protocol, whereas in Japan the use of S-1 as a single-agent therapy is widely utilized. Furthermore, it was shown in this study that a three-drug combination is better than a two-drug combination in terms of survival as well as tumor response [10].

Clinical trials to study the effectiveness of the novel microtubule-dynamic-instability-inhibiting agent eribulin are currently underway.

But which patients are best suited for palliative chemotherapy? Overall, the effectiveness of chemotherapy has to be weighed against chemotherapy-related toxicities and side effects. The most important factor to predict the benefit of palliative chemotherapy is to evaluate whether the patient is generally fit for this aggressive treatment. Hepatic, renal and cardiopulmonary function should be taken into account. The toxicity increases with the number of chemotherapy agents which are administered in combination. To date, there is no evidence about preoperatively available clinical or pathohistological factors that could predict the response to chemotherapy.

A first step towards a target specific chemotherapy might be the administration of trastuzumab, an inhibitor of the Her2/Neu-receptor. Van Cutsem and co-workers published the data from the ToGA study in 2009 with the main result that patients who were positive for the Her2/Neu receptor chemotherapy plus trastuzumab had a median survival of 13.8 as compared to a median survival of 11.1 months in patients who underwent chemotherapy only. Furthermore, the study group who was treated with the combination chemotherapy showed a higher overall tumor response rate (47% versus 35%), a higher complete response (5% versus 2%) and a longer time to progression (7.1 versus 5.6 months). This treatment has been shown to be effective in patients who are at least double positive for the receptor measured by the FISH test [29]. Trastuzumab was the first molecular target agent showing a survival benefit in patients with advanced gastric cancer. The next step towards target-specific treatment might be the AVAGAST trial which investigates the benefit of the angiogenesis inhibitor bevacizumab plus chemotherapy versus chemotherapy alone [30]. Several studies investigating the survival benefit of further novel angiogenesis inhibitors, such as sorafenib, sunitinib, cediranib and axitinib are currently underway. The survival benefit of cetuximab – an inhibitor of the epidermal growth factor receptor – is currently investigated in a phase 3 trial. In summary, there is a growing selection of target specific agents that are thought to have an impact on the clinical course of advanced gastric cancer but to date only one agent (trastuzumab) has been approved for use in the clinical routine.

The second column of the canonical palliative treatment strategy is the management of severe tumor related complications. Many authors suggest that patients who develop such complications should be treated most preferably by interventional procedures, such as endoscopy or radiological intervention. Only in those cases where interventional approaches are not feasible or where interventional treatment fails and the complication either relapses or persists, patients are considered for surgical treatment. Furthermore, this surgical treatment should be limited to the most restricted possible procedure whereas larger tumor resections should be reserved for rare individual cases. In particular, palliative resections should be avoided [5,27].
The most frequently occurring complications are tumor bleeding, gastric obstruction and tumor perforation. Kang and co-workers analyzed data from 1856 patients with metastasized gastric cancer. Among these, there were 32 patients who had a tumor perforation during palliative chemotherapy. 17 patients underwent emergency surgery with a median survival of 5 months after the perforation whereas 15 patients received antibiotics only and had a median survival of 1 month after the perforation [31]. These data show that survival in patients treated by surgery was longer than that with non-surgical treatment strategies. Other studies demonstrated that patients who were treated with palliative resection had a lower perioperative mortality as compared to those who underwent simple closure of the perforation only [32].

Tumor bleeding is a frequently observed event in patients with unresectable gastric cancer. Some authors regard substitution of up to 2 units of red blood cells per week as acceptable with respect to tumor bleeding which can be treated by blood transfusion alone [33,34]. However, palliative chemotherapy administration might be limited by persistent bleeding which finally may affect overall survival. Other authors suggest treatment of those patients with short-course radiotherapy up to 30 Gy. Recently, Asakura and co-workers reported a response rate to radiotherapy of 73% [35]. The endoscopic approach provides the opportunity for active and direct hemostasis by local injection of epinephrine, clip application, fibrin application, argon plasma coagulation or stent implantation. In cases of persistent uncontrolled tumor bleeding, surgical treatment has been suggested as an last resort [27]. However, emergency surgery for tumor bleeding usually requires palliative resection and is associated with a high rate of perioperative mortality [35].

The symptoms of progressive tumor-related gastrointestinal obstruction range from dysphagia and nausea to manifest ileus. The endoscopic approach provides a multitude of procedures, such as stent implantation (or even in due course stent-in-stent implantation), argon plasma beam, laser therapy and percutaneous endoscopic assisted gastrostomy. A considerable number of patients receiving endoscopic treatment relapse with obstructive symptoms. Selected patients may undergo surgical treatment, especially those who develop manifest ileus or in cases of endoscopic treatment failure. Whereas patients with lower gastric cancer benefit from a gastrointestinal bypass with low perioperative mortality rates, patients with gastric cancer at the gastroesophageal junction usually require palliative resection associated with higher perioperative mortality rates.

In summary, severe tumor-related complications frequently occur in patients with unresectable gastric cancer. They not only require invasive treatment in the majority of cases but also affect further palliative chemotherapy and, thus, affect overall survival and quality of life.

4. Neoadjuvant chemotherapy plus non-curative surgery for incurable gastric cancer

Whereas the canonical palliative treatment strategy can be regarded as the widely used standard, the combination of chemotherapy with cytoreductive non-curative resection is still under intensive debate.

4.1 Intentions of primary non-curative resection

One intention is to reduce the overall tumor mass by removing the primary tumor with a local R0 stage and by resecting secondary tumor mass. The reduction of secondary tumor growth includes liver metastases, positive lymph nodes and peritoneal carcinosis.
Several molecular considerations make this strategy sensible. Gross tumor formations are thought to be affected in a limited way by chemotherapy agents. Furthermore, it has been demonstrated that the primary tumor produces a local environment presumably via currently not fully understood molecular pathways that creates the precondition for the nidation of circulating tumor cells which subsequently can develop into distant metastases. The second intention is to reduce the incidence of tumor related complications. In other words, the potentially complications-producing tumor is removed before these complications occur. In fact, the natural course of gastric cancer growth is associated with a considerable number of severe tumor related complications. At least 50% of all patients with non-resected advanced gastric cancer will develop such complications within the remaining life time. These complications frequently require invasive treatment by endoscopic or radiological interventions and emergency surgery in a considerable number of cases. However, emergency procedures are associated with high mortality rates. Based on a retrospective analysis, we found that by primary non-curative gastric resection the incidence of severe tumor related complications decreased as compared to that in patients who did not undergo resection (data not published).

Based on these intentions, primary non-curative resections are implemented to improve overall survival of palliative patients and to improve the quality of life within the remaining life time.

4.2 Study results on non-curative gastric resection

Gastric resections in patients with incurable gastric cancer have been reported for more than 50 years now. The intention to perform such procedures as well as the criteria dedicated to define suitable patients have changed over that relatively long period. Furthermore, the allocation of patients to curative and non-curative strategies becomes increasingly complex: a considerable number of patients with an initially unresectable stage of gastric cancer respond to neoadjuvant chemotherapy and eventually become resectable. To date and for the understanding of this chapter it is important to distinguish two different categories of gastric resections with a postoperative non-R0-result: first the so-called palliative resection, which encompassed initially a collective term for patients who were resected with curative intention but had R1- or R2-situations postoperatively, as well as for those who were primarily resected with palliative intention either due to tumor-related complications or for potential improvement of overall survival; and secondly the term “non-curative gastric resection” which includes patients who have at least one non-curative factor but nevertheless undergo primary gastric resection as a part of the multimodal concept.

Based on data of the last decades, the range of recommendations for palliative surgical treatment is wide. Some authors recommend to perform surgical treatment only in those cases where severe tumor related complications or symptoms are evident and interventional options have failed [27,36]. Other authors proposed that primary palliative resections should be performed whenever technically possible [9]. Palliative gastric resection is not a novel procedure. According to today’s benchmarks, the early beginnings of gastric surgery can be regarded as palliative procedures: the first documented gastric resections have been performed by Pean in 1879 and by Rygydier in 1880, both patients died within the perioperative period. The first successfully performed gastric resection traces back to Billroth (1881). The patient survived four months and died from local tumor recurrence. The first publication on larger series of palliative gastric resections was in 1958 by Lawrence and McNeer. Data of 1.623 patients who underwent surgery for gastric carcinoma from 1931
to 1955 were analyzed. It was demonstrated that palliative resections (141 cases) achieved remarkable symptom relief as well as it increased the survival time. Perioperative morbidity and mortality, however, were high [24].

Another frequently quoted paper was published in 1979: ReMine et al. reported about 206 patients with non-curable gastric carcinoma who underwent surgical treatment. Palliative partial gastric resection was reported in 46 cases, while gastrectomy was performed in six cases. The other patients underwent gastroenteral bypass or no surgical treatment at all. The decision to extend the procedure from gastric resection to gastrectomy was due to additional proximal tumor infiltration. Although the perioperative mortality was 0% in the gastrectomy group, further survival was disappointing: five of the six patients died within nine months. Patients with palliative gastric resection showed significantly better survival: 20% of these patients lived more than two years. According to these findings, ReMine et al. judged resection to be the superior procedure compared with gastrectomy [25].

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Median survival (months)</th>
<th>Perioperative morbidity</th>
<th>Perioperative mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. [7]</td>
<td>2010</td>
<td>n=365</td>
<td>10.5</td>
<td>14-27%</td>
<td>0.5-6%</td>
</tr>
<tr>
<td>Kunisaki et al. [8]</td>
<td>2008</td>
<td>n=164</td>
<td>9</td>
<td>15%</td>
<td>4%</td>
</tr>
<tr>
<td>Lin et al. [6]</td>
<td>2008</td>
<td>n=183</td>
<td>20</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Mizutani et al. [37]</td>
<td>2007</td>
<td>n=13</td>
<td>12</td>
<td>65%</td>
<td>0%</td>
</tr>
<tr>
<td>Onate-Ocana et al. [38]</td>
<td>2007</td>
<td>n=71</td>
<td>12.4</td>
<td>32%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Lim et al. [39]</td>
<td>2007</td>
<td>n=63</td>
<td>13</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Nazli et al. [40]</td>
<td>2007</td>
<td>n=29</td>
<td>10.4</td>
<td>35%</td>
<td>27%</td>
</tr>
<tr>
<td>Saidi et al. [41]</td>
<td>2006</td>
<td>n=24</td>
<td>16.3</td>
<td>33%</td>
<td>9%</td>
</tr>
<tr>
<td>Miner et al. [27]</td>
<td>2004</td>
<td>n=147</td>
<td>8.3</td>
<td>54%</td>
<td>6%</td>
</tr>
<tr>
<td>Medina-Fr. et al. [42]</td>
<td>2004</td>
<td>n=40</td>
<td>13</td>
<td>26%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Hartgrink et al. [26]</td>
<td>2002</td>
<td>n=156</td>
<td>8.1</td>
<td>38%</td>
<td>12%</td>
</tr>
<tr>
<td>Monson et al. [43]</td>
<td>1991</td>
<td>n=53</td>
<td>19</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Bozetti et al. [9]</td>
<td>1987</td>
<td>n=61</td>
<td>8</td>
<td>No data</td>
<td>11%</td>
</tr>
<tr>
<td>Meijer et al. [44]</td>
<td>1983</td>
<td>n=26</td>
<td>9.5</td>
<td>No data</td>
<td>8%</td>
</tr>
</tbody>
</table>

Table 1. Published data on palliative gastric resection from 1983 - 2010

Over the last 20 years, several published series of palliative gastric resections showed significant improvement in symptom control, survival and quality of life [6,9,26,37]. In addition, several cases of long term survival following combined palliative treatment have been described. However, in the majority of the published data the definition of “palliative
"intention" was not properly outlined. Frequently, curatively intended procedures with a postoperative R1-situation were included. In some publications, elective and emergency resections were not separated even though for emergency surgery there is a high rate of perioperative mortality. In several studies, the period of inclusion spans more than 20 years. An overview of the most important publications on palliative gastric resections is shown in Table 1. The median survival ranged from 8 to 20 months, whereas morbidity and mortality ranged from 12% to 65% and from 0% to 27%, respectively. In comparison, data from our hospital based on retrospectively analysed data from 48 patients with non-curable gastric cancer showed a median survival of 15 months with a morbidity of 32% and a mortality of 4% (emergency gastrectomies excluded). Furthermore, long term survival was observed in three cases.

Which patients are suitable for the non-curative gastric resection? The most pronounced benefit can be expected in cases with a limited number of tumor locations (2 tumor locations = primary tumor plus one more secondary tumor formation). Furthermore, younger patients seem to have a better survival following non-curative gastric resection. In a recently published study, Kunisaki and co-workers identified chemotherapy as an independent factor for longer survival in patients with no more than one “non-curative” factor. In our own study population, we found a significantly longer survival for younger patients (<50 years) and for those who had no more than two tumor locations, furthermore the highest benefit was achieved in those patients who underwent chemotherapy according to the ECF scheme.

Generally, at present, non-curative gastric resections should be performed preferentially in patients who can be included in a clinical trial investigating the clinical outcome of palliative surgery. Furthermore, non-curative resections should be part of a multimodal treatment strategy. The personal preferences of the individual patient should be taken into account in the decision-making process and every patient should be discussed in an interdisciplinary tumor conference.

4.3 Surgical treatment for peritoneal carcinosis

Peritoneal carcinosis from gastric cancer commonly indicates an advanced stage of the tumor disease and most frequently is associated with poor prognosis. The median survival time of patients with peritoneal carcinosis from gastric cancer is 3 months [45,46]. In comparison, for colorectal cancer it is 5 months and for ovarian cancer it is 12 – 23 months [47,48]. The degree of peritoneal involvement prior to cytoreductive resection is most frequently described by the peritoneal carcinosis index score (PCI) [49,50]. This index is a combination of peritoneal tumor size and the number and distribution of peritoneal tumors. There is a strong correlation between the PCI value and the prognosis. This has been demonstrated in patients with peritoneal carcinosis from colorectal cancer: patients with PCI up to 10 had 50% overall 5-year survival whereas for PCI 11-20, it was 20% and for PCI more than 20, there was no 5-year survival at all. The cytoreductive surgery in combination with intraperitoneal chemotherapy was first described by Sugarbaker in 1989. The surgical procedure may include parietal and visceral peritonectomy, resection of the liver capsule and the resection of adjacent organs located within the peritoneal cavity [51]. The surgical result is determined by the “completeness of cytoreduction score (CCR)” based on the macroscopic presentation to the surgeon at the end of the procedure [52]. Table 2 gives an overview on the details of PCI.
Table 2. Peritoneal carcinosis index

<table>
<thead>
<tr>
<th>Number of the region</th>
<th>Region</th>
<th>Size of the largest regional lesion</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>central</td>
<td>no lesion detectable</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>right cranial</td>
<td>lesion size smaller than 5mm</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>epigastric</td>
<td>lesion size from 5 to 50mm</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>left cranial</td>
<td>lesion size larger than 50mm</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>left side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>left caudal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>pelvic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>right caudal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>right side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>upper jejunum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>lower jejunum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>upper ileum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>lower ileum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Calculation of the PCI-score:
Every region is allocated to the score 0-3.
Then all scores are added up.
PCI can reach a maximum score of 36.

Table 3 shows the classification of the cytoreduction result according to the “completeness of cytoreduction score”.

<table>
<thead>
<tr>
<th>Size of residual tumor</th>
<th>CCR value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no residual tumor</td>
<td>0</td>
</tr>
<tr>
<td>largest residual tumor smaller than 2.5mm</td>
<td>1</td>
</tr>
<tr>
<td>largest residual tumor 2.5-25mm</td>
<td>2</td>
</tr>
<tr>
<td>largest residual tumor larger than 25mm</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 3. Classification of the cytoreduction result according to the “completeness of the cytoreduction score”

It is generally accepted that cytoreductive peritoneal resection should be performed in combination with intraperitoneal chemotherapy. Surgery only or surgery in combination with intravenous chemotherapy are not sufficient because some chemotherapy agents, such as 5-FU do not reach an appropriate concentration within the peritoneal cavity to kill cancer cells whereas other agents, such as taxans do not even cross the blood-peritoneal barrier because of their high molecular weight. For that purpose, three procedures depending on the date of administration are available: preoperative intraperitoneal plus systemic chemotherapy (NIPS), hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC) [52].

The best results from that combination therapy are achieved when the PCI is low, the CCR is 0 or 1 and there are no free intraperitoneal cancer cells. The Peritoneal Surface Malignancy Group (PSMG) defined several criteria that indicate a high probability for achieving a CCR 0 or 1 in patients with peritoneal carcinosis from colorectal cancer, these criteria are shown in Table 4.

For cytoreductive surgery for peritoneal carcinosis from gastric cancer, the PCI should be limited to a maximum score of 15.
Generally in cases of peritoneal carcinosis from gastric cancer, survival is worse than in other entities, such as ovarian cancer or colorectal cancer. For the combination of surgery
with HIPEC, overall median survival from 10 to 16 months and 5-year-survival of 7%-8% have been reported. For colorectal cancer, it was demonstrated that HIPEC has a better clinical outcome in terms of survival than EPIC [53]. Cheong and co-workers observed a median survival of 11 months following cytoreductive surgery combined with EPIC in 154 patients with very advanced gastric cancer [52].

<table>
<thead>
<tr>
<th>ECOG performance status 0-2*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>no evidence of extraabdominal tumor lesions</td>
<td></td>
</tr>
<tr>
<td>up to 3 small, resectable parenchymal liver metastases</td>
<td></td>
</tr>
<tr>
<td>no evidence of biliary obstruction</td>
<td></td>
</tr>
<tr>
<td>no evidence of ureter obstruction</td>
<td></td>
</tr>
<tr>
<td>no evidence of intestinal obstruction at more than 1 location</td>
<td></td>
</tr>
<tr>
<td>small bowel involvement: no evidence of gross disease in the mesentery with several segmental locations of partial obstruction</td>
<td></td>
</tr>
<tr>
<td>small volume disease in gastro-hepatic ligament</td>
<td></td>
</tr>
</tbody>
</table>

*ECOG: Eastern Cooperative Oncology Group

Table 4. Several criteria that indicate a high probability for achieving a CCR 0 or 1 in patients with peritoneal carcinosis from colorectal cancer, defined by the Peritoneal Surface Malignancy Group

4.4 Surgical treatment of liver metastases from gastric cancer

Generally, liver metastases from gastric cancer develop less frequently as compared to other gastrointestinal tumor entities, but in most cases they are unresectable due to general as well as hepatic non-curative factors. Whereas liver metastases develop in approximately 50% of all patients with colorectal carcinoma, the incidence of liver metastases from primary gastric cancer ranges from 5% to 9%.

Liver resection for secondary tumor growth is performed mainly in cases of colorectal liver metastases with resection rates between 20% and 30% and a 5-year survival rate of 25% to 58% [54,55]. In contrast, liver resection for hepatic metastasized gastric carcinoma is a rarely performed procedure: resection rates of liver metastases from gastric cancer range from 11% to 21% [56,57].

The majority of patients remain incurable due to several frequently occurring factors even if extended or multivisceral surgery had been performed. Those incurable factors include bilobar multinodular tumor spread, gross peritoneal dissemination, diffuse affection of distant lymph nodes or unresectable local recurrence. Especially bilobar tumor spread within the liver is more frequent in gastric cancer as compared to other gastrointestinal malignancies in spite of the same venous drainage via the portal vein which rises the question if the pathway follows the portal venous flow or if liver metastases from gastric cancer are caused by free circulating tumor cells and, thus, have to be regarded as a generalized stage of the tumor disease. This distinct biological behavior may also reflect that molecular signalling and gene expression pattern are different from other gastrointestinal tumors. Even in cases of potentially resectable gastric liver metastases, many medical professionals are reluctant to consider these patients for radical surgical treatment.

The first publication on the clinical outcome after liver resection for gastric cancer metastases was presented by Ochiai and co-workers: they described serosal perforation of the primary tumor (in cases of synchronous liver metastases) as well as lymphangiosis and
venangiosis to be negative prognostic factors and reported a median survival time of 18 months and an overall 5-year survival rate of 19% [56]. One of the first western publications with focus on resection of gastric liver metastases was presented in 2001 by Zacherl and co-workers: the median survival of the 15 resected patients was 8.8 months while two of these patients survived more than three years [58]. In a recently published review, 19 studies were analysed to compare the survival following liver resection for hepatic metastasized gastric cancer. Median survival for all 436 patients was 17 months and 5 year survival was 26.5%. No prognostic factor was found to be statistically significant across all studies [59]. Table 5 shows further studies on the topic of radical surgery for gastric liver metastases that have been published since 1994. At present, there are no data available on results from a prospectively conducted trial. Although the currently available study results indicate a significant improvement in terms of disease free and overall survival, all conclusions drawn from these studies are based on retrospectively performed analyses on small patient populations. Therefore, a prospective study should be performed to evaluate the impact of liver resection in patients with isolated liver metastases from gastric cancer.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Number of cases</th>
<th>Median survival in months</th>
<th>Overall 5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ochiai et al. [56]</td>
<td>1994</td>
<td>n=21</td>
<td>18</td>
<td>19%</td>
</tr>
<tr>
<td>Miyazaki et al. [60]</td>
<td>1997</td>
<td>n=21</td>
<td>NA</td>
<td>9,5%</td>
</tr>
<tr>
<td>Fujii et al. [61]</td>
<td>2001</td>
<td>n=10</td>
<td>16,3</td>
<td>10%</td>
</tr>
<tr>
<td>Imamura et al. [62]</td>
<td>2001</td>
<td>n=17</td>
<td>12</td>
<td>0%</td>
</tr>
<tr>
<td>Ambiru et al. [63]</td>
<td>2001</td>
<td>n=40</td>
<td>12</td>
<td>18%</td>
</tr>
<tr>
<td>Zacherl et al. [58]</td>
<td>2002</td>
<td>n=15</td>
<td>8,8</td>
<td>NA</td>
</tr>
<tr>
<td>Saitura et al. [64]</td>
<td>2002</td>
<td>n=10</td>
<td>25</td>
<td>20%</td>
</tr>
<tr>
<td>Okano et al. [57]</td>
<td>2002</td>
<td>n=19</td>
<td>21</td>
<td>34%</td>
</tr>
<tr>
<td>Shirabe et al. [65]</td>
<td>2003</td>
<td>n=36</td>
<td>NA</td>
<td>36%</td>
</tr>
<tr>
<td>Sakamoto et al. [66]</td>
<td>2003</td>
<td>n=22</td>
<td>11</td>
<td>38%</td>
</tr>
<tr>
<td>Thelen et al. [67]</td>
<td>2006</td>
<td>n=26</td>
<td>9</td>
<td>10%</td>
</tr>
<tr>
<td>Tsujimoto et al. [68]</td>
<td>2010</td>
<td>n=17</td>
<td>34</td>
<td>31,5%</td>
</tr>
</tbody>
</table>

Table 5. Studies on radical surgery for gastric liver metastases from 1994-2010

5. The role of quality of life

Health-related quality of life has become a major criterion in the decision-making process in patients with gastric cancer as well as other malignancies. In most recently randomized trials it is an important endpoint parameter [20]. The ultimate challenge in this field, however, is to measure quality of life. In fact, health-related quality of life is a complex
variable with a multi-dimensional structure [69]. Although a multitude of publications have
been dedicated to this topic during the last two decades, a generally accepted and consistent
definition does not exist. The essential tool for measurement of this variable are
questionnaires. One of the major problems of interpretation of data related to quality of life
is that uniform questionnaires are too unspecific and disease-related questionnaires are
limited to small areas of clinical research. The questionnaires refer to four dimensions of
patients’ perception: physical functions, the emotional experience, the social interactions
and symptoms related to the disease itself as well as adverse effects of treatment [69]. The
QLQ-30 is one of the most frequently used site-specific questionnaires in the field of cancer
research. It can be further particularized by entity-specific questionnaire modules, such as
the STO-22 for gastric cancer. Moreover, it has been observed that the baseline physical
scores as well as role function and the global quality of life correlate with overall survival
which makes several paramaters measured by QLQ-30 valuable in predicting clinical
outcome [70].

The impact of surgery on patients who underwent oesophagectomy for oesophageal cancer
has been measured by using the QLQ-30 questionnaire. In the early postoperative course, all
aspects of the quality of life except the emotional function decreased remarkably. Few
scores, such as dysphagia were improved but were overshadowed by other symptoms, such
as anorexia, nausea and diarrhoea. Overall, the deterioration of most key aspects resulted in
reduced overall scores. Within the following nine months a gradual recovery of those
symptoms was observed.

Svedlund and co-workers compared the quality of life of patients with gastric cancer at the
time of diagnosis with that of the general population: lower mood, reduced sexual interest,
insomnia and poor appetite have been observed in tumor patients as compared to the
normal population. Several studies indicated that weight loss as a significant parameter not
only for the quality of life but for survival and chemotherapy response. Furthermore, it has
been shown by other authors that the preservation of a gastric remnant as well as
construction of stomach-like reservoirs resulted in improved quality of life [71,72].

The course of quality of life in patients who undergo cytotoxic treatment mirrors the
interplay of disease-related symptoms and treatment-associated toxicity. Glimelius and co-
workers compared the clinical outcomes including quality of life of incurable gastric cancer
patients who underwent palliative chemotherapy plus best supportive care in comparison to
those who received best supportive care only. Both groups showed similar levels of quality
of life [73]. Bamias and co-workers showed that patients who underwent palliative
chemotherapy according to the ECF scheme had reduced physical and role functioning after
12 weeks whereas emotional functioning remained unaffected over that period. Within the
posttreatment period, the global quality of life value improved in comparison to the baseline
when the treatment had started. In addition to that, 6 years later it has been demonstrated
that the ECF scheme is better tolerated than MCF (epirubicin exchanged with mitomycin)
[74]. Furthermore, the comparison between irinothekan-based and docetaxel-based
palliative chemotherapy resulted in similar effects on the quality of life: role function,
emotional function, social function and sleep function improved 6 months after
chemotherapy as compared to the baseline for both chemotherapy regimens but did not
differ significantly from each other [75].

Currently, there is only little known about the impact of adjuvant and neoadjuvant
chemotherapy in patients with advanced gastric cancer.
6. Perspectives for the strategy of non-curative resection

Due to the aggressive biological behavior of gastric cancer and the late onset of symptoms, 50% have to be regarded as non-curable cases. The well accepted treatment options of palliative chemotherapy as well as best supportive care including the management of severe tumor related complications can be summarized as the so-called canonical palliative treatment strategy.

Due to the lack of prospective randomized trials in this field, to date no recommendation for the value of palliative gastric resection can be given. Nevertheless, there are numerous references that indicate a survival benefit in selected cases. Therefore, the currently available study results show that the impact of non-curative gastric resection in combination with chemotherapy on survival as well as on the quality of life should be evaluated by conducting a prospective study.

Multimodal treatment of peritoneal carcinosis including cytoreductive surgery is effective in cases of PCI up to 15 and if CCR 0-1 can be achieved.
Liver resection or radiofrequency ablation can be performed in cases of limited liver involvement and if extrahepatic secondary tumor growth has been excluded.

7. References


Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, Helicobacter-pylori, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

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