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Preoperative Staging of Gastric Cancer as Precondition for Multimodal Treatment

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Abstract. Preoperative staging of gastric cancer plays a crucial role in every multimodal treatment protocol. At present, staging intends to be far more than evaluation of the depth of tumor infiltration into the organ wall, that is, T stage, nodular status (N category), and the presence of distant metastases (M stage) according to UICC criteria. In modern surgical oncology it includes more often the evaluation of prognostic factors such as the RAS-protein, p53 tumor suppressor gene, growth factor receptors, cell adhesion molecules, proteolytic factors, and proliferation-associated antigens. Furthermore, evaluation of nodular status is possible by sophisticated computer programs. The conventional staging of gastric cancer using endoscopy and sonography, conventional ultrasonography, computed tomography, and magnetic resonance imaging is discussed. Possible improvements of staging in oncologic centers should include surgical laparoscopy, laparoscopic ultrasonography, and meticulous evaluation of an abdominal lavage including immunohistochemical detection of free tumor cells. The most promising tumor biology-related prognostic factors in gastric cancer are briefly discussed.

The aim of every surgical treatment for gastric cancer is complete resection (UICC R0) of the tumor. Preoperative evaluation to determine the complete resectability of a tumor, including its lymphatic drainage system, plays a crucial role in the decision-making process for or against a primary operation. Only if an R0 resection is expected can the prognosis of the patient be improved by surgery. The presence or absence of residual tumor at the end of an operation is one of the most important independent prognostic factors for gastric cancer [1, 2]. Staging of gastric cancer is, by definition, the exact evaluation of the tumor stage, which means of the depth of tumor infiltration into the organ wall (T category), nodular status (N category), and the presence of distant metastases (M category) according to the criteria of the UICC [3, 4]. However, with modern surgical oncology, applying multimodal treatment strategies, staging intends to be far more: evaluation of as many prognostic factors as possible (Table 1), such as the tumor grading and investigation of tumor-biology-related prognostic factors. This evaluation includes invasive procedures, such as endoscopy, endoluminal ultrasonography (EUS), biopsy, and surgical laparoscopy to inspect the whole abdominal cavity and to obtain abdominal lavage. It is furthermore possible to predict nodal involvement by sophisticated computer programs if the T stage is known [5]. Last but not least, a risk analysis of the patient is recommended.

Extensive staging is useful only if the results have a direct impact on the selection of the treatment strategy. If surgery alone is considered to be the only therapeutic modality, only patients with unresectable tumors can benefit from the various diagnostic procedures if surgery is omitted. If multimodal treatment strategies are applied, however, a tumor stage-dependent therapy should be achieved, which is the case for gastric cancer.

In the following sections the diagnostic methods and their impact on therapy are discussed. We have also included modern techniques and tumor biology-related factors that up to now have only been under scientific discussion. In the first part we discuss the basic information that must be obtained for every case of gastric cancer before a therapeutic decision can be made. Staging of cancer of the esophagogastric junction (cardia) and of the proximal third of the stomach is the same as for gastric cancer.

Conventional Staging of Gastric Cancer—Primary Tumor

In the patient care study of the American College of Surgeons the diagnosis of gastric cancer was established in 94% of the patients by *endoscopy* and *biopsy* [6]. These two procedures can also be used to establish the site of the tumor and its *macroscopic appearance* (Borrman classification). The first biopsy can provide the *histopathologic type* of the tumor. Gastric cancer is mainly adenocarcinoma. Gastric lymphoma [Malt] must be excluded before beginning treatment because these entities are treated by different modalities [7]. The histopathologic subclassification according to the *Laurén classification* of tumor growth (intestinal versus nonintestinal type) [8] can also be applied. It provides additional important information about the luminal extent of the surgical resection required. From this first biopsy the *grade of differentiation* (1 to 3, i.e., well to poor) is also reported. The grading, however, is handled in different ways by different pathologists.

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Table 1. Established prognostic factors for gastric cancer and prognostic factors under evaluation.

Established factors
TNM stadium
R category
Number of invaded lymph nodes
Lymph node ratio (removed/invaded)
Histopathologic grading
Borrmann and Lauren classification
Factors under evaluation
Cell proliferation-related
DNA content
ploidy/S-phase
mitotic count/index
cell kinetic (in vitro BrdU)
AgNOR
Proliferation-associated antigens
Ki-67
PCNA
p105
Proto-oncogenes
c-*myc*
c-*erb*B-2/neu
c-Ha-*ras*
c-Ki-*ras*
int-2
hst-1
Tumor suppressor genes
nm 23
p53
Cell adhesion
Integrins
e-Cadherin
CD 44
Various others
CEA, Ca 19-9, Ca 195
EGFR
TGF-α
mdr
uPA/PAI

Table 2. Accuracy of EUS for local staging of gastric carcinoma.

Stage	No.	Accuracy of EUS (%)	Overstaging (%)
T 1	27	81	19
T 2	52	71	27
T 3	151	87	5
T 4	24	79	

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Because the *depth of infiltration* is one of the most important prognostic factors [1, 2] EUS is still the first step for further diagnostic planning, as shown in Table 2. As the overall sensitivity of T staging using EUS is about 85%, problems sometimes still arise to differentiate the T2 (subserosal invasion) from the T3 stage. These two stages are crucial, as they discriminate locally from locally advanced tumor growth. The use of EUS is hampered by the problem of overstaging or understaging. It is often difficult to differentiate between a cancer tissue, inflamed surrounding soft tissue, and even fibrous change. Furthermore, EUS cannot detect the microinvasiveness of the cancer [10]. We found that in a group of 167 patients 17% were overstaged or understaged, mainly in the T2 group [9].

There are only a few studies suggesting [9, 11] that EUS can predict accurately the R0 resectability (i.e., microscopically and macroscopically tumor-free). Dittler [9] reported that the prediction rate of R0 resection using EUS is 81%, with an 78% actual R0 resection rate. Moreover, one of our studies [9, 12] showed that the endoscopic staging system based on macroscopic tumor appearance (Borrmann classification) was not much inferior to EUS staging. Maehara [13] found a distinctly lower survival rate for patients presenting with Borrman type IV gastric carcinoma after gastric resection.

Table 3. Reported overall accuracy of T staging for gastric carcinoma: EUS versus CT.

Study (first author)	Patients	EUS (%)	CT (%)
Botet [16]	50	92	42
Sanft [17]	71	80	44
Grimm [18]	117	85	15
Dittler [9]	254	84	NR

NR: not reported.

In cases of carcinoma of the cardia the stenosis caused by the tumor is often not passable. It has been proved in two studies that in such cases a T3 or T4 stage is present in about 88% of the patients, leading to a staging sensitivity of about 85% [9, 14]. It must be mentioned that the use of EUS is highly dependent on the training and experience of the investigator. The excellent results published in various studies for other cancers, such as pancreatic cancer [11, 14], have been obtained by well trained, specialized "endosonographists."

Up to now the use of EUS is restricted to centers that already have sufficient experience with this sophisticated technique. It must be further evaluated with respect to clinical consequences in a search for the best available method [15]. EUS is superior to computed tomograph (CT) for determining the overall T stage (Table 3). Lightdale [19] found a concordance of 92% comparing EUS to surgical pathology and only 42% concordance with CT scanning.

N Category

The diagnostic accuracy of determining the N category for gastric cancer is reported to be 78% to 87% [12] using EUS. However, in our study [9] we found an accuracy of only 65% for N1 stage and 52% for N2 stage. In our experience the method seems to lack reliability. The problem is that EUS can visualize lymph nodes only in close vicinity to the gastric wall. The N2 stage (lymph nodes more than 3 cm distant from the primary lesion) is more difficult to detect. As with other imaging methods, EUS can detect only enlarged lymph nodes. Nodules that are invaded but not enlarged cannot be differentiated. It is discussed below that there is a distinct correlation between the T stage and the number and sites of invaded lymph nodes. T3 tumors have 88% positive lymph nodes [5].

Overall, EUS seems to be more sophisticated than percutaneous ultrasonography or CT for evaluating the N stage (Table 4). Cho et al. [20] reported an accuracy of 70% when assessing regional lymph node metastases using dynamic CT. The detection rate of lymph nodes was low when perigastric lymph nodes were close to the primary tumor, but it was relatively high in the case of extraperigastric nodes because enlarged lymph nodes were clearly distinguished from adjacent, highly enhanced vessels during the

Table 4. Reported overall accuracy of N staging for gastric carcinoma: EUS versus CT.

Study (first author)	Patients	EUS (%)	CT (%)
Botet [16]	50	78	48
Sanft [17]	71	80	68
Grimm [18]	117	87	25
Dittler [9]	254	66	NR

NR: not reported.

Table 5. Surgical laparoscopy: how to do it.

1. General anesthesia
2. Patient in anti-Trendelenburg position (head up)
   a. Inspection of left upper quadrant, anterior stomach, diaphragm, liver (ventral and dorsal surface), peritoneum
   b. Dissection of the greater omentum, opening of the lesser sac; inspection of hiatus, posterior stomach, pancreas, celiac axis
   c. Laparoscopic ultrasonography
3. Trendelenburg position: inspection of the lower abdominal part.

For technical details see Feussner et al. [31].

early phase of dynamic CT. It seems possible that dynamic CT could close the gap in the evaluation of N2 stage. However, the best method for exact determination of lymphatic spread of the tumor is surgical laparoscopy.

M Category

Because of the embryonic rotation of the stomach, gastric cancer metastasizes not only into the lymph nodes of the greater and lesser omentum but also into those around the celiac axis and the retroperitoneal space along the large abdominal vessels. The tumor itself can reach "per continuitatem" the liver, pancreas, small and large bowel, and sometimes the spleen [21, 22]. Seldom (in about 2% of the cases) the tumor metastases early into the bone marrow [22, 23]. In female patients metastasis in the ovary is a common finding (Krukenberg tumors). The different subtypes of the Laurén classification have also different ways of metastasizing. The intestinal-type metastases preferentially affect the liver and lymph nodes, whereas the diffuse type spreads into the peritoneum [23]. Taking these routes of tumor spread into account, CT examination of the whole abdominal cavity is necessary. One crucial point about distant spread of gastric cancer must be noted: The peritoneal metastases can be visualized only by CT scanning when ascites is demonstrable. As stated below, laparoscopic examination can overcome this pitfall.

Conventional ultrasonography (US), CT scanning, CT arterial-portography (CT-AP), and magnetic resonance imaging (MRI) are the methods of choice for detecting liver metastases. Small metastases (< 10 mm in diameter) impose a serious problem because they evade the established diagnostic methods, and it this size of metastasis that is predominantly found. As detection depends on size, only 50% to 60% of the metastases are detected using simple CT scans. Heiken et al. [24] reported an overall detection of liver metastases of 81% using CT-AP. Small metastases (< 10 mm) were detected in only about 61%. The results were shown to be comparable to those seen with intraoperative US (sensitivity 72%) and much superior to those with MRI (52% sensitivity). Soyer et al. [25] reported a sensitivity of 94% for CT-AP and 78% for high field strength MRI. They considered CT-AP to be the preoperative gold standard for detecting liver metastases. In our study [26] we found a sensitivity of 75% for intraoperative palpation and 90% for intraoperative US. Combining the two methods provided a sensitivity of nearly 100% with a specificity of about 98%.

Percutaneous abdominal US has problems similar to those described for CT scanning. Although it is fairly sensitive for detecting metastases > 15 mm (sensitivity 80.5%), the sensitivity for detecting liver metastases < 10 mm diameter is only 37% [27]. Percutaneous US ought to be used as a screening method. If a surgical procedure is being considered, CT scanning and CT-AP are preferable. The gold standard for detecting liver metastases is still intraoperative (or intralaparoscopic) US. However, new imaging techniques are under evaluation using MRI. It is still under discussion if these new techniques will produce better results with the MRI investigation of the liver.

This staging is completed by bone scintigraphy for detecting bone metastases and conventional chest radiography.

Possible Improvements in Staging

To improve the still dismal prognosis of patients with locally advanced gastric cancer, combined modality approaches (preoperative chemotherapy, intraoperative radiotherapy, and preoperative and postoperative chemotherapy) are under clinical evaluation. For these approaches, exact and complete evaluation of the individual tumor stage is mandatory. The areas of special interest before such a therapy planning process can be undertaken are tumor spread in the abdominal cavity, regional lymph node involvement, and possibly micrometastases in the bone marrow. With these special topics, conventional staging has definitive "white spots." To overcome these pitfalls, more and more sophisticated staging procedures are under scientific evaluation. In the following sections we discuss one of the most promising new techniques for staging lesions and recognizing prognostic factors.

Surgical Laparoscopy and Laparoscopic Ultrasonography

There is a definite lack of accuracy in staging the N and M categories using the various imaging techniques that have been available. Both categories have a large impact on therapy planning; for example, if peritoneal carcinosis (M1 Per) is present the patient would profit from neither an operation nor systemic chemotherapy. There is so far no chance for cure, and intensive treatment does not prolong survival but decreases quality of life [21].

Modern video-laparoscopy and laparoscopic ultrasonography (LUS) performed under general anesthesia are far more sophisticated than the formerly done direct laparoscopy performed under local anesthesia. LUS not only permits visual inspection of the whole abdominal cavity [28, 29], it also provides an opportunity to inspect formerly inaccessible regions, such as the lesser sac. Surgical laparoscopy (Table 5) already has distinct implications for staging the T, N, and M categories for locally advanced gastric cancer [30]. The T stage can be assessed by direct inspection of the primary lesion and the movement of the stomach. Especially the T2 and T3 stages (subserosal invasion or serosal perforation) can be differentiated with high accuracy. Evaluating the N category, it is possible to inspect suspicious lymph nodes and to obtain biopsy

Table 6. Surgical laparoscopy for gastric carcinoma.

Condition	Patients	
	No.	%
Up-staging	29	26
Down-staging	17	16
Additional information	6	5
No additional information	59	53
Total	111	100

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specimens from various sites. The lymph nodes around the celiac axis ($M1_{Lym}$) can also be evaluated. The most advantageous use of laparoscopy for staging lies in evaluating the M stage. The peritoneal spread of a tumor is easily visualized and confirmed by a video-guided biopsy. Feussner et al. [31] found peritoneal carcinosis in 23% of 111 patients during laparoscopy. This condition had been undetected after complete conventional staging. Intralaparoscopic US probably leads to the detection of even small liver metastases. As mentioned, the most significant impact of video-laparoscopy on staging lies in the detection of peritoneal carcinosis. In our study [31] additional information with therapeutic impact was found in 47% of 111 patients with gastric cancer following laparoscopy. The results are summarized in Table 6. The potential hazards of the method, such as free tumor cell implantation into the abdominal wall, must be evaluated further [32, 33].

Abdominal Lavage

In addition, surgical laparoscopy provides the possibility of obtaining abdominal lavage before and at the end of the procedure. With modern immunohistochemical methods the cytologic evaluation of the lavage fluid provides additional valuable information.

If gastric cancer penetrates the mesothelial layer of the serosa, tumor cells are detectable in the abdominal cavity. Boku et al. [34] described definite prognostic significance of serosal invasion and free intraperitoneal cancer cells for gastric cancer. However, a positive result of cytologic evaluation using conventional staging techniques depends on the amount of involved serosa, which must be about 20 cm^2 [35].

It is valuable to microscopically evaluate the cell samples obtained by lavage following immunocytological staining. The application of monoclonal antibodies against epithelial cells increases the rate of detection of free tumor cells in the abdominal cavity over that seen with conventional staining techniques. In our prospective study [36] we investigated the impact of this new method in 118 patients before R0 resection. During routine panoptic cytologic evaluation five patients (5%) were diagnosed and another six had suspected disease. In the same group of patients, free tumor cells were detected in 24 patients (20%) following immunocytologic staining. The observation of tumor cells was significantly correlated to the pT and N categories and tumor size.

The presence of tumor cells in the abdominal cavity has a significant impact on survival. In a multivariate analysis, the nodal status, free tumor cells, and distant lymph node involvement were independent prognostic factors. The detection of free tumor cells has the most impact on the prognosis for T2 and T3/4 patients [36]. Applying abdominal lavage and subsequent immunocytologic staining of the cells, it is possible to discover patients with a high risk for subsequent diffuse metastasis [37]. It must be proved in additional studies whether patients with free tumor cells can profit from multimodal treatment strategies (e.g., neoadjuvant or intraperitoneal chemotherapy). It seems obvious that this group of patients even with early T2 stage disease could profit from these regimens.

Carcinoembryonic Antigen A Level in Peritoneal Lavage

It is useful to investigate abdominal lavage for the presence of tumor markers. In a study by Asao et al. [38], antibody to carcinoembryonic antigen (anti-CEA) was found in peritoneal washings. They found a correlation between CEA levels in preoperative lavage and survival times after curative operation. It was concluded that CEA levels above 100 ng/g of protein indicate a poor prognosis and could be a sensitive detector of so far invisible peritoneal dissemination (microinvasion).

Cytokeratin-Positive Cells in Bone Marrow

The use of anti-epithelial monoclonal antibodies has led to a new and promising method: detection of cytokeratin-positive cells in the bone marrow [39]. Discussions still arise whether gastric cancer at an early stage is not a local disease but already a systemic one. After the research by Riethmüller and colleagues [40] it is now possible to detect micrometastases (i.e., single tumor cells in the bone marrow) using bone marrow aspirates. Tumor cells from gastric cancer are detected by applying a monoclonal antibody against a cytokeratin. In the first published results [41] the presence of tumors cell in the bone marrow seems to be an strong predictor of early relapse and overall poor prognosis.

New Prognostic Factors

Detection of patients who have resectable high risk disease is being increasingly taken into account by surgeons and oncologists. Although we have the generally accepted TNM staging system, which is a fairly good instrument for describing wall infiltration and the overall tumor spread of gastric cancer, this system is mechanistic. There is still much to learn about the individual growth behavior of an individual tumor. A large number of tumor biology-related factors have been investigated, mainly by molecular biologic methods, but so far there is little impact of these investigations on treatment. We briefly discuss the most promising "modern" prognostic factors. To evaluate these factors basic research must be done following R0 resection. Multivariate analysis must be performed to evaluate the impact of a single factor on overall survival. Unpredictable therapeutic effects should be excluded. Only those patients should be taken into account who are treated according to standardized and strict treatment protocols.

Up to now, much progress has been made in identifying abnormalities of proto-oncogenes, tumor-suppressor genes, and growth factors and their receptors. The field of molecular biology-related prognostic factors is often complex. Most factors are evaluated retrospectively in paraffin-embedded material. It must be stressed again that each factor that is supposed to have an

impact in prognosis has to be tested prospectively following R0 resection in a multivariate analysis. Only when this standard is followed can any factor be proved.

Ras Protein

The ras-protein p21 is encoded by three *ras* genes: H-*ras*, K-*ras*, and N-*ras*. It is thought normally to have a role in signal transduction, proliferation, and differentiation [42]. Correlation of *ras* immunostaining with depth of invasion, metastases, and worse prognosis has been reported in the large survey of 171 cases [43] but not in smaller studies [44]. *ras* Overexpression, however, does not appear to be specific for carcinoma [45]. A study by Yamamoto et al. [46] of 174 gastric carcinomas showed that increased co-expression of *ras* and transforming growth factor α (TGFα) correlated with stage, grade, depth of invasion, metastases, and worse prognosis. That finding raises the question that differences in *ras* expression among tumors may reflect different proliferation rates rather than different patterns of differentiation.

p53 Tumor Suppressor Gene

The p53 tumor suppressor gene mutation is the most common defect found in human cancer [47]. Studies have found a large number of abnormalities in gastric carcinoma by direct DNA analysis. Abnormalities have been found in both intestinal and diffuse types and more commonly in metastases than in primary cancer. p53 immunopositivity is associated with poorer survival [48]. Further evaluation of p53 as a prognostic and diagnostic marker for use on biopsy and cytologic specimens is merited.

Growth Factor Receptor

Abnormalities of several growth factor receptor systems have been found for gastric cancer. The hst-1 oncogene encodes fibroblast growth factor 4 (FGF-4) and is often co-amplified with the int-2 oncogene encoding FGF-3. The reports, however, are not clear about how often they are co-amplified in gastric carcinoma. An impact on prognosis has not yet been shown. Intestinal-type tumors tend to show a higher frequency of overexpression of receptors of the epidermal growth factor (EGF) system than do diffuse or undifferentiated tumors. It has been shown with receptors for EGF, IRBB2, and IRBB3. The situation with the numerous ligands is less clear; elevated levels of TGFα and EGF have been shown in both intestinal and diffuse carcinomas [49]. Although more advanced tumors in most studies have higher levels of expression of both receptors and ligands than early cancer [50], there are conflicting reports as to their prognostic value [42].

Cell Adhesion Molecules

To understand the mechanisms of metastasis, it must be determined how cancer cells detach from primary tumors. Mainly, two adhesion molecules are under scientific evaluation: CD 44 and E-cadherin. CD 44 is a highly glycolysated cell surface molecule that appears to be involved in cell–cell and cell–matrix interactions [51]. The molecule has aroused interest because of the discovery that the expression of one isoform of CD 44 distinguished metastatic from nonmetastatic adenocarcinoma cell lines. It was proved by transfection with cDNA encoding this isoform

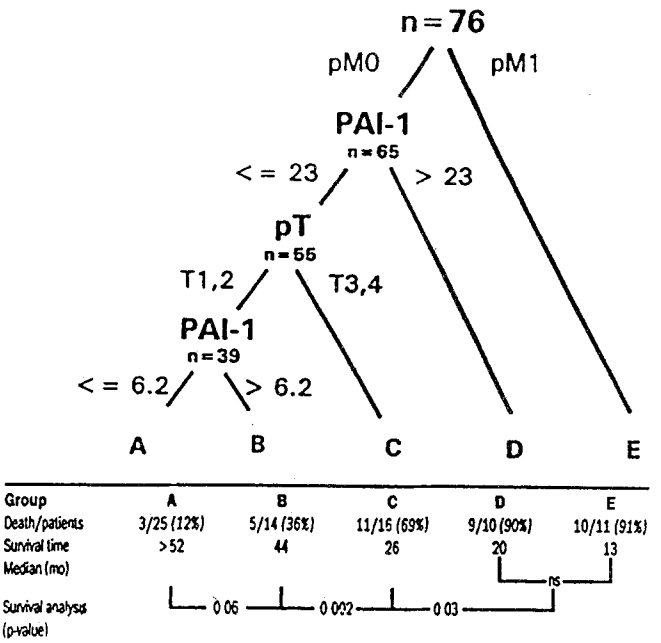

Fig. 1. CART (classification and regression tree) analysis and survival in 76 patients with R0 resected gastric cancer [58]. An elevated level of the proteolytic factor PAI-1 allows identification of a subgroup of high risk gastric cancer patients. In future study protocols this group could provide candidates for neoadjuvant or adjuvant therapy.

that CD 44 itself plays a role in metastasis [52]. In a prospective and multivariate-tested investigation, Mayer et al. [53] reported that CD 44 expression was correlated with distant metastases at the time of diagnosis and with recurrence and increased mortality following R0 resection.

The calcium-dependent homophilic adhesion molecule E(epithelial)-cadherin has been shown to suppress invasive growth of epithelial cells in vitro; loss of its expression is suspected to be important to the invasion and metastatic potential of epithelial tumors in vivo [54]. In an immunohistochemical analyses, down-regulation of E-cadherin was found to be correlated with cellular dedifferentiation and glandular disintegration [55]. An article by Becker et al. [56] provided strong evidence that E-cadherin mutations, which were not present in normal mucosa, contribute to the development of metastatic human tumors.

Proteolytic Factors

Another promising field in prognostic parameter research is investigation of the proteolytic factors urokinase-type plasminogen (uPA) and plasminogen activator inhibitor type I (PAI-1). In a prospective study [57, 58] we showed by multivariate analysis that both proteins could serve as independent prognostic factors for gastric cancer. Furthermore, high levels of PAI-1 could be important for reimplantation of circulating tumor cells at distant places [59] (Fig. 1).

Proliferation-Associated Antigens

The interest in proliferation kinetics of tumors has steadily grown. Through the discovery of the various "cyclin systems," which

obviously trigger the cell cycle, the problem of tumor growth has become focused and has evoked new interest. It was shown recently that high levels of proliferating cell nuclear antigen (PCNA), a proliferation-associated antigen, have prognostic significance in gastric cancer [60]. The correlation has failed, however, for Ki-67, also a proliferation-associated antigen.

Using the thymidine analog bromodesoxyuridine (BrdU) in vivo, it is possible to label S-phase cells of the tumor. Using flowcytometric techniques, a potential doubling time of gastric tumors could be achieved [61]. With this method it is possible to obtain a fairly accurate insight on individual proliferation kinetics. Wilson et al. [62] showed that using homogenates of labeled cells the heterogeneity of the tumor is negligible. The prognostic value of the potential doubling time and the BrdU. labeling index has been reported for colon and gastric cancer [63], although the results are somewhat contradictory [64].

Knowledge of molecular pathogenesis and cell proliferation in gastric carcinoma is at an early stage. Differences in the pathohistologic types (Laurén classification) have been found, and some studies have shown a correlation with prognosis. However, tumor biology-related techniques cannot yet be recommended for routine diagnostic use. Up to now, no newly found prognostic factor has changed the therapy for gastric cancer. Exploration of this complex disease, however, has an exciting future and is of high clinical relevance.

Computer-Assisted Staging

A totally different field is the development of computer programs for preoperative staging to predict lymph node involvement and individual prognosis. It has been tried with a computer program to fill the gap in the staging of the N category, as no diagnostic method can so far distinguish between invaded but not enlarged lymph nodes. Even using video-laparoscopy it is not possible to biopsy every inspected lymph node.

Maruyama et al. [5] analyzed data from 3040 patients operated on for gastric cancer in the National Cancer Center of Tokyo. From this analysis a computer program was developed for evaluating survival time and infiltration of lymph nodes in individual cases. For the computerized prediction of lymph node involvement, the same information is needed as for therapeutic decision making (e.g., tumor type, depth of infiltration, location, diameter of the primary, and histologic type). The program analyzes the variables mentioned above and calculates the probability of metastastic lymph nodes for each of the 16 lymph node groups according to the criteria of the Japanese Research Committee for Gastric Cancer [65]. Comparing survival rates and lymph node involvement between Japanese and German patient populations with gastric cancer the results were comparable [66].

The Maruyama computer program was evaluated in a cohort of German patients with gastric cancer to examine the validity of its prediction in this population [67]. The program was accurate in its prediction for incidence of metastasis. For lymph nodes (LN) in positions 13 to 16, a sensitivity of 100% and specificity of 95% was calculated. For LNs in areas 7 to 16, infiltration was predicted correctly as well. The validity of the program with respect to positions 1 to 6 was lower.

The most important measure of the validity of this method is the negative predicted value. It indicates the number of patients with unpredicted lymph node metastases found after surgical exploration. Using the Maruyama computer program for German patients, it occurs in only 2% of cases [67].

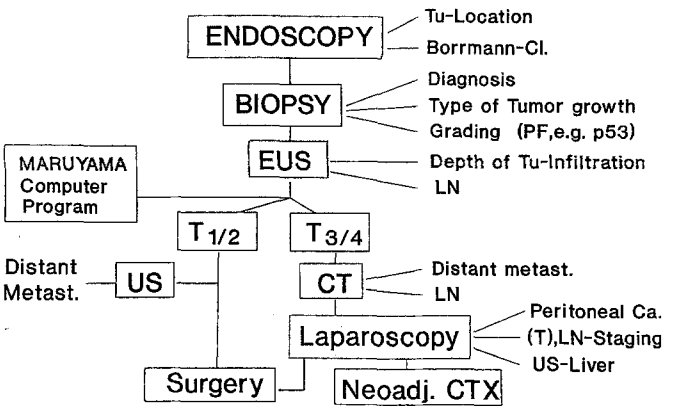

Fig. 2. Recommended diagnostic procedure for gastric cancer for oncologic centers prepared to administer multimodal treatment. PF: prognostic factor.

To reduce the number of false-positive results even more, we developed a program using the method of artificial neuronal networks (ANN). In neuroinformatics the knowledge of the nervous system is used to emulate biologic neuronal networks interpreted as information-processing systems with artificial neuronal network. We use a simple ANN that consists of three parts: an input layer, an output layer, and weighted junctions between these layers ("synapses"). The weights of these junctions are learned by training the ANN with prepared data and special algorithms [68]. The preliminary results demonstrated that when using the ANN the number of false-positive predictions can be reduced. The mean frequency of correct predictions for the various lymph node areas is 88.7%. Thus artificial intelligence can provide techniques such as neural networks or knowledge-based systems, which can offer a variety of capacities for solving the problem of staging the nodal status in patients with gastric cancer.

Conclusions

Meticulous, sophisticated pretherapeutic staging is the precondition for any multimodal individual treatment. Neoadjuvant treatment becomes possible only after accurate preoperative staging. Basic staging of gastric carcinoma should include endoscopy, biopsy, EUS, CT scans of the whole abdominal cavity, and for stages T2B/T3 video-laparoscopy. Modern staging procedures should include evaluation of abdominal lavage to detect hidden free tumor cells and tumor markers.

The biology of growth patterns of gastric carcinoma is under exciting scientific evaluation. The results of molecular biology and cell cycle research are still somewhat conflicting. The ongoing research will provide us with new insights on the prognosis of an individual patient.

The routine diagnostic procedure shown in Figure 2 is recommended for oncologic centers prepared to administer multimodal treatment.

Résumé

La détermination préopératoire du stade du cancer gastrique a une place importante d'abord dans chaque bilan et ensuite pour la

mise en route du protocole thérapeutique. A présent, il faut considérer le <<staging>> comme bien plus que la simple détermination de l'infiltration pariétale de la lésion, *i.e.* le stade <<T>>, de l'état des ganglions, la catégorisation <<N>>, et de la présence ou non des métastases à distance, ou le stade <<M>>, selon la classification de l'UICC. De plus en plus, il faut inclure l'évaluation des facteurs pronostiques tels que la RAS-protéine, le gène suppreseur p 53, les récepteurs des facteurs de croissance, les molécules d'adhésion cellulaire, des facteurs protéolytiques, et des antigènes en rapport avec la prolifération. Une amélioration de l'évaluation de l'état des ganglions (classification <<N>>) est possible grâce aux techniques modernes informatisées. Le <<staging>> conventionnel fait appel à l'endoscopie conventionnelle et l'échoendoscopie, l'échographie conventionnelle, la tomodensitométrie et l'imagerie par résonance magnétique. D'autres progrès sont attendus de la laparoscopie avec échographie per laparoscopie et de l'analyse du liquide de lavage péritonéal y compris la détection des cellules tumorales libres par l'immunohistochimie. Les facteurs pronostiques biologiques les plus promettants sont discutés.

Resumen

La estadificación preoperatoria del cáncer gástrico juega un papel crucial en la aplicación de protocolos de tratamiento multimodal. En los tiempos actuales la estadificación trata de ir más allá de la simple evaluación de la infiltración tumoral de la pared del órgano, o sea el estado T, de la condición de los ganglios (categoría N) y de la presencia de metástasis distantes (estado M), en concordancia con los criterios de la UICC. La estadificación incluye, en términos de la oncología quirúrgica moderna, más y más la evaluación de los denominados factores de pronóstico, tales como la proteína RAS, el gen supresor T53, los receptores de fctor de crecimiento, las moléculas de adhesión celular, factores proteolíticos y antígenos asociados a la proliferación. Además, ahora la evaluación del estado ganglionar es posible mediante sofisticados programas de computador. En el presente artículo se discute la estadificación convencional del cáncer gástrico utilizando endoscopia y sonografía, ultrasonido convencional, escanografía computadorizada e imagenología por resonancia magnética. Posibles avances en cuanto a estadificación en centros oncológicos deberán incluir la laparoscopia quirúrgica, la ultrasonografía laparoscópica y la evaluación meticulosa de un lavado peritoneal orientado a la detección immuno-histoquímica de células tumorales libres. También se discuten brevemente los factores de pronóstico de naturaleza de biología tumoral que aparecen más promisorios en la valoración del cáncer gástrico.

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