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REVIEW

Treatment of Gastric Cancer: Early-Stage, Advanced-Stage Cancer, Adjuvant Treatment

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ABSTRACT

With advances in understanding the spread of the primary tumor and patterns of recurrences of adenocarcinoma of the stomach and the availability of long-term follow-up data, a trend towards a tumor stage-stratified treatment strategy has increasingly received considerable attention.
Because management and prognosis of early gastric cancer and advanced gastric cancer substantially differ and current advances in imaging technology allow us with increasing accuracy a pre-treatment staging of the disease, that is precondition for a differentiated treatment, we separately review the therapeutic approach of early and advanced gastric cancer. Emphasis is given on the risks and potential benefits of such a treatment strategy.

EARLY GASTRIC CANCER

There has been an increase in the rates of detection of gastric cancer at earlier tumor stages in the recent decades world-wide. However, this increase is much larger in Japan than in the USA and Europe. As a result of a well established nation-wide screening program in Japan, the proportion of EGC has been increased from 15%, a few decades ago, to 50% currently of all endoscopically diagnosed gastric cancers,[1,2,3] whereas in the West where the low incidence of gastric cancer cannot justify a cost-effective screening program, EGC accounts for approximately 15% only.[4]

Traditional surgery with partial or total gastrectomy with limited (D1) or extended (D2) lymph node dissection is associated with high overall survival rates of about 90% even in the West and a low, 2-3% rate of relapse at 10-years.[5] Although, there was controversy in the past as to whether limited or extended lymph-node dissection should be performed for EGC,[5,6] there is now an agreement that D1 node dissection is suitable for most cases.[7] Conventional surgery has resulted in excellent long-term results that probably cannot be improved upon further. Thus the clinical and research interest in the last decade has been focused more on trying to improve QOL. Recently, there has been a trend toward minimally invasive treatment with endoscopic mucosal resection (EMR), laparoscopic surgery, and function preserving gastrectomy to minimise morbidity and to improve QOL. However, the well-accepted principles of surgical oncology should always be respected and long-term follow-up data are needed to establish that survival rates after these less radical operations are similar to those achieved by conventional surgery.

The rationale for a minimally invasive treatment is the low incidence of lymph node metastasis for mucosal cancer (T1m). Recent reports of the histopathologic features of more than 13.000 patients, mainly Japanese, with EGC establish that only 2 % (range 0-4.8%) of patients with mucosal cancer have positive lymph nodes.[1, 5-18]

However, when the tumor invades the submucosal layer (T1sm) this rate is increased to about 20 % (range 15- 25%). Interestingly, the metastasis is not confined to the perigastric nodes (N1 level) only, but in about 5% (range 2.8 -6.4%) of patients with submucosal cancers the extraperigastric lymph nodes (N2 level) are also positive. Risk factors for N2 disease are patients with a submucosal lesion which is larger than 2cm.[8,11] This finding is of clinical importance: there is a clear consensus that R0 resection is the most important independent treatment-related prognostic factor and a complete removal of metastatic N2 nodes would only be achieved by the more radical D2 lymph-node dissection.

The histological data on the likelihood of lymph node

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metastasis indicate that, from an oncological perspective, EMR and laparoscopic surgery can be performed safely in most patients with mucosal cancer with a low risk of residual disease in perigastric nodes. On the basis of these studies,[1,5-18] there has been a trend towards minimally invasive treatment for the management of EGC, notably in Japan and Korea[11,17-21] where the incidence of EGC is high, but these techniques are so far still experimental in some specialised Western institutions.[22]

However, there are several problems preventing a wider application of minimal treatment outside specialised centers. These are:

1. The differentiation between mucosal and submucosal lesions

Despite the use of endoscopic ultrasound (EUS) the differentiation of T1m from T1sm is not always satisfactory. The accuracy rate range between 70% [23,24] and 95%.[18,20]

2. Incomplete resection of the primary lesion

A complete resection of the lesion by EMR can not always be achieved. Initially, the incomplete resection rate by EMR was unacceptably high, about 80%.[17] To minimise this rate, EMR is currently suggested only for selected patients with mucosal cancers smaller than 1 or 2 cm with an intestinal type carcinoma. Diffuse type carcinomas require more extensive surgical margins. With the use of these selective criteria the incomplete resection rate has fallen to 10%.[21] Laparoscopic surgery is proposed, instead of EMR, for more sufficient surgical margins, in lesions larger than 10 mm and smaller than 25 mm with excellent rates of R0 resection. However, even with laparoscopic wedge resection 3.3% (2/60) of patients developed local recurrence in the staple-line.[18] The findings indicate the need for more precisely and carefully determined selection criteria.

3. Residual disease in lymph nodes

The prediction of lymph-node status still remains a major problem. The enlarged lymph nodes detected by EUS or CT-scan are nor always involved and lymph-nodes smaller than 1 cm may be infiltrated. However, the prediction of node-negative patients with a high diagnostic accuracy is possible using a combination of endoscopic and histological criteria. These criteria are: (a) depth of tumour invasion confined to the mucosal layer only, (b) size of lesion smaller than 2 cm, (c) macroscopic elevated or flat type; and (d) histological type (well-differentiated, intestinal type carcinoma). The use of these criteria varies among different institutions[8, 11-22] but there is a strong suggestion that fulfilment of all these criteria may accurately predict the lymph node status.

Micrometastatic residual disease is suggested as an argument against the use of these new techniques. However, micrometastasis in perigastric lymph nodes, using immunohistochemical methods, was rarely found in EGC that were node-negative by routine histology.[25] In addition, the prognostic significance of the micrometastasis in lymph nodes is unknown.[26]

4. Lack of prospective well documented long-term follow-up data

The available preliminary follow-up results from observational studies after EMR or laparoscopic surgery are encouraging.[8,14-19] However, there is a lack of prospective well documented long-term survival data and longer follow-up data are needed.

The above reported data indicate that the selective criteria for minimal invasive therapy have not yet been precisely determined. Thus the patient should always be prepared for a secondary approach when histology of the resected specimen indicates that there is invasion into the submucosal layer or the surgical margins are not sufficient.

A function preserving gastric resection has also become an important consideration in the treatment of EGC.[27-29] Evidence is rapidly accumulating that preservation of pylorus, vagus nerve and gastric reservoir significantly improves gastrointestinal function and QOL. However, long-term survival data are needed before limited surgery can become more widely accepted.

Taken together all the current data for the treatment of EGC it can be concluded that traditional surgical resection with a proven very low 10-year recurrence rate remains the procedure of choice outside specialised centers. However, the low rate of nodal metastasis for mucosal cancer, justifies the trend towards less radical management for carefully selected patients. It is expected that the number of patients who will benefit from the application of a more patientfriendly minimal invasive therapy will be increased in the coming years. Screening programmes to increase early detection, further advances in diagnostic and treatment technology and increased experience with minimally invasive treatment will make the selection criteria for the optimal treatment option among EMR, laparoscopic surgery and conventional or function preserving gastrectomy more precise. However, for submucosal cancer with substantially high incidence of lymph node metastasis conventional surgery remains, at present, the standard procedure.

ADVANCED GASTRIC CANCER

The general term advanced gastric cancer includes all gastric cancer cases, apart of EGC. The definition of EGC includes cases with tumor invasion confined to mucosal or submucosal layer only irrespective of the presence of metastases in lymph nodes. Advanced gastric cancer according to prognosis can be divided into two major categories: cases with potentially complete tumor resection and cases with incomplete tumor resection or cases with unresectable lesions or distant metastasis at the time of diagnosis. In contrast to EGC, the prognosis of advanced gastric cancer remains poor

and little progress has been observed in the last years. The 5-year survival rates of resected gastric cancer patients with UICC stage III or IV disease in USA are between 3% and 13%.

Surgical treatment

In the 1980s surgical efforts to reduce recurrence rates and to improve survival using more aggressive surgical procedures consisted of standard total gastrectomy and pancreaticosplenectomy have been performed. However, this extensive approach was associated with increased postsurgical morbidity and mortality while overall longterm survival could not be improved.

Extent of surgery

Total gastrectomy "de Principe" for advanced gastric cancer is preferred by some surgeons because it eliminates the possibility for recurrence in the gastric stump or the surrounding right and left paracardial lymph nodes that are left behind after a subtotal gastrectomy. There is now a consensus that for tumors located in the proximal or in the middle third of the stomach total gastrectomy is indicated. Some controversy persists only for distal tumors. Most surgeons consider subtotal gastrectomy sufficient, on the basis of randomised trials in which there was no significant survival difference between patients treated with total or subtotal gastrectomy.[30] However, total gastrectomy is preferred in some European countries for better local control, and as a result of this strategy the proportion of total gastrectomies in Europe is about 70%,[31,32] compared with Japan where it is not higher than 30% of all resected cases.[33] This difference is partially explained also by the higher proportion of proximal gastric cancers, which occur in the West, compared with Japan.

Frozen section examination of proximal resection lines for detection of residual cancer, with a possibility for a re-resection of the distal oesophagus, remains a standard principle. However, it has little clinical relevance for distal surgical margins applied 2-3 cm from pylorus because infiltration of distal resection lines is relative rare. Even if this occurs, an extensive Whippleoperation procedure, which is rarely justifiable, would be required to achieve an R0 resection.

It is not clear well whether patients with an advanced gastric cancer benefit more from preservation rather than resection of the spleen. The following consequences need to be considered: the risk of residual disease in splenic hilar nodes when the spleen is preserved, the effect of splenectomy on short-term postoperative morbidity and mortality, and the impact of splenectomy on long-term survival.

Lymphatic drainage to the splenic hilum nodes is strongly related to the tumour location and depth of invasion (T-stage of disease). In the Japanese experience with splenectomy, the incidence of hilar nodal metastases ranged from 0-2% for distal and middle third gastric cancers, respectively, to 15% for proximal third tumors, and 21% for tumors that infiltrate the whole stomach.[34] In the West hilar node metastases were found only in patients with proximal advanced T3, T4 tumours.[35] These data strongly suggest that splenectomy in early stages or in distal tumours, for removal of hilar nodes, is unnecessary because these nodes are rarely involved. Two parameters, tumour stages and location, should be used as predictors of metastatic hilar nodes. At present, preoperative detection by CT-scan or endoscopic ultrasound is not reliable, and even intraoperatively the macroscopic diagnosis is not possible.[36] The strong correlation between tumor location and splenic hilum nodal status explains why survival was not significantly different for patients with antral carcinoma who underwent a combined total gastrectomy plus splenectomy or a simple subtotal gastrectomy.[37,38]

The adverse effect of splenectomy on postoperative morbidity and mortality has been shown in retrospective series[35,39-42] and was confirmed recently in two major European randomised trials that compared D1 with D2 gastrectomy.[43,44] However, the impact of splenectomy, from an immunological aspect, on longterm survival is unknown. Several retrospective series have shown significantly higher survival rates for patients with spleen preservation,[41,45] but in others splenectomy was not an important independent prognostic factor when analysed by multivariate analyses.[39,40,42,46,47] In the recently published Dutch trial, the cumulative risk of relapse was lower in patients with spleen preservation than in those with splenectomy, but the aim of the study was to compare D1 and D2 resections.[44] Although there is some evidence of long-term survival benefit from spleen preservation this is not conclusive. It is possible that the spleen has an indirect positive effect on survival through association with other cofactors. Spleen preservation should probably be recommended in most patients, unless there is infiltration through the gastric serosa into the spleen or suspected enlarged hilar nodes for whom splenectomy increases the chances of a R0 resection. Resection of the spleen is also required, even when these criteria are not met, for advanced proximal gastric tumors because the risk of residual disease at the splenic hilum nodes is about 15% to 20%. Unfortunately, the prediction of this high-risk subgroup is not possible, so that splenectomy in all patients with proximal tumour is in about 80% of these patients unnecessary.

Several surgeons propose combined splenectomy with left-sided pancreatectomy, as part of en-bloc resection with the stomach, as a radical procedure for complete removal of metastatic lymph nodes along the splenic artery. However, resection of the distal pancreas has proved to be very dangerous in randomised trials.[37,43,44] In the British (MRC) trial, both morbidity (58%) and mortality (16%) rates were 100% higher in the D2 resection group when distal pancreaticosplenectomy formed part of the resectio.[43] In the Dutch trial pancreaticosplenectomy in the D2 group was associated not only with increased postoperative morbidity and mortality, but also with increased risk of relapse ($p<0.02$).[43] Furthermore, Marujama et al[48] found in a retrospective comparative clinicopathologic study

that patients with proximal tumors survived significantly longer after gastrectomy and splenectomy with preservation of the pancreas compared with those undergoing pancreaticosplenectomy. In this study histological examination indicated that the involved lymph nodes were not found within the pancreatic parenchyma but on its surface. A complete removal of these nodes could therefore be achieved with a pancreas preserving total gastrectomy and splenectomy.[48] At present, distal pancreatectomy is indicated only for the achievement of an R0 resection when there is direct infiltration of the pancreas by the tumour through the gastric serosa .

Extent of lymph-node dissection

The optimal extent of lymph-node dissection has not yet been established . On the basis of observational studies with superior long-term survival data after extended lymph-node dissection, the high-incidence countries, notably Japan, have adopted this procedure as a standard operation for gastric cancer.[33] Extended node dissection in Japan is now so widely accepted that, a Western-type limited (D1) dissection is considered as an insufficient and thus unethical procedure. Despite the increasing worldwide interest in D2 dissection, its therapeutic benefit has not been demonstrated in randomised trials.[43,44] However, the results of these studies are not conclusive, because there is controversy on the most appropriate design. Thus, at present there is no clear consensus to the optimal extent of lymphadenectomy.

The description D dissection for the determination of extent of lymph node dissection arises from the Japanese classification (JRSGC)[68] and not that of the UICC/AJCC 1997 classification . D1 to D4 dissection correspondences to the anatomical site of dissection of levels N1 to N4. The rationale for extended lymph node dissection is that it achieves a R0 resection due to clearance of the metastatic extraperigastric lymph nodes that can not be removed with a limited D1 node dissection. Thus, it increases the curative resection rate, reduces the locoregional recurrence rate and may improve survival.[26] This hypothesis for improvement of both local control and survival after D2 dissection is supported by a large number of Japanese observational studies that based on historical comparisons.[33,49] Furthermore, several prospective but non-randomised studies[31,50] and other observational Western series have shown encouraging long-term results with D2 dissection.[51-53] However, many surgeons in the West argue against the therapeutic value of D2 dissection and are clearly against the routine use of D2 dissection for Western patients. In their opinion, D2 dissection increases postoperative morbidity and mortality rates and does not improve long-term survival. This argument has been based on retrospective studies, which have failed to demonstrate any survival benefit in favour of D2 dissection.[54-56]

The conflicting results of observational studies emphasise the need for well-designed randomised trials. Two major European multicenter randomised trials comparing D1 with D2 dissection have been conducted, one by the Medical Research Council (MRC) in the United Kingdom[43] and the other by the Dutch Gastric Cancer Group in the Netherlands[44] 711 and 400 patients in the Dutch and MRC trials respectively underwent the randomly assigned treatment with curative intent. Early reports of both studies indicated that the rates of short-term morbidity and hospital mortality (10% vs 4% and 13% vs 6%) were substantially higher among the patients who underwent D2 dissection. The final long-term results of Dutch trial were published recently.[44] There was no long-term improvement in survival (five-year survival rates: 45% for D1 group and 47% for D2 group) or decrease in the risk of relapse (43% for D1 and 37% for D2 group at five years; p=0.22) among patients who had the more radical operation. As a result, these investigators do not recommend extended lymph-node dissection for Western patients. Similar preliminary results from the MRC trial have been reported.[43]

What reasonable conclusions can we draw from the two randomised trials? Should the results of these studies be considered conclusive and remove any indication for D2 dissection for Western patients? A detailed analysis of the quality control in both controlled trials is necessary. Criticisms in the design and conduct of the Dutch trial have already been made in a related Editorial.[57] The main argument and, at the same time, the main disadvantage of these trials, is their finding that D2 dissection increases short-term pïstoperative morbidity and in-hospital mortality. Pancreatico-splenectomy was inappropriately performed in D2 group[106] and the trial included surgeons who were less familiar with the D2 dissection technique.[57] These two factors probably are probably responsible for the higher complication rates rather than the lymphadenectomy itself.[26] Excellent short-term results from surgeons experienced in D2 dissection have been reported.[58,59] Postoperative mortality, assessed by a nation-wide Japanese registry of gastric cancer with 260,000 registered patients and more than 10,000 new patients each year, with 75% undergoing a D2, D3 resection, is now very low at less than 1%.[60] Similarly postoperative mortality of less than 2% has been reported by an experienced Western center.[61] Similar results from multi-institutional studies in Germany[31] and Italy[62] are now being achieved. Table 1, summarises the results from the major trials to date and indicates that D2 dissection by experienced surgeons, with spleen and pancreas preservation, can be performed with similar safety as the D1 procedure. Dr. Brennan, in his editorial for the Dutch trial underlines, that the patient can only be harmed by an extended lymph-node dissection when it is performed by an inexperienced surgeon.[57]

Whereas the effect of D2 dissection on short-term outcome is now clear, its beneficial effect on long-term survival is still controversial. Observational studies have shown a better stage-specific survival after D2

dissection,[10,31,33,49-53] but are not conclusive because of the confounding influence of stage migration.[44,63] This phenomenon, in which D2 dissection providing more examined lymph nodes refines pathological staging, increases stage-specific survival in D2 group without a real survival improvement.[64] Stage migration can learly be eliminated only by the comparison of long-term survival among all patients who had a D1 or D2 dissection with curative intent. However, at present none of the randomised studies have shown an overall survival benefit[65] (Table 3).

In the Dutch trial, D2 dissection did not improve longterm survival or decrease the risk of relapse. However, the D1 and D2 groups were not well balanced. Resection of the spleen was an independent risk factor for reduced survival but splenectomy and pancreatectomy was significantly more often performed in the D2 than the D1 group ($p<0.05$). For the subgroup without pancreaticosplenectomy, the risk of relapse was significantly lower in the D2 than D1 group ($p<0.02$). Despite the great efforts of the authors for standardisation and quality control, major non-compliance, indicated by an incomplete node dissection to the intended level, was noted in 26% of D2 patients and nodal dissection beyond that allocated and above the intended level of dissection was noted in 23% of D1 patients.[66] The substantially high rate of major non-compliance in the D2 group underlines the problems of trial participation by surgeons unfamiliar with the D2 approach. It is likely that residual metastatic N2 nodes leading to subsequent fatal relapse existed in a substantial proportion of patients in the D2 group . The overall survival benefit of D2 dissection, if it exists, appears to be small and is limited to a selected subgroup of patients, indicating the need for large trials if this question is to be answered.[31] In addition, a number of variables may obscure the distinction between the two procedures and confound the results of randomised trials. According to a recently described concept, D2 node dissection is required for curative resection for patients with positive extraperigastric lymph-nodes (pN2 disease: stations no. 7 through no. 12) because these N2 nodes are left behind after a D1 dissection and are the source of subsequent fatal relapse.[61,67] Prospective studies show that 50% of patients with node-positive disease undergoing a D2 dissection have positive extra-perigastric N2 nodes.[61,67,68] Thus histopathological data establish that the risk of residual disease and fatal relapse among the patients with nodepositive disease undergoing D1 dissection with apparently "curative" intent is very high, about 50%.[61,63,67,68] D1 dissection for patients with nodepositive disease is thus inevitably a noncurative resection in one half of patients, and a contradiction to the clear consensus that an R0-resection should be the goal of surgery.[4]

Several new therapeutic modalities are proposed for gastric cancer treatment and there is a need for an evidence-based evaluation before any of the innovations can be widely applied. However, the reliance of evidence based medicine[69] on randomised trials, although of great importance, does not provide all the answers.[70-74] Furthermore, substantial benefits derived from an innovation may be lost in the time period required for reliable long-term follow-up data. In a recent review, according to the estimation of the author , the effectiveness of different treatments currently used summarized in the Table 4. The ranking of evidence methods proposed by Ellis et al.[74] and Troidl[72] have been used, taking into account the appropriateness, adequacy and generalizability of RCTs[70,71] as well as the lower level of evidence from prospective, uncontrolled trials with relevant endpoints.

Postoperative adjuvant treatment

In the Western world more than 80% of patients at diagnosis have an advanced gastric cancer. Radical surgery with extended total gastrectomy, resection of neighbouring organs and extended lymph-node dissection has increased the R0-resection rate, but the recurrence rate is high resulting in a poor survival. Locoregional relapse, peritoneal dissemination, liver metastasis, distant metastasis and combinations of these are the causes of treatment failure and fatal outcome even after a R0 resection. The Japanese experience has shown that radical surgery may reduce loco-regional recurrence but has no or little effect on preventing liver metastasis and peritoneal dissemination.[33,75,76] Thus, the rationale for the elimination of micrometastatic disease or the circulating free cancer cells after a R0 resection with an adjuvant treatment is clear. Postoperative chemotherapy has been evaluated for more than three decades, but at present no standard adjuvant chemotherapy has been established. A variety of traditional regimens such as FAM (5-FU, adriamycin, mitomycin-c), FAMTX (5-FU, adriamycin, methotrexate), FEP (5-FU, etoposide, cisplatin), FAP (5-FU, adriamycin, cisplatin), EAP (etoposide, adriamycin, cisplatin) and ECF (infusional 5-FU, epirubicin, cisplatin) have been tried without clear benefit and are associated with significant toxicities. Thus, new drugs and innovative chemotherapy protocols are required. In advanced gastric cancer, recent combinations using taxanes, CPT-11 and oral 5-FU prodrugs have shown high tumor response rates of 50-63%, but we are a long way from a satisfactory treatment. Postoperative adjuvant radiotherapy has also been evaluated in order to improve local control but in a randomized study of the British Stomach Cancer Group had no effect on survival.[77]

A survival benefit with immunochemotherapy after R0 resection for advanced stage III tumors has been demonstrated in two randomised trials from Korea and Japan,[78,79] but this effect has not yet been confirmed by other groups and has not gained wide application. Experimental studies have revealed that changes in residual tumour cell kinetics occur within 24 h of removal of a primary tumour. A week later a measurable increase in tumour size can be observed.[80] Chemotherapy is least effective when it is administrated 7 days after resection of the primary tumour.[81] In a meta-analysis of randomised trials conducted in western

centres, delayed systemic adjuvant chemotherapy, initiated 4-6 weeks after operation has failed to show an effect on survival.[82] It appears therefore, that the most favourable time for administration of adjuvant chemotherapy may be around the time of operation.[83] The optimal timing of administration of chemotherapy (preoperative, intraoperative, or early postoperative) has become therefore, of increased interest.

Locally advanced gastric cancer (LAGC): Adjuvant treatment

The majority of patients world-wide, with the exception of Japan, are diagnosed with locally advanced gastric cancer (T3-4N0-2M0). A resection with curative intent can be achieved in only about 50% of these patients, and even after a R0 resection about 60% of these patients will recurs within the first 2 to 3 years after surgery even when this includes extended lymph-node dissection.[84,85] Thus, the concept of preoperative chemotherapy to improve both the rates of R0 resection and survival has been proposed and investigated. Since, at present, the patients that may benefit from this strategy are those with an advanced stage (T3-4N0-2M0) the pre-treatment selection is critical. The diagnostic procedures that are required include CT-scan of abdomen for detection of distant metastases, EUS for exact determination of Tcategory and surgical laparoscopy for exclusion of peritoneal tumor spread and the possibility to look for free tumor cells by peritoneal lavage. The accuracy of prediction of lymph-node status has been increased by EUS and CT-scanning, but has not yet reached the high level of accuracy needed for treatment decisions.

Numerous clinical trials have shown that preoperative chemotherapy is feasible and able to increase the rate of R0 resection.[86] A phase II study with the combination of cisplatin-leucovorin-5-FU (PLF) has shown encouraging results with low toxicity and a R0-resection rate of 73%[87] and thus a phase III randomized trial with this regimen co-ordinated by the EORTC is ongoing.[88] Two small randomised trials from Asia reported significantly more downstaging and curative resection in patients with LAGC who received preoperative chemotherapy with cisplatin-etoposide-5-FU [PEF] or cisplatin/etoposide/mitomycin and UFT.[89,90] However, despite the encouraging results of several phase II/III studies with response rates between 40% and 60% and R0-resection rates of up to 80%,[85] there is no evidence for improvement in survival. Furthermore, in the Dutch randomised chemotherapy trial that compared preoperative chemotherapy with 4 courses FAMTX followed by surgery with surgery alone, there was no difference in curative respectability rates between the two groups.[91] The present data show that about 50% of patients with LAGC have no benefit from preoperative chemotherapy which may also be associated with significant toxicity or result in a delay in definitive surgery. Thus prediction, of patients with LAGC, who will respond to chemotherapy, is critical. At present chemotherapy prior to surgery cannot be advocated outside controlled trials.

Peritoneal dissemination is the most common type of recurrence after curative surgery for gastric cancer.[33] Clinical and autopsy studies have established that about two-thirds of early recurrence occurring in the first 2-3 years after a R0 resection are within the abdominal cavity whereas extraabdominal metastases are observed late in the course of the disease.[83-85] Recurrences in the gastric bed and peritoneal cavity may arise from exfoliated tumor cells. The exact mechanism by which this occurs has not been fully elucidated. Tumor cells that exfoliate from the serosal surface before or during resection are viable and able to implant and proliferate.[92,93] Serosal surface invasion, free intraperitoneal cancer cells, Bormann type IV and diffuse type carcinomas are risk factors for peritoneal recurrence.[94-97] These observations form the rationale for the development of treatment modalities to destroy exfoliated tumor cells after curative resection and their investigations have focused on the hypothesis of "tumor cell entrapment".[83]

Peritonectomy and intraoperative peritoneal chemotherapy have been tried but with no beneficial effect. In contrast, encouraging results with hyerthermia with or without intraoperative or early postoperative peritoneal chemotherapy after curative resection for T3/T4 tumors have been reported. These studies have suggested that intraperitoneal chemotherapy is only effective in reducing peritoneal metastases when it is administrated intraoperatively or in the early postoperative phase.[98-100] On the basis of these findings intraoperative and early postoperative intraperitoneal chemohyperthermia has been recently adopted in Korea for advanced gastric cancer with minimal peritoneal metastases.[101,102]

Another technique for prevention of peritoneal carcinomatosis was recently developed in Japan. In this study,[113] patients with serosal invasion and a resection with curative intent were randomly allocated to treatment with radical surgery plus intraperitoneal chemotherapy of 50 mg of a delayed release preparation of mitomycin C bound to activated carbon particles or to surgery alone.

Survival after 3 years was significantly higher in the mitomycin group (66%) than in the control group (20%: $p<0.01$) without any difference in postoperative morbidity.[103] Similar encouraging results were demonstrated by Sugarbaker et al.[104] However, in a European trial this treatment modality was associated with a high rate of postoperative complications resulting in a premature closure of this phase III-trial.[105]

Theoretically, a combination of preoperative systematic chemotherapy and intra-, or early postoperative administration of intraperitoneal chemohyperthermia appears to be an attractive strategy to enable both a R0 resection and prevent peritoneal dissemination in LAGC. This combined treatment has

already undergone preliminary evaluation in clinical trials[106] but further investigations are needed.

Intraoperative radiotherapy (IORT) to increase the local tumor dose to the tumor bed has also been valuated. Although the local recurrence rate was decreased, no improvement of survival was seen.[107,108]

Conclusions

Surgical resection with curative potential (R0) is the only treatment modality of scientific proven effectiveness. Current results of gastric cancer treatment compared with historical data show a marked improvement. Overall 5-year survival rates for patients who had a R0-resection have increased from 20%[109] to about 50% in the Western world,[31,44,61] or more than 70% to 80% in the East.[60,84]

This improvement is attributable largely to detection of gastric cancer at earlier tumor stages, which have a relatively good prognosis, and partially to the use of an appropriate surgical resection. Long-term outcome for EGC after conventional surgery is excellent but the prognosis of advanced gastric cancer remains very poor. There is a great need for an effective adjuvant treatment, but at present none is established. Patients may substantially benefit in both survival and QOL from a tailored treatment depending largely on tumor staging. Thus, management by experts in specialised surgical oncology units may be beneficial for patient outcome.

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