

Dealing with the gray zones in the management of gastric cancer: The consensus statement of the İstanbul Group

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ABSTRACT

The geographical location and differences in tumor biology significantly change the management of gastric cancer. The prevalence of gastric cancer ranks fifth and sixth among men and women, respectively, in Turkey. The international guidelines from the Eastern and Western countries fail to manage a considerable amount of inconclusive issues in the management of gastric cancer. The uncertainties lead to significant heterogeneities in clinical practice, lack of homogeneous data collection, and subsequently, diverse outcomes.

The physicians who are professionally involved in the management of gastric cancer at two institutions in İstanbul, Turkey, organized a consensus meeting to address current problems and plan feasible, logical, measurable, and collective solutions in their clinical practice for this challenging disease.

The evidence-based data and current guidelines were reviewed. The gray zones in the management of gastric cancer were determined in the first session of this consensus meeting. The second session was constructed to discuss, vote, and ratify the ultimate decisions.

The identification of the T stage, the esophagogastric area, imaging algorithm for proper staging and follow-up, timing and patient selection for neoadjuvant treatment, and management of advanced and metastatic disease have been accepted as the major issues in the management of gastric cancer. The recommendations are presented with the percentage of supporting votes in the results section with related data.

Keywords: Gastric cancer, neoadjuvant treatment, adjuvant treatment, staging, surgical treatment

INTRODUCTION

Gastric cancer is the third leading cause of cancer-related death in the world (1). The frequency of gastric cancer varies based on the geographical location. The biologic and environmental differences cause significant variations in its treatment (2). The 2014 report records of the Turkish Ministry of Health Cancer Control Department reported that the national prevalence of gastric cancer ranks fifth and sixth among men and women, respectively (3). Compared with the national reports, there are some differences and inconclusive issues present in the international guidelines from the Eastern and Western countries (4-11). While there are some comprehensive reports on planning a treatment strategy for gastric cancer, the lack of a national consensus results in remarkable heterogeneities in clinical practice, deficient data collection, and diverse outcomes in Turkey (12,13). Similar issues do exist in the Western Asian and Eastern European countries (14). Therefore, the physicians who were professionally involved in the management of gastric cancer at two

institutions in İstanbul, Turkey, assembled a consensus meeting to clarify problems and establish feasible, logical, measurable, and collective solutions in their clinical practice for this challenging disease.

MATERIALS AND METHODS

The physicians at the Departments of Gastroenterology, General Surgery, Genetics, Medical Oncology, Nuclear Medicine, Radiation Oncology, Radiology and Pathology of the Acıbadem Mehmet Ali Aydınlar University and Koc University organized a consensus meeting on the management of gastric cancer. This consensus meeting focused on the management of gastric adenocarcinoma only. The other rare types of gastric cancers, including gastrointestinal stromal tumors, lymphomas, and neuroendocrine tumors were excluded. An organizing committee planned the methodology and statements of the consensus meeting. Each department-Gastroenterology, General Surgery, Genetics, Medical Oncology, Nuclear Medicine, Pathology, Radiation Oncology, and Radiolo-

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gy-formed a working group prior to the meeting to determine the controversial topics of the current guidelines and lack of data on particular topics in the gastric cancer management. The evidence-based data and current guidelines were reviewed.

At the first session of the meeting, a selected faculty member from each branch presented the evidence-based data and guidelines recommendations. Each presentation was followed by an open discussion on controversial topics. The specific items and problematic issues with regard to diagnosis, staging, treatment, and follow-up were determined in the first session and discussed in the second session. Panel discussions took place about the consensus statements for the identified challenging conditions and voted one after another to ratify the ultimate decisions. If all the participants accepted a statement, this meant it had a full support (Level A recommendation). If more than 80% of the participants agreed with a statement, this meant it had a strong support (Level B recommendation). If more than 50% and less than 80% agreed with a statement, then this meant it had a moderate support (Level C recommendation). Statements with the support of less than half of the consensus were excluded.

RESULTS AND DISCUSSION

The consensus program focused on the implementation of a successful strategy for gastric cancer. Ninety-two physicians from the faculty voted and formed the consensus statements. The disease staging was determined based on the eighth version of the AJCC-UICC/TNM classification.

Presentation and Diagnosis

The symptomatic characteristics of gastric cancer are strictly associated with geographic location, which strongly reveals the impact of the environmental factors, life style, and nutritional habits on its pathophysiology (6,14). Smoking, salty diet, the *Helicobacter Pylori* (*H. pylori*) infection, smoked foods, pickled vegetables, previous gastric surgery, pernicious anemia, adenomatous polyps, chronic atrophic gastritis, and radiation exposure are the major environmental risk factors for the gastric cancer development. Dysphagia, dyspepsia, vomiting, abdominal pain, weight loss, and iron deficiency anemia are among the common signs and symptoms (15). The incidence of gastric cancer varies among the countries. Gastric cancer is relatively frequent in the East Asia, South America, and Eastern Europe compared to the Western countries (12-14). It is the fifth most common type of cancer and

the fourth most common cause of cancer-related death in Turkey. A definitive treatment of gastric cancer should be based on tissue biopsy (16) (Statement 1).

Statement 1: The definite diagnosis of gastric cancer in routine practice is made by histopathologic evaluation of an endoscopic biopsy. (Level A recommendation)

Features of a standard biopsy for diagnosis

All suspicious gastric lesions should be biopsied during an upper gastrointestinal endoscopy. Description of the characteristics and precise location of abnormal lesions are the crucial components of an endoscopic evaluation (17,18). In addition to a standard pathological evaluation, additional tissue samples are usually needed for genetic and immunologic tests. Considering all those required steps, obtaining adequate tissue material is crucial for diagnosis. The number of biopsies should be at least six from a suspicious lesion. Additionally, a minimal number of five samples of biopsy material should be collected from tumor-free sites of the stomach (Statement 2). All biopsy samples should be placed in separately labeled containers based on their location. Cytologic brushings or washings can be useful in confirming the presence of cancer but are inadequate for definitive diagnosis (5).

Statement 2: The number of biopsies is recommended to be at least six and five from the tumor and tumor-free sites, respectively. Biopsies from the tumor can be collected into a single container; biopsies taken from the tumor-free areas should be placed in separate containers. (Level A recommendation)

Patients suffering from the aforementioned symptoms need to have a gastroscopy after a careful clinical assessment. The mean age at diagnosis of gastric cancer is 56 years in Turkey (12). Currently, there is no screening program for gastric cancer in Turkey. The screening programs have been designed based on the local characteristics and frequency of gastric cancer. The Japanese and Korean guidelines recommend gastric cancer screening beginning at early 40s (19). The North American guidelines do not support screening due to lack of evidence supporting its value in reducing mortality. However, gastroscopy after the age of 45 is recommended by some centers since the incidence of gastric cancer is relatively higher after 50s in Turkey (20).

When not to perform biopsy and when to proceed with a direct endoscopic submucosal dissection or endoscopic mucosal resection at the time of diagnosis

The surface erosion, ulceration, fold involvement, wall deformity, pitting, and non-lifting patterns are important characteristics of a lesion to determine the local resectability. For a gastric lesion, which seems removable with ESD in experienced hands, conventional biopsy may complicate the success of ESD by creating fibrosis in the body of the lesion and may disrupt its integrity (Statement 3). The European Society of Gastrointestinal Endoscopy guideline recommends endoscopically removing superficial gastric lesions with a low risk of lymph node metastasis (21). While diagnosis of a well-defined lesion is relatively straightforward with a conventional biopsy, diagnosis of a diffuse-type gastric cancer (i.e., linitis plastica) can be challenging. Because cancer cells migrate into the submucosa in linitis plastica, a conventional endoscopic biopsy cannot provide a useful material for pathological diagnosis. The endoscopic mucosal resection (EMR) or snare biopsy may provide a better tissue sample compared to the standard technique and subsequently increase the diagnostic yield in those patients (22).

Statement 3: When a neoplastic lesion seems suitable for endoscopic treatment, advanced endoscopic evaluation techniques can be used to identify characteristics of the tumor without biopsy if experienced personnel and equipment are available. If an advanced endoscopic setting is not accessible, all suspicious lesions, including T1a tumors, should be biopsied. If an endoscopic biopsy is inconclusive, an ESD- or EUS-guided biopsy can be performed. (Level A recommendation)

A good-quality pathology report and its clinical relevance

A pathology report reveals the status of the disease and the quality of a resected specimen (Statement 4). For a complete clinical evaluation of a gastric cancer specimen, a pathology report should include the type of surgery, tumor location, macroscopic type, histologic type of cancer, tumor differentiation, tumor grade, tumor pattern, invasion depth, total harvested lymph node number, metastatic lymph node number, location of metastatic lymph nodes, size of metastatic lymph nodes, presence of perineural invasion with its sizes, number of tumor deposits, location of tumor deposits, presence of lymphovascular invasion, presence of perineural invasion, presence of tumor invasion at surgical margins, margin width, the Mandard and College of American Pathologists (CAP) classifications if neoadjuvant treatment was given, and distance between the tumor and resection margins (23-25). The latest version of the AJCC-UICC/TNM classification should be used to stage gastric cancer.

Evaluation of some biologic markers in the biopsy specimen is useful for planning a chemotherapeutic regimen. The human epidermal growth factor receptor 2 (HER2 or CerbB-2) is a protooncogene that plays a key role in regulating the signal transduction pathways related to cell growth and differentiation (26). The HER2 overexpression varies between 4% and 53% in gastric cancer, and it is a major denominator when selecting patients for molecular-targeted therapy (26). Majority of series consider that the HER2 positivity is associated with poor survival (27). Trastuzumab is one of the first developed molecular-targeted drugs, and it was initially introduced for the treatment of HER2-positive advanced breast cancer (28). While other types of molecular HER2-targeted agents are currently being tested, trastuzumab is the first molecular agent approved as a standard treatment in gastric cancer. Based on our consensus statement, HER2 and the microsatellite instability (MSI) status can be evaluated up on oncologists request (29,30).

Another emerging biomarker is PD-1, which downregulates excessive immune responses by binding to its ligands, namely PD-L1 and PD-L2. The PD-L1 expression has been detected in more than 40% of patients with gastric cancer. Targeting of the PD-1 pathway in gastric cancer has shown some promising results (31). Pembrolizumab is approved in some countries for the treatment of advanced melanoma, and it has been approved in the United States for the treatment of metastatic non-small-cell lung cancer that has progressed, or after platinum-containing chemotherapy, and which expresses PD-L1 (32). Because we do not have much evidence to recommend a standard PD-L1 analysis for pembrolizumab treatment on routine basis, our faculty supports PD-L1 tests for only experimental purposes.

Statement 4: The histopathology of tumor, carcinoma patterns with ratios, and the World Health Organization and Lauren's classification should be reported in all pathology reports evaluating the resected gastric specimen. The HER2 and microsatellite instability can be assessed in the endoscopic biopsy materials based on physician's request and can be performed routinely in resected specimens of radical gastrectomies. The PDL-1 test can be evaluated for experimental purposes. (Level A recommendation)

Staging

The best imaging modality

A multislice computed tomography (M-CT) of the thorax, abdomen, and pelvis with an oral and intravenous

contrast agent is the standard component of staging (Statement 5). Generally, 1 liter of an oral contrast agent is used for M-CT of the thorax, abdomen, and pelvis. It is recommended that 750 mL of the contrast agent 30 minutes and 250 mL immediately prior to imaging should be taken orally. Antiperistaltic agents may improve the quality of M-CT in elective conditions (33,34). In routine clinical setting, a patient can be referred to a tertiary center with a definitive histological diagnosis and a positron emission tomography-computed tomography (PET-CT). If the quality of a PET-CT is satisfactory for planning the required treatment, re-imaging with M-CT is not necessary. However, it should be reminded that a PET-CT has a low sensitivity in defining diffuse and mucinous gastric tumors.

Statement 5: A multislice computed tomography (M-CT) of the thorax, abdomen, and pelvis with oral and intravenous contrast agent is the standard component of staging. Using an antiperistaltic agent and oral intake of 250 mL of additional contrast agent immediately before the imaging can improve the quality of the assessment. (Level A recommendation)

If a CT-guided biopsy reveals no metastasis in a suspicious lymph node, and there is still a strong clinical doubt for metastatic disease

Detection of metastases in the regional and distant lymph nodes plays a key role in the planning of neoadjuvant or systemic treatment. While an EUS may help gastroenterologists to perform biopsy, identification of non-regional distant metastases can be challenging in gastric cancer. The efficacy of PET-CT for evaluating mucinous adenocarcinoma can be limited. The FDG uptake increases with the tumor cellularity and decreases with the amount of mucin. A PET-CT for detecting mucinous adenocarcinoma has a lower sensitivity compared with non-mucinous adenocarcinomas (35,36). While there is no high-level evidence, the high FDG uptake areas can correlate with the presence of invasive mucinous adenocarcinoma (37). If there is a clinical benefit to guide further treatment step (Statement 6), a PET-CT can be preferred in the assessment of biopsy-negative lymph nodes to guide the implementation of re-biopsy in selected cases.

Statement 6: A PET-CT can be preferred in the assessment of biopsy-negative lymph nodes to guide re-biopsy. (Level B recommendation)

Should PET-CT be performed in esophagogastric cancer?

Considering the aggressive nature of these cancers, detecting of regional lymph node and distant organ metastases is crucial for planning a proper treatment modality. Our faculty supports the administration of neoadjuvant treatment with chemoradiation for Stage 2 patients carrying risk factors for lymph node metastasis and all patients with Stage 3 esophagogastric cancers. PET-CT is the most sensitive imaging modality that provides a whole-body evaluation to clarify the N and M status at the time of index diagnosis (5). No further imaging is needed if a multiple distant metastatic disease is confirmed with a PET-CT (Statement 7).

Statement 7: A PET-CT is used in Stage 2-4 cancers of the esophagogastric junction, including mucinous and diffuse adenocarcinoma of the stomach, and it is unnecessary for early stage cancers in the pretreatment evaluation and follow-up after neoadjuvant treatment. All patients undergoing neoadjuvant chemoradiotherapy for esophagogastric junction cancers should have a PET-CT scan preferably at the time of radiotherapy. A PET-CT is not necessary for M1 patients, except for the assessment of oligometastatic disease, which may be suitable for curative treatment. (Level A recommendation)

Role of positron emission tomography-for clarifying distant organ metastases in patients with locally advanced gastric cancer confirmed by a multislice computed tomography

When a good quality M-CT shows no distant organ and no regional lymph node metastasis, clinicians can feel strong about the decision-making process for planning the required treatment. However, there can be a clinical or a laboratory sign of a particular organ metastasis without an imaging documentation. In such circumstances, there is a need to determine and plan neoadjuvant or induction chemotherapy. For example, if a M-CT of the thorax, abdomen, and pelvis reveals multiple regional lymph node metastases, and the next step is planning neoadjuvant treatment (Statement 8), a PET-CT can be performed to clarify distant organ metastasis as the second line imaging modality (38). Since this statement has a borderline support from the faculty, a MDTB decision may help clinicians to guide further imaging modality in these complicated clinical situations.

Statement 8: PET-CT can be performed to assess a distant metastatic disease in the presence of multiple regional lymph node metastases. (Level C recommendation)

Best imaging modality for follow-up after treatment

Using the same imaging modality for monitoring neoadjuvant or induction treatment provides measurable and reliable data to evaluate the efficacy of therapy. Despite the lack of dynamic imaging, M-CT provides more detailed information compared to PET-CT for evaluating lesions that are less than 1 cm in diameter and not utilizing FDG (Statement 9).

Statement 9: Preference of the same imaging modality at the time of index assessment and monitoring is recommended during the follow-up. Another imaging modality can be used if the treatment strategy must be changed due to new findings. If the patient had a PET-CT as the index-imaging modality, and the result is inconclusive for a metastatic disease, a M-CT can be used for further investigation. MRI should be performed for the assessment of liver metastases if either an interventional treatment is planned or the index-imaging modality is inconclusive for describing lesions. (Level A recommendation)

When to use EUS for diagnosis

Clarification of risk factors for lymph node metastasis and description of tumor invasion is the purpose of the EUS use in the management of gastric cancer (Statement 10). The sensitivity and specificity of EUS to discriminate the T1-2 lesions from the T3-4 lesions are 0.86 and 0.91, respectively. EUS can identify the lymph node metastasis with a 0.69 sensitivity and 0.84 specificity. A local excision can be considered in experienced hands for lesions approximately 2 to 3 cm in diameter with the features of a low-risk SM1 invasion based on the EUS findings (39).

Statement 10: EUS is the major tool to determine the T status in patients who have no proven lymph node or distant metastasis. For patients with no lymph node metastasis, EUS may or may not be preferred in early stage tumors (T1a) if the tumor is less than 2 cm in diameter in relation with the experience of the endoscopist. EUS should be performed if there is no radiologically proven lymph node and distant organ metastasis when a local excision is planned according to extended resection indications. (Level A recommendation)

When to prefer the EUS-guided lymph node biopsy

Kwee et al. (40) reported that the diagnostic accuracy of M-CT for overall T-staging of gastric cancer varies between 77.1% and 88.9%. The sensitivities and specificities for the blinded and unblinded reviews on M-CT are 19%-27% and 98%-100%, respectively (41). A PET-CT

has a 76% and 78% sensitivity and specificity, respectively, for detecting distal esophageal and esophagogastric junction cancers. Considering the acceptable quality of detection rates with conventional imaging modalities, the routine use of EUS-guided biopsy is not recommended (Statement 11). For patients who are not candidates for surgery, EUS can be used selectively to discriminate a lymph node involvement in early gastric cancers with a mild or increased risk for metastasis (42).

Statement 11: Routine use of the EUS-guided lymph node biopsy is not recommended. (Level B recommendation)

When to perform diagnostic laparoscopy and peritoneal lavage

Although it is a time-consuming procedure that adds a considerable cost to the overall hospital expenses, diagnostic laparoscopy and peritoneal lavage (DLPL) is recommended in all the stages of the disease, beginning with 1b (5). The risk of a positive peritoneal cytology remarkably increases in T3 and T4 tumors. A DLPL prevents unnecessary laparotomies by detecting radiologically unproven metastases. Positive cytology is one of the most important factors affecting the long-term outcomes in patients with gastric cancer. In patients undergoing neoadjuvant treatment, the DLPL provides valuable data for monitoring the course of treatment. Peritoneal cytology via laparoscopic peritoneal lavage aims to detect free circulating cancer cells as a way to identify microscopic intra-abdominal spread in the absence of gross dissemination (43). The most widely used technique consists of saline irrigation of the pelvis and re-aspiration of the peritoneal fluid (44).

There are several techniques to identify malignant cells in the aspirated peritoneal fluid, such as the conventional cytology reverse transcriptase-polymerase chain reaction (45). A positive peritoneal cytology is accepted as M1 gastric cancer. However, there are some controversies in the management of the intraperitoneal metastases of gastric cancer. Positive peritoneal cytology adversely affects the prognosis, as well as the presence of gross metastases in gastric cancer (46). An eradication of positive cytology in patients with radiologically unproven metastasis prolongs survival (47). Considering the technical requirement in the operating room, appropriate laboratory setting and its realistic application in Turkey, a DLPL should be performed for all patients with T3 and T4 tumors and for all patients undergoing neoadjuvant treatment if referral to a tertiary center is not possible. Centers capable of per-

forming DLPL in their routine practice are recommended to follow the international guidelines (Statement 12). Centers capable of performing DLPL in their routine practice are recommended to follow the international guidelines as mentioned above.

Statement 12: A diagnostic laparoscopy and a peritoneal lavage should be performed for all patients with T3 and T4 tumors and for all patients undergoing neoadjuvant treatment if referral to a tertiary center is not possible. Centers capable of performing DLPL in their routine practice are recommended to follow the international guidelines. (Level A recommendation)

The role of nutrition in gastric cancer management

Weight loss is one of the most common symptoms in patients with gastric cancer. More than a 10% of body weight loss in less than a year is seen in over one-tenth of patients with gastroesophageal cancer at the time of diagnosis. The majority of patients diagnosed with advanced gastric cancer suffer from malnutrition of different severity (48). In addition to hypermetabolic state of gastric cancer, obstruction of the upper digestive tract tumor results in malnutrition. Poor nutritional status is a strong denominator for poor overall survival (49). Thus, identifying and treating malnutrition early in the course of gastric cancer is critical for improving patients' short- and long-term outcomes (50). Proper nutritional support should be planned preoperatively, and the biochemical work-up including vitamin levels should be checked in patients undergoing gastrectomy. Correction of anemia and monitoring and supplementing vitamin B12 are crucial steps. The enteral and parenteral routes in the hospital or home setting can be preferred based on patient's condition and tolerance (Statement 13).

Statement 13: Nutritional assessment and support should be planned for all patients with gastric cancer. (Level A recommendation)

Treatment

Local excision

Therapeutic role of endoscopic submucosal dissection and endoscopic mucosal resection

Clinical experience and advanced endoscopic technology have allowed physicians to prefer local excision as a curative treatment alternative in selected cases (Statement 14). T1 tumors that are less than 2 cm in diameter with good differentiation and without lymphovascular invasion are good candidates for local excision. In some experienced

centers, there are extended indications for local excision in gastric cancer; an en-bloc local excision can be performed for well-differentiated, non-ulcerous tumors larger than 2 cm in diameter that have no lymphovascular invasion. If the presence of an ulcer is confirmed, the size of tumor should be less than 3 cm in diameter; if the lesion is undifferentiated, the size of tumor should be less than 2 cm in diameter for a local excision; in the presence of T1b gastric cancer with less than 500-micron invasion from the muscularis mucosae, it can be followed up after a local invasion in experienced hands (4). The outcomes of local excisions should be presented regularly at the MDTB.

Statement 14: Endoscopic submucosal dissection and endoscopic mucosal resection can be used as a curative treatment modality for stage 1a gastric cancer without aggressive features. (Level A recommendation)

Neoadjuvant treatment

Patient selection for neoadjuvant treatment

The neoadjuvant treatment for gastric cancer has a remarkable role to improve the oncological outcomes in gastric cancer (51). Neoadjuvant treatment allows physicians to evaluate the response to therapy, to select patients for radical surgery, and to assess biological response to a particular chemotherapy regimen that may affect the choice of postoperative regimen (51,52). Early trials failed to show the proposed benefits of neoadjuvant chemotherapy in gastric cancer (53). However recent prospective randomized trials including stage T2 or higher resectable gastric (74%), distal esophageal (11%), or esophagogastric junction adenocarcinomas (15%) proved the efficacy of neoadjuvant treatment (54,55). While the European Organization for Research and Treatment of Cancer trial failed to show the expected benefits of neoadjuvant chemotherapy on survival, this trial revealed that neoadjuvant treatment improves the quality of surgery and downstages the disease by reducing the risk of lymph node metastasis (56).

In addition to chemotherapy, neoadjuvant treatment includes radiotherapy for esophagogastric cancer (57). An improved quality of surgery and prolonged survival are observed in patients undergoing neoadjuvant chemoradiation for esophagogastric cancer (51,58).

The NCCN guideline recommends the neoadjuvant treatment for gastric cancers with lymphatic involvement and all T2 tumors or higher gastric wall invasion, regardless of the lymph node invasion (5). European guidelines support this recommendation (59).

Drawbacks of clinical staging directly affects the treatment planning in gastric cancer. While EUS is the mainstay tool for preoperative staging in non-metastatic gastric cancer, the gastric wall invasion cannot be precisely determined in almost one-third to one-fourth for early gastric cancers. EUS can identify 77% of T1, 65% of T2, 85% of T3, and 79% of T4 tumors with 64% specificity and 74% sensitivity. The accuracy of EUS for N stage is only 64% and for T stage 75%, with better accuracy in T3 and T4 tumors than in T1 and T2 tumors (52). Additionally, achieving a detailed histopathologic evaluation may not be possible in every center especially for grading and immunohistochemical assessment in Stage 2 patients with gastric cancer. While centers with an excellent level of EUS experience and ability to document preoperative staging in detail are recommended to follow the international guidelines, our faculty recommends neoadjuvant treatment for all patients with Stage 3 gastric cancers and for high-grade Stage 2 gastric cancer considering the level of EUS experience in Turkey (Statement 15). The efficacy of neoadjuvant treatment for early and T2N0 gastric cancer is not clear. Thus, radical surgery may be the first-choice treatment option in those patients (39).

Statement 15: Neoadjuvant treatment is recommended in patients with high-grade T2N0 tumors, all T3 and T4, and any T-stage tumors with regional lymph node metastasis of gastric cancer. The neoadjuvant treatment for patients with low-grade T2N0 tumors is not routine. The modality for neoadjuvant treatment is chemoradiotherapy for esophagogastric and chemotherapy for the corpus and antral tumors. The neoadjuvant regimen for esophagogastric cancer should involve taxane plus platinum-based regimen with at least a total dose of 41.4 Gy external beam radiation therapy. The neoadjuvant treatment for gastric cancers located in the corpus and antrum should be assessed within 2 months before the surgery. The minimum time interval between the completion of neoadjuvant treatment and surgery is recommended as 6 weeks for patients with esophagogastric cancer and 4 weeks for patients with tumors located in the gastric antrum or corpus. The timing of radical surgery should be calibrated considering bone marrow toxicity. (Level B recommendation)

Management of obstructive gastric tumors requiring neoadjuvant treatment

Survival and operative benefits of neoadjuvant treatment in patients with distal gastric cancer are not clear. Large distal gastric cancers located in the antrum are prone to develop mechanical obstruction causing aspiration and

malnutrition. Neoadjuvant treatment can be performed following stenting when feasible. Since palliative by-pass surgery can complicate future radical procedure radical surgery can be considered as the first-choice treatment in potentially resectable obstructed distal gastric cancers regardless of the T stage (Statement 16).

Statement 16: Neoadjuvant treatment should be planned for patients with obstructing gastric cancer after attaining passage for nutritional support. A radical surgery can be performed as the first-choice treatment if a by-pass procedure cannot be accomplished in potentially resectable obstructed distal gastric cancers. (Level B recommendation)

Radical Surgery

Rationales of radical surgery

Except for the early stage, the only curative treatment method in gastric cancer is radical surgery with R0 resection (Statement 17). A total or subtotal gastrectomy is performed based on the location, type, and extent of tumor spreading (5,60-62). A total gastrectomy is the procedure of choice in the presence of proximal gastric tumors, signet-ring cell carcinomas in which the proximal border estimation is difficult due to diffusely spread pattern, hereditary diffuse-type stomach cancers due to the risk of multifocality, and large tumors of the greater curvature. If there is no dysplasia in the remnant gastric tissue and no other contraindications, a distal subtotal gastrectomy can be performed for distal gastric cancers.

Planning the resection type for esophagogastric cancer is usually challenging. While Siewert Type 1 and 2 tumors require a total or a partial esophagectomy, Type 3 tumors can be treated with a gastrectomy. The Japanese guideline recommends a distal esophagectomy with proximal gastrectomy for esophagogastric cancer (4). An esophagectomy can be done via a transthoracic or transhiatal route based on the experience and preference of the surgeon. Maintenance of the intestinal continuity can be performed with stomach, colon, or small intestine. Removal of the esophagus or stomach has no impact on the survival and recurrence in patients with esophagogastric cancer (60,63).

Minimally invasive radical gastrectomy

Although laparoscopic gastrectomy has been shown to be a method that provides general advantages of minimally invasive surgery and adequate oncologic radicality, controversies exist regarding its role, especially in the

management of advanced gastric cancers (4-7,64-66). The survival results of three prospective randomized trials (CLASS-01, KLASS-02, JLSSG-0901) evaluating the role of laparoscopic technique for gastric cancer are expected to be published soon. Based on the retrospective data, minimally invasive surgery seems to be safe and feasible for the surgical treatment of gastric cancer in experienced hands.

Extent of lymphadenectomy

An adequate lymphadenectomy is one of the most important parameters of radical gastric surgery. Although increased lymph node removal has been shown to improve staging and survival (67), harvesting of at least 16 lymph nodes for the R0 gastric resection is still accepted as adequate for accurate staging (5). In addition to providing an accurate staging, a proper lymphadenectomy potentially reduces the risk of local recurrence and may provide a better survival. While D2 lymphadenectomy has been the standard in Asia, the associated morbidities and lack of survival benefits of D2 dissection in Western trials (68-71) prevented European and American surgeons from performing D2 as a standard procedure routinely. In the following years, increased operative experience and improved medications have directed the vision of both Eastern and Western countries toward a similar direction. The Italian Gastric Cancer Study Group showed a comparable morbidity after D1 and D2 lymphadenectomy with gastrectomy in a prospective trial (72). The long-term results of the Dutch Gastric Cancer Trial revealed better survival and decreased local recurrence in patients undergoing D2 lymphadenectomy group (73). In the meantime, there have been some changes in the Japanese attitude too. It has been shown that D3 lymphadenectomy is associated with long operating times and excessive bleeding without improving long-term outcomes compared to D2 lymphadenectomy (74). The European Society for Medical Oncology (ESMO) and other main Western guidelines recommend D2 lymphadenectomy for physically fit patients (6,60).

Simultaneous organ resection with radical gastrectomy

In the past, splenectomy and distal pancreatectomy were proposed as part of the D2 resection in proximal gastric tumors. The rationale behind these additional procedures was to provide a better lymphadenectomy. The Dutch MRC and Italian studies have shown that these procedures significantly increase morbidity and mortality (67-72), suggesting that a splenectomy and a pancreatectomy should not be routinely performed. Based on the Western guidelines and Eastern data, routine splenec-

tomy, pancreatectomy, total omentectomy, and bursectomy are unnecessary unless there is a tumoral invasion into those organs (4,5,7,60,75).

Dissection of the visceral peritoneum covering the anterior pancreas and superior transverse mesocolon is named bursectomy. This procedure has been performed to prevent dissemination of microscopic tumor deposits in the lesser sac. While no long-term benefits have been proven following bursectomy, it is associated with an increased risk of bleeding and pancreatic fistula. Although Japanese guidelines recommend bursectomy for T3 and T4 tumors (4), a bursectomy is not recommended for T3 and T4 tumors in the JCOG 1001 trial (76). A total omentectomy is recommended for T3 or T4 tumors routinely. A partial omentectomy can be performed for T1 and T2 gastric tumors (4).

Statement 17: Gastric resection with D1 lymphadenectomy can be performed for palliation or for wide T1 gastric tumors. Otherwise, subtotal/total gastrectomy with D2 lymphadenectomy is the standard surgical approach for gastric adenocarcinoma. A total gastrectomy should be the procedure of choice in patients with signet-ring cell and poorly cohesive gastric carcinoma regardless of the tumor location, but distal gastrectomy can be performed for early stage tumors. If there is no dysplasia in the remnant gastric tissue, a distal subtotal gastrectomy can be performed for distal gastric cancers. A total omentectomy should be performed in all patients who had neoadjuvant treatment and T3 and T4 tumors. A partial omentectomy can be performed for T1 and T2 tumors. Distal pancreatectomy, splenectomy, bursectomy, and removal of the capsule of the pancreas are not recommended as a routine procedure with radical gastrectomy, unless there is an invasion. The quality of D2 lymphadenectomy should be evaluated based on the dissected nodal stations, but the minimum number of harvested lymph nodes is expected to be 25. Minimally invasive approach can be performed in case of surgical treatment of gastric cancer in experienced hands. (Level A recommendation)

Assessment of the surgical margins

Microscopic surgical margin positivity is related to an increased risk of local recurrence and poor survival (Statement 18). Tumor invasion in the resection margin is usually associated with aggressive disease. In some conditions including diffuse cancers and signet-ring cell histology, it can be difficult to achieve tumor-free surgical margins. Considering high probability of resection margin positiv-

ty, a routine frozen section assessment is recommended after radical surgery for gastric cancer. The surgical borders should be assessed by frozen section during surgery, especially in high-risk patients. For the proximal surgical margin negativity, a 4-cm and 5-cm tumor-free surgical margin is recommended by the NCCN and ESMO guidelines, respectively (5,6). The Japanese guidelines offer an algorithm for tumor-free resection margin based on the tumor invasion in the gastric wall as follows: T1, 2 cm; T2 and higher invasion, 3 cm; diffuse tumors, 5 cm (4-6). Achieving a 20-mm tumor-free margin is acceptable in patients with esophagogastric cancer. Considering the requirement of esophagectomy to achieve a tumor-free resection margins, the decision to perform a re-resection should be calibrated based on the patient's physical condition and stage of the tumor (77,78). The distance of proximal resection margin does not seem to affect the prognosis of gastric cancer in patients with tumor-free resection margins (79).

Statement 18: Frozen section evaluation of the surgical margins is recommended especially for cancers of the esophagogastric junction. While 5-cm clear surgical margins are expected for gastric tumors located in the corpus and antrum, achieving tumor-free margins is adequate depending on the type of surgery in esophagogastric tumors (total esophagectomy, distal esophagectomy with proximal gastrectomy, or a total gastrectomy). The decision between re-resection and systemic chemotherapy after surgery in patients with surgical margin positivity is made based on the extension of disease (ratio of metastatic lymph nodes and overall harvested lymph nodes) and the patient's physical condition. Re-resection should be performed in the same session when the frozen section is positive for all physically fit patients. (Level B recommendation)

Adjuvant treatment

Denominators of the adjuvant treatment

Advanced age, comorbid factors, poor socioeconomic status, proximal tumor location, early cancers without lymph node involvement, and clinical T1/2 and N0 classifications are associated with omission of the adjuvant therapy (80). There is good-quality evidence to support the survival benefit of adjuvant treatment after radical surgery for gastric cancer (81,82). Adjuvant treatment seems to be more efficient in node-positive patients (83). This topic is currently under investigation with prospective trials (84). It has been shown that the 5-year survival for patients randomized to perioperative epirubicin, cis-

platin, and fluorouracil has a better survival compared to those undergoing surgery alone (54,85). The ARTIST trial tested whether the addition of radiotherapy to adjuvant chemotherapy improved disease-free survival in patients with D2-resected gastric cancer. Patients with gastric cancer who underwent gastrectomy with D2 lymph node dissection were randomly assigned to either six cycles of adjuvant chemotherapy with capecitabine and cisplatin (XP) or two cycles of XP followed by chemoradiotherapy and then two additional cycles of XP (XPRT). This study revealed that including routine chemoradiotherapy in the adjuvant treatment has no additional benefit (86). The CRITICS trial evaluated the role of postoperative chemoradiation in patients with stage 1B-4A resectable gastric and gastroesophageal adenocarcinoma. After undergoing surgery following preoperative chemotherapy, patients were randomized to postoperative chemotherapy or chemoradiation. Chemoradiation did not improve the overall survival (87).

Fluoropyrimidine-based regimens are usually preferred for chemotherapy. S-1 is an oral prodrug of 5-FU, which has been used for the gastric cancer treatment (88). Both adjuvant S1 and CAPOX treatment regimens seem to improve the survival after gastrectomy with D2 lymphadenectomy. However, the efficacy of medications may vary based on geographic location. While Asian patients with gastric cancer tolerate the S1 treatment well compared to their Western counterparts gastric cancer patients Western origin have a better response to preoperative chemotherapy. While it has no value for N0 patients, adding XELOX in the adjuvant therapy may improve disease-free survival in patients with lymph node metastasis (81,89). Our general view on planning adjuvant treatment is summarized in Statement 19.

Statement 19: Adjuvant chemotherapy is required in patients with selected T2, T3-4 tumors or any T with metastatic lymph nodes. Chemotherapy is given after surgery following neoadjuvant treatment as it is planned prior to surgery. The MSI and Her-2 positivity can be considered when planning adjuvant chemotherapy. For gastric cancers located in the corpus and antrum, radiotherapy can be used based on the MDTB decision. An addition of adjuvant radiotherapy can be considered in patients undergoing surgery without neoadjuvant treatment, patients with suboptimal lymph node dissection, metastatic lymph nodes, resistant disease to neoadjuvant treatment, metastasis at non-regional distant lymph nodes, positive surgical margin(s) and cancer located on the posterior gastric wall. (Level B recommendation)

Immunotherapy for advanced disease

Recent studies reported promising results with immunotherapy for gastric cancer. The concept of immunotherapy has not been included in the routine treatment protocols, but tailored strategy-based mutations (90-92). While it is not a standard care as an adjuvant treatment after curative surgery, trastuzumab ought to be added to the first-line treatment in Stage 4 disease due to its positive effect on the overall survival (93). Pembrolizumab, a monoclonal antibody against PD-1, has a approval by the Food and Drug Administration for advanced PD-L1-positive gastric and gastroesophageal junction adenocarcinoma in patients whose cancer has progressed despite at least two prior lines of chemotherapy (Statement 20). However, there is a potential to develop resistance to pembrolizumab treatment (94-96). The tumor and adjacent tissue must stain positively for the programmed cell death ligand 1 (PD-L1) protein by companion diagnostic testing. However, some patients with PD-L1-negative tumors also benefit from pembrolizumab. A high MSI and tumor mutational load (TML) are positive predictive biomarkers for immune checkpoint inhibition in other tumors. The PD-L1 testing alone fails to detect patients who may benefit from the immune checkpoint inhibition. Tumor mutational load, MSI, and alternative PD-L1 testing thresholds may serve as predictive biomarkers for the response to immune checkpoint inhibition (94).

Statement 20: Immunotherapy can be given for advanced stage disease. (Level C recommendation)

Recurrent and persistent disease

Encouraging results after surgical treatment for recurrent gastric cancer are possibly related to good patient selection (97). Metachronous isolated oligometastatic disease in patients with a good response to systemic therapy can be treated interventionally (98). However, a MDTB should monitor this treatment until more reliable data on this subject are available (Statement 21).

Metastectomy for recurrent disease

The role of metastectomy or resection for recurrent gastric cancer has not been well known. Oligometastatic disease is being characterized by the presence of fewer than five metastases (99). The location and aggressiveness of metastases clearly change the management strategy. There is lack of evidence for recommending a curative approach in metastatic gastric cancer. While the liver is the most common site for metastases in patients with gastric cancer (100), the percentage of patients undergoing a curative liver resection for recurrent gastric

cancer is less than 1% due to the multiple, bilateral, and extrahepatic nature of metastatic disease (101).

Cytoreductive surgery for advanced gastric cancer

Cytoreductive surgery (CRS) is not a standard gastric treatment. Due to lack of evidence-based data, only retrospective results and anecdotal case series exist on the management strategies for recurrent and chemo-/radiation-resistant disease. CRS with hyperthermic intraperitoneal chemotherapy (HIPEC) has shown promising results with a relatively high perioperative morbidity in improving the disease-free and overall survival in nonelderly patients with low carcinomatosis index (102). Results of future trials will determine the safety, tolerability, and feasibility of CRS and HIPEC in the management of locally advanced and recurrent gastric cancer (103).

Statement 21: The decision on curative surgery for oligometastatic gastric cancer following systemic chemotherapy should be made by the MDTB. In patients with isolated peritoneal metastasis, CRS with HIPEC can be performed if the peritoneal carcinomatosis index is low and if disease is under control with systemic chemotherapy. Surgical treatment should be considered for recurrences, if feasible; otherwise radiotherapy can be planned. Trastuzumab should be added for Her-2 positive tumors. Intraoperative radiotherapy can be performed for selected recurrent cases. The MDTB decision is required for the surgical treatment of all types of recurrences and for all non-standard treatment modalities in gastric cancer. (Level B recommendation)

Non-operative management and palliation for unresectable disease

There is no long-term data on the outcomes in patients who had a complete clinical response to neoadjuvant treatment. Therefore, this is completely an unknown clinical scenario that we need to decide on by considering patients' benefits and medical ethics (Statement 22). On the other hand, non-operative management can be employed due to the aggressive nature of the tumor and poor life expectancy in patients who are unfit for surgery. In a selected group of patients who had radical surgery for linitis plastica, it has been shown that survival is not significantly different from that in patients who had surgery for non-linitis plastica diffuse gastric cancer (104). Therefore, it should not be forgotten that radical surgery with proper medical treatment is the gold standard treatment for all non-metastatic types of adenocarcinoma of the stomach in patients who are fit for a major laparotomy. Stenting or by-pass surgery can be performed based

on the life expectancy of patients with obstructive gastric cancer.

Statement 22: If there is a contraindication for surgery, non-operative management can be suggested in patients with pathologically proven complete response after neoadjuvant treatment based on the MDTB decision by discussing with patients all current data indicating that this is not a standard treatment for gastric cancer. The follow-up data of all patients undergoing non-operative management are expected to be presented at the MDTB. (Level B recommendation)

Follow-up

Follow-up criteria are well documented in the current guidelines with their rationale based on the characteristics of the disease, patient condition, and cost effectiveness of the monitorization modality (Statement 23). *H. pylori* infection is an important risk factor for gastric cancer in Turkey. This infection is frequently seen in patients with distal gastric tumors in Eastern Turkey (105,106). Considering the clinical entity, the eradication of the infection should not be underestimated to prevent recurrence.

Statement 23: A routine follow-up can be performed every 3 months with physical exam, the assessment of tumor markers and the M-CT imaging every 6 months. There is no need for endoscopic assessment after total gastrectomy, unless there is a symptom requiring further investigation. In patients undergoing distal subtotal gastrectomy, upper gastrointestinal endoscopy can be performed 1 to 3 years intervals. However, this interval can be shortened depending on the existence of risk factors such as the presence of dysplasia. Eradication of *H. pylori* is recommended after distal subtotal gastrectomy. (Level A recommendation)

Management of hereditary gastric cancer

There is no vast experience in the management of hereditary gastric cancer in Turkey. A multidisciplinary team approach is needed to prevent, treat, and follow-up these patients (Statement 24). Around one-tenth of gastric cancer patients have a positive family history of the disease and 1%-3% of gastric cancer arises in the setting of hereditary diffuse gastric cancer (HDGC). Diagnosis at a young age and germline mutations in CDH1 and CTNNA1 are the main characteristics of HDGC (107). While abnormal E-cadherin immunoreexpression with lacking or very low membranous expression is its main feature, identification of membranous E-cadherin can be seen

with HDGC. Immunoreexpression of Ki-67 and p53 are evaluated to determine the indolent to aggressive forms of HDGC. Gastric adenocarcinoma and proximal polyposis of the stomach is another form of the familial gastric cancer syndrome, which is related to germline mutations in the promoter 1B of the APC gene. It is described by fundic gland polyposis with focal dysplasia and intestinal or mixed-type adenocarcinoma. This clinical entity can be seen in familial adenomatous polyposis and MYH-associated polyposis syndromes. Lynch, Li-Fraumeni, Peutz-Jeghers, and hereditary breast/ovarian cancer syndromes as well as familial adenomatous polyposis and juvenile polyposis syndromes are also associated with an increased risk of gastric cancer (107).

Statement 24: Patients with gastric cancer who are younger than 40 years, people who have two documented cases of gastric cancer at any age in their family (at least one with confirmed diffuse gastric cancer), and people who have a first-degree family member with diffuse gastric cancer younger than 50 years should be directed to genetic counseling. An E-cadherin gene mutation analysis is recommended for the assessment of familial gastric cancer. A follow-up for risky population for gastric cancer syndrome should be done by a team including gastroenterologists. A genetic consultation and complete colonoscopy should be requested for patients with a positive MSI. A decision for prophylactic gastrectomy should be made by the MDTB. (Level A recommendation)

Conclusions

The consensus statement is a general outline specifically focusing on inconclusive conditions for the management of gastric cancer. A considerable number of physicians came together and had a clear consensus on over 20 critical subjects related to gastric cancer management. We recommend that all the physicians who are involved with the treatment of gastric cancer should follow the internationally accepted guidelines if there is a clear indication and recommendation on a particular issue. For the clinical conditions which have no clear direction in the current guidelines, our consensus statement may guide the clinicians to manage the patients with gastric cancer in Turkey. In two institutions, our aim is to treat gastric cancer considering the consensus statements in a standardized fashion. The short- and long-term outcomes, including postoperative complications, histopathologic results, and oncologic outcomes of the treatment modalities, which are tailored based on the consensus, are planned to be published in upcoming studies.

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