Polish Consensus on Treatment of Gastric Cancer; update 2017

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ABSTRACT:

The "Polish Research on Gastric Cancer" project has been continued since 1986. The main aim of this project, which is a multicenter and interdisciplinary research, is enhancing the treatment results of gastric cancer patients by developing and promoting the use of optimal methods for diagnosis and treatment, both surgical as well as combined.

One of the more important achievements of the project is the development and publication of a document named "Polish Consensus on Treatment of Patients with Gastric Cancer", whose first version was published in 1998. Following versions were updated adequately to changing trends in the proceedings in patients with gastric cancer.

A scientific symposium on "Polish Consensus on Treatment of Gastric Cancer – update 2016" was held in 3-4 June 2016 in Cracow. During the symposium a panel session was held during which all authors publicly presented the Consensus assumptions to be discussed further. Moreover, the already mentioned session was preceded by a correspondence as well as a working meeting in order to consolidate the position. It has to be underlined that the directions and guidelines included in the Consensus are not the arbitrarily assumed rules of conduct in a legal aspect and as such every doctor/team of doctors is entitled to make different decisions as long as they are beneficial to a patient with gastric cancer.

The Consensus discusses as follows: a) recommended qualifications (stage of advancement, pathological, lymph node topography and the extent of lymphadenectomy, division of cancer of the gastroesophageal junction), b) rules for diagnostics including recommendations regarding endoscopic examination and clinical evaluation of the advancement stage, c) recommendations regarding surgical treatment (extent of resection, extent of lymphadenectomy, tactics of proceedings in cancer of the gastroesophageal junction), d) recommendations regarding combined treatment with chemotherapy or radiotherapy, e) place of endoscopic and less invasive surgery in the treatment of gastric cancer. This publication is a summary of the arrangements made in the panel session during the abovementioned scientific symposium in Cracow in 2016.

KEYWORDS: Gastric Cancer, Helicobacter pylori, Laparotomy, Non-steroidal anti-inflammatory drugs, Immunohistochemistry, Surgical treatment, Panendoscopy, Biopsy

INTRODUCTION

The "Polish Research on Gastric Cancer" project has been continued since 1986. The main aim of this project, which is a multicenter and interdisciplinary research, is enhancing the treatment results of gastric cancer patients by developing and promoting the use of optimal methods for diagnosis and treatment, both surgical as well as combined.

One of the more important achievements of the project is the development and publication of a document named "Polish Consensus on Treatment of Patients with Gastric Cancer", whose first version was published in 1998. Following versions were updated adequately to changing trends in the proceedings in patients with gastric cancer.

The current issue of the Consensus, i.e. 2017 update, was created in a particularly important time. Firstly, recently new staging classifications of gastric cancer have been widely approved, including UICC TNM, and, which is more important, for the first time "Japanese" and "Western" classifications are parallel to each other. Secondly, new classification of Japanese scientific societies concerning the definition of topography and the extent of lymph node excision has been significantly simplified and is "friendly" for the surgeon community worldwide.

Thirdly, based on EBM results, an agreement has been reached in the lasting over 30 years discussion concerning surgical treatment (the extent of resection, the extent of lymph node excision, splenectomy) and combined treatment (perioperative chemotherapy, chemoradiotherapy, adjuvant chemotherapy).

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Fourthly, in the current version of the Consensus, the role of endoscopic treatment of early gastric cancer and the role of less invasive methods (laparoscopy and robotics) have been taken into consideration. Both methods are becoming important elements in the treatment of patients with gastric cancer.

To recapitulate, the current update of the Consensus is both an analysis and a synthesis of the current knowledge on the subject of gastric cancer treatment, with the consideration of both reports from the world literature and own experience of the centers which actively participate in the "Polish Research on Gastric Cancer" project.

The contents of this publication was prepared by the authors based on the basic rules of creating a consensus.

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1. CLASSIFICATIONS

Classification of gastric cancer advancement stage

An accurate assessment of the tumor advancement stage is a basis for introduction of the appropriate disease treatment and prognosis. It also serves as a standard in reporting new tumors and results of treatment.

The authors of the Consensus recommend using the 7th issue of TNM/AJCC classification to assess the advancement stage for patients with gastric cancer.

In 2010 American Joint Committee on Cancer (AJCC) published a new, modified 7th issue of TNM classification on gastric cancer (1,2).

The following 8th issue of this classification, whose publication is announced to be in the nearest future, is under preparation.

The new classification is used only for gastric cancer, it does not apply to other stomach neoplasms. Cancers with mixed glandular and neuroendocrinal pattern are classified the same way as gastric cancer.

It should be emphasized that in the new edition the neoplasms of gastro-esophageal junction are included in the TNM classification for esophagus cancer (1, 3).

The most important changes in the new classification as compared to the previous one from 2002 are as follows:

The definition of each category in T parameter has been changed. Five new groups of T parameter have been determined, which made it similar to the one used for other gastrointestinal cancers, i.e. T1, T2, T3, T4a and T4b (Tab. 1). Changes have been introduced for tumor with T2 parameter, where the neoplasm may infiltrate the muscle layer of stomach wall and spread by gastrocolic and gastrohepatic ligament as well as by greater or small omentum.

In case of tumors classified as T3, the tumor infiltrates connective tissue located under the serous layer but does not infiltrate the visceral peritoneum and the surrounding structures. In T4 tumors, the tumor infiltrates the peritoneum or the surrounding structures. Following structures are considered as surrounding: spleen, transverse colon, liver, diaphragm, pancreas, wall of abdominal cavity, adrenal gland, kidney, small intestine and retroperitoneum. Intramural spreading of a neoplasm to the duodenum and esophagus is classified with consideration of the greatest depth of infiltration on the listed sections of gastrointestinal tract, including the stomach. In the previous, 6th edition, the criteria T, T2a and T2b (describing the infiltration of the muscular and submucosal layer) had been reclassified to T2 and T3. This change has introduced a significant difference in a five-year survival rate of patients with tumors that infiltrate the muscular layer in comparison with the ones in whom the submucosal layer is infiltrated.

The previous T3 category has now been changed to T4a and T4b at the moment when the surrounding structures are included in infiltration. From now on, T4b tumors do not necessarily mean the 4th group of neoplastic disease by definition.

The new classification proposes also another approach in case of determining the degree of lymph node affection N (Tab. 2). The most recent classification of TNN 7th edition divided the so-far used N1 category (1 to 6 affected nodes in the region) on N1 (1-2 nodes) and N2 (3-6 nodes), with N3a parameter currently meaning 7-15 affected nodes (replaced N2), and the N3b parameter meaning 16 or more affected nodes (replaced N3) (Tab. 3).

Notably, in order to adequately assess the advancement stage of the lymph node affection by metastasis it is necessary to evaluate at least 16 lymph nodes as surgical specimens.

The diagnosis of metastasis in abdominal cavity lymph nodes other than regional lymph nodes (e.g. mesenteric, retroperitoneal, paraaortic) is classified as a presence of distant metastasis (M1 parameter). Microscopic metastatic focus of gastric cancer in the adipose tissue adjacent to the gastric cancer without changes in the lymph node pattern should be classified as a metastasis in the lymph node. The same focus on the surface of the peritoneum is classified as a distant metastasis (M1). M1 parameter is currently accepted only in case of the distant metastases. It is of particular importance in the case of total resection en-bloc for T4 tumors, which may become a treatment therapy (Tab. 3).

Stages of clinical advancement for gastric cancer are presented in the table (Tab. 4). There are some important changes introduced in the current 7th edition. First and foremost, by the division of stage II into A and B, stage II includes cases from the previous group III. The highest advancement stage IV is reserved only for the cases with distant metastases and local tumors that are very

Tab. I. Primary tumor – T parameter

7TH EDITION	IN COMPARISON TO 6TH EDITION
Tx – Primary tumor cannot be evaluated.	NO CHANGES
T0 No signs of primary tumor.	NO CHANGES
Tis Carcinoma in situ: intraepithelial neoplasm that does not infiltrate lamina propria mucosae	NO CHANGES
T1 Tumor infiltrates lamina propria, lamina muscularis mucosae, or submucosa.	Division of T1 group into T1a and T1b
T1a Tumor infiltrates lamina propria, lamina muscularis mucosae	previously T1
T1b Tumor infiltrates submucosa.	previously T1
T2 tumor infiltrates muscular layer.	previously part of T2
T3- Tumor infiltrates connective tissue located under the serous layer but does not infiltrate visceral peritoneum and surrounding structures	previously part of T2
T4 Tumor infiltrates visceral peritoneum and surrounding structures	2 subgroups separated – T4a and T4b
T4a Tumor infiltrates visceral peritoneum.	previously T3
T4b Tumor infiltrates surrounding structures.	previously T4

Tab. II. Regional lymph nodes – N parameter

7TH EDITION	IN COMPARISON TO 6TH EDITION
NX- Regional lymph nodes cannot be evaluated	NO CHANGES
N0- No metastasis is found in regional lymph nodes	NO CHANGES
N1- The presence of metastasis is found in 1-2 regional lymph nodes.	lower number of affected nodes – previous N1 is currently N1 and N2 collectively
N2- The presence of metastasis is found in 3-6 regional lymph nodes.	lower number of affected nodes – previous N1 is currently N1 and N2 collectively
N3- The presence of metastasis is found in >=7 regional lymph nodes.	previously N2
N3a- The presence of metastasis is found in 7-15 regional lymph nodes.	previously N2
N3b- The presence of metastasis is found in >=16 regional lymph nodes.	previously N3

advanced were degraded from stage IV to the newly formed stage IIIC. Therefore there is a visible tendency to lower the advancement stage regarding the changes in classification of T parameter. Only stages 0 and I were not affected by changes.

1.2. Standards of pathologic examination and histopathological classifications

The authors of the Consensus recommend the guidelines presented by the Gastrointestinal Group of the Polish Society of Pathologists (4). These guidelines, based on the rules of proceedings of both international and national science societies (5-14) are as follows.

The aim of pathologic diagnostics is to determine the diagnosis of a neoplasm, assess its advancement stage and study the prognostic and predictive factors being a basis for choosing the optimal method of treatment.

Materials for diagnostics include:
1. A small endoscopic biopsy (sample) collected during endoscopic examination.
2. A lesion extracted locally using endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).
3. Frozen samples examined during intraoperative examination.
4. Surgical specimen of the entirely or partially removed stomach with the tumor and surrounding tissues (lymphatic system, omentum, surrounding organs, e.g. spleen, pancreas etc.).

In each case a referral with patient information, clinical diagnosis, place and method of collecting material, results of previous tests and all necessary clinical information about the course of disease should be provided for the laboratory performing examination together with the tissue sample. In case of a sample or lesions that were removed endoscopically the description of the endoscopic examination including the macroscopic assessment of a lesion should also be attached.

A fixative that is used in case of tissues examined in a normal mode (after submerging in paraffin) is a 10% buffered formalin. Endoscopic samples should be immediately submerged in formalin (and not the other way round), and the topography of the sample location should be described. Information about the location and number of obtained samples from suspicious lesions and the location of the biopsy sample on the blotting paper in perpendicular plane to the surface of sample, so that the whole mucous membrane cross-section can be assessed, are the key factors to perform correct histopathological diagnosis. Lesions excised locally using endoscopic methods are then stretched on a cork, wooden or paraffin board.

Surgical specimen should be delivered to the laboratory fresh and not submerged in formalin. In case surgical specimen needs to be secured during transportation, surgeon cuts the stomach open along the greater curvature of the front wall, stretches it on a cork, wooden or paraffin board and pours formalin over the specimen. In each case it is recommended for the operating doctor to separate excised lymph nodes into groups and send each of the groups in a separate container with the description of their topography.

The material obtained for intraoperative examination should be sent for examination fresh and not poured over either with fixative or with saline.

Essential pathological data included in the description of examination

Small endoscopic biopsy.

In the endoscopic biopsy a histological type of gastric cancer is assessed according to WHO and Lauren classification (intestinal type, diffuse or mixed), as well as its differentiation grade (*Grading – G*). In the age of molecular targeted therapies, endoscopic biopsy of gastric cancer has become a useful material for examination of aberrations of *HER2* gene, both using immunohistochemical and molecular methods. However, it should be noted that a small sample of tumor may not be representative for the entire neoplasm mass due to the microscopic heterogeneity of gastric cancer. The final diagnosis may only be made after a histopathological examination of the entire tumor.

Difficulties in interpreting a small endoscopic biopsy regard the interpretation of precancerous conditions (exacerbation of atrophic gastritis and intestinal metaplasia) and lesions (intraepithelial dysplasia/neoplasia), inflammatory processes with regeneration of mucous membrane that imitates cancer infiltration and differentiating chronic inflammation, lymphomas and undifferentiated, small cell carcinoma. In the abovementioned examples it is recommended to perform immunohistochemical staining using a panel of antibodies (1 to 6 antibodies).

Lesions extracted locally using endoscopic methods (EMR, ESR).

The pathological report in abovementioned cases additionally includes examination of a lateral margin within the mucous membrane and a margin deeper in the membrane, assuming a distance of 2 mm as microscopically radical (R0). In case of difficulties in the assessment of foci of microinvasions, single diffuse cancer cells can be detected using an immunohistochemical method using keratin antibodies.

Frozen samples examined intraoperatively

In primary gastric cancer resection in cases of uncertainty of the radicalness of tumor resection an intra-operative examination of proximal or distal margin is recommended. If a diffuse type of cancer with the presence of little diffuse groups or single cells infiltrating perivascular parenchyma is being found, it is easy to miss them in a frozen specimen. That is why the examination of frozen specimens from surgical margin has its limitations in microscopic interpretation. It is sometimes required to confirm the finding in histopathological samples by an immunohistochemical examination with the use of one antibody (keratin). Another indication for intraoperative examination is a microscopic evaluation of cancer metastasis to lymph nodes or the omentum in order to determine the primary diagnosis and/or assess the advancement stage of the tumor. Intraoperative collection of stomach wall samples from the side of serous membrane is contraindicated as it breaks the natural barrier limiting cancer infiltration and may have consequences in the form of neoplasm dissemination.

Surgical specimen of stomach with a tumor

Histopathological report that includes the essential clinically useful data is based on a macro- and microscopic assessment of a surgical specimen of the stomach with a neoplastic tumor.

Tab. III. Distant metastases – M parameter

M0	No distant metastases are found to be present.
M1	Distant metastases are present.

Tab. IV. Clinical advancement stages of a neoplasm

Clinical advancement stage of a neoplasm	T parameter	N parameter	M parameter
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
	T1	N1	M0
IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
IV	Every T	Every N	M1

Macroscopic examination consists of determining the following parameters:

- Dimensions of surgical specimen: stomach length (along the greater and lesser curvature), esophagus and/or duodenum length if these organs are delivered for examination.
- Location of the tumor in the stomach near:
- stomach cardia, fundus, body, pyloric part,
- greater curvature, lesser curvature,
- anterior and posterior stomach wall.
- Largest dimension of the tumor.
- Macroscopic type of the tumor including the classification for early and/or advanced gastric cancer.
- Approximate depth of neoplastic infiltration of stomach wall with the specification of stomach wall layers affected by infiltration and evaluation whether the infiltration involves the tissues surrounding the stomach.
- The condition of proximal and distal margins while describing whether the margins are affected by the neoplastic process and providing the distance between the margin and the neoplastic infiltration.
- The description of lesions on the surface of serosa with marking them using ink.
- The condition, location and number of lymph nodes with the specification of a number of enlarged lymph nodes suspected of metastases.
- Condition of lesser and greater omentum and the surrounding tissue.
- The description of spleen if it is present in surgical specimen.

Microscopic examination includes the following parameters:

- histological type according to the World Health Organization (WHO) classification (2010) (Tab. 5) and Lauren classification (obligatory) as well as according to Goseki (conditionally). Lauren classification consists of intestinal type, diffuse type and mixed type.
- cancer histological differentiation grade according to grades: G1 – highly differentiated, G2 – moderately differentiated, G3 – poorly differentiated.
- cancer advancement stage according to the 7th edition of pTNM (AJCC/UICC) classification that was presented in chapter 1.

It has to be emphasized that adenocarcinomas involving gastro-esophageal junction are evaluated according to the TNM classification of esophagus cancer.

In case when there are less than 16 lymph nodes, N parameter is described as pNX (yet it is crucial to provide the number of excised lymph nodes and the number of lymph nodes with metastases).

- d. surgical margins according to R-UICC classification defining the radicality of tumor resection, where:

Degree R0 – means a total macroscopic and microscopic radicality of resection with no neoplastic infiltration in the proximal, distal and radial margin

Degree R1 – means only microscopically, but not macroscopically found cancer infiltration in the proximal and/or distal and/or radial margin

Degree R2 – means macroscopically and microscopically found cancer infiltration in proximal and/or distal and/or radial margin, and/or in the cancer tissue left after the cancer tissue resection

- angioinvasion,
- infiltration of nerve trunks,
- evaluation of HER2 expression.

Warning: In case of cancers that involve the gastro-esophageal junction, radial margin is assessed for (lack of coverage with serosa, adventitia tissues constitute the margin).

The evaluation of HER2 expression should be performed when a referring doctor assumes that the patient will receive postoperative chemotherapy (15-18).

The evaluation of HER2 receptor expression using immunohistochemical method and amplification of HER2 gene using in situ hybridization (ISH) is recommended in pathological diagnostics of gastric cancer. It is included in the histopathological report according to the guidelines of American Society of Pathologists, which is presented in the Tables 6 and 7.

1.3. Classification of lymph node topography and the extent of lymph node resection

The consensus recommends using a topography classification and nomenclature of the specific stations (groups) of lymph nodes as well as the definition of the resection extent according to the most recent recommendations of International Gastric Cancer Association and Japanese Gastric Cancer Association from 2011, taking into consideration current TNM classification discussed above (7, 12, 13, 19, 20).

Tab. V. Histopathological classification according to World Health Organization (WHO), 2010.

	HISTOPATHOLOGICAL TYPE OF GASTRIC CANCER
1	Adenocarcinoma
1.a	Papillary adenocarcinoma
1.b	Tubular adenocarcinoma
2	Mucinous adenocarcinoma
3	Poorly cohesive carcinoma including signet ring cell carcinoma and other variants
3.a.	Mixed adenocarcinoma
4	Adenosquamous carcinoma
5	Carcinoma with lymphoid stroma (medullary carcinoma)
6	Hepatoid adenocarcinoma
7	Squamous cell carcinoma
8	Undifferentiated carcinoma

Tab. VI. Criteria for the evaluation of HER2 immunohistochemical staining with interpretation.

SCALE FOR THE EVALUATION OF HER2 IMMUNOHISTOCHEMICAL STAINING WITH ITS INTERPRETATION	
Result	Interpretation
0, 1+	Negative status
2+	Border status (requires further diagnostic proceedings – evaluation using in situ hybridization method)
3+	Positive status

Classification of lymph node topography

Table 8 presents the classification of stations (groups) of lymph nodes.

Nomenclature and definitions regarding the extent of lymph node excision (lymphadenectomy)

Current definitions of the extent of lymphadenectomy in surgeries with stomach resection differ depending on the extent of resection (total or peripheral stomach resection).

For the total stomach resection the following nomenclature applies:

D0: lymphadenectomy at the extent lesser than D1
D1: excision of lymph nodes of stations 1 to 7
D1+: excision of lymph nodes within the range D1 and additionally stations no. 8a, 9, 11p
D2: excision of lymph nodes within the range D1 and additionally stations no. 8a, 9, 10, 11p, 11d, 12a. Moreover, for tumors infiltrating esophagus, lymph nodes from stations no. 19, 20, 110 and 111 should be removed

D2 +: excision of lymph nodes in range D2 and additional excision of lymph nodes from stations no. 16, 19, 20, 110, 111

For the peripheral (subtotal) stomach resection the following nomenclature applies:

D0: lymphadenectomy at the extent lesser than D1

D1: excision of lymph nodes from stations 1, 3, 4sb, 4d, 5, 6, 7

D1+: excision of lymph nodes within the range D1 and additionally stations no. 8a, 9

D2: excision of lymph nodes within the range D1 and additionally stations no. 8a, 9, 11p, 12a

1.4. Classification regarding adenocarcinoma of gastro-esophageal junction

The consensus recommends routine using of topography classification according to Siewert for patients with adenocarcinoma involving gastro-esophageal junction, which is a basis for the tactics of surgical treatment (21). Additionally, in accordance with the 7th edition of TNM/AJCC classification, the TNM classification for esophagus cancer should be used for the evaluation of the advancement stage of gastrointestinal neoplasms in patients with adenocarcinoma involving gastro-esophageal junction.

2. DIAGNOSIS OF GASTRIC CANCER AND CLINICAL EVALUATION OF THE ADVANCEMENT STAGE

2.1. Medical history and physical examination

Most gastric cancer patients report symptoms already in the early stage of the disease. Yet these are non-specific symptoms, most often niggling pain, pain in the abdomen, feeling of fullness after eating, and nausea. The symptoms subside or are alleviated after medications inhibiting gastric secretion. In the patients with early stage of gastric cancer the physical examination is most often normal. Basic blood test results are also correct.

That is why the Consensus recommends performing an endoscopic examination of the upper part of the gastrointestinal tract in any patient, regardless of age, that reports the abovementioned symptoms.

2.2. Endoscopic examination

The basic examination in the diagnostics of gastric cancer is a „classic endoscopy" using white light, with collection of tissue samples for morphological assessment. The diagnostic efficiency is increased by using the high resolution ultrasound machines, with the image magnification and virtual/digital staining. The endoscopic examination should be documented with photographs/videos.

In Japan, in order to enhance the quality of endoscopy the patients receive 100 ml of water with mucus and foam reducing agents 30 minutes before gastroscopy. This preparation enhances the visualization of stomach mucous membrane and should be routinely used (22). The first and the most important stage of the examination is a very careful visual inspection of stomach mucous membrane, with performing the so-called inversion (additional evaluation of stomach cardia, fundus and angle) after the initial removal of mucus, foam or liquid and stretching of the gastric folds. . During endoscopy, stomach peristalsis and the behavior of gastric folds during air insufflation should be assessed.

Tab. VII. Evaluation of HER2 gene amplification and result interpretation.

Evaluation of HER2 gene amplification and its interpretation		
indicator	**Presence of amplification**	**Interpretacja**
<=1.8	Lack of HER2 gene amplification	Negative status
< 1.8 < 2.2	Amplification uncertain	Border status – requires repeating of the evaluation of amplification
>2.2	HER2 gene amplification	Positive status
In the repeated examination performed using FISH method > 2.0	HER2 gene amplification	Positive status

FISH - fluorescent in situ hybridization

Aiming for the early detection of cancer, attention should be paid to the subtle changes of mucous membrane color or surface. In classical endoscopy, the characteristic features of a lesion suspected of early gastric cancer are focal:

- change of coloration– reddening or fair/white mucous membrane
- surface elevation
- loss of smoothness/shining of the mucous membrane
- spontaneous bleeding

In case of finding a focal lesion suspected of an early detected cancer, it is necessary to use indigocarmine/methylene blue staining (visualization of lesion margins/surface, choosing the optimum place for biopsy). In new generation endoscopes instead of classic staining light "staining" (visual inspection of lesions in narrow band of light - narrow band imaging, NBI) and image magnification are used. NBI with image magnification gives the possibility to visualize the vascular pattern. On the basis of the vascular pattern, the surface structure and the margins of focal lesion, an initial differential diagnosis between the benign and the malignant lesion can be performed (the so-called optical biopsy) (22,23).

In the endoscopic examination with magnification and NBI the characteristic features of early gastric cancer are:

- apparent/sharp margin between the focal lesion and surrounding mucous membrane
- irregular/heterogeneous coloration and structure of surface
- irregular vascular pattern or lack of vascular pattern

Using the above listed criteria it is possible to correctly diagnose the neoplasm in 97% of early gastric cancer cases (23).

The last stage of diagnostic gastroscopy is the collection of sample material for morphological examination. The sample material is collected using biopsy forceps. Suspecting that a lesion in the stomach is an early cancer, the number of biopsies should be limited to 1-2 samples, best using NBI and image magnification (23-25).

Tab. VIII. Topography of gastric cancer lymph nodes

STATION OF LYMPH NODES	LOCATION
1	Right cardiac lymph nodes, including the ones along the esophagus-cardia branch, the highest ascending branch of left gastric artery.
2.	Left cardiac lymph nodes, including the ones along the esophagus-cardia branch of left subdiaphragmatic artery.
3a.	Lymph nodes of lesser curvature along the branch of left gastric artery.
3b	Lymph nodes of lesser curvature along the distal part of right gastric artery and its branches.
4sa	Lymph nodes of greater curvature (left) along the gastric short vessels (perigastric area).
4sb	Lymph nodes of greater curvature (left) along the left gastro-omental artery (perigastric area).
5	Suprapyloric lymph nodes along the proximal part of right gastro-omental artery and its branches.
6	Infrapyloric lymph nodes along the first branches and a proximal part of right gastro-omental artery to the run-off height for right gastro-omental vein and the anterior superior pancreaticoduodenal vein.
7	Lymph nodes along the trunk of left gastric artery from the branching from the celiac artery to the division into its ascending branches.
8a	Anterior-superior lymph nodes along the common hepatic artery.
8b	Posterior lymph nodes along the common hepatic artery.
9	Lymph nodes near the celiac artery.
10	Lymph nodes of the splenic hilum and along the ending section of splenic artery, along the tail of pancreas and short gastric vessels above the junctions with branches of left gastro-omental artery.
11	Lymph nodes along the proximal part of the splenic artery from its branching from celiac artery to the half of the length of the tail of pancreas. Lymph nodes along the distal part of the splenic artery from the half of the length of the tail of pancreas to its end.
12a	Lymph nodes of hepatoduodenal ligament, along the hepatic artery proper from the head of pancreas to the height of the junction between the left and right hepatic ducts.
12b	Lymph nodes of hepatoduodenal ligament along the common bile duct from the head of pancreas to the height of the junction between left and right hepatic ducts. Lymph nodes of hepatoduodenal ligament along the portal vein from the height of the head of pancreas to the height of the junction between left and right hepatic ducts.
13	Lymph nodes of posterior surface of the head of pancreas, of the region of the ampulla of Vater.
14	Lymph nodes along the superior mesenteric vein.
15	Lymph nodes along the middle colic vessels.
16a1	Para-aortic lymph nodes in the region of the diaphragm vessel openings.
16a2	Para-aortic lymph nodes between the upper brim of celiac artery and the lower brim of left renal vein.
16b1	Para-aortic lymph nodes between the lower brim of left renal vein and the upper brim of the inferior mesenteric artery.
16b2	Para-aortic lymph nodes between the branching of inferior mesenteric artery and the bifurcation of aorta.
17	Lymph nodes of the anterior surface of the head of pancreas.
18	Lymph nodes along the lower brim of the body of pancreas.
19	Subdiaphragmatic lymph nodes, mostly along the subdiaphragmatic artery.
20	Lymph nodes in the esophageal foramen of the diaphragm.

Collection of larger number of samples may cause lesion fibrosis and make it more difficult to remove the lesion using an endoscopic method. In the literature (mostly Japanese) we find guidelines according to which biopsy should not be performed in such cases, but the lesion should be solely carefully visually inspected (magnification, NBI), and then removed en-bloc and microscopically evaluated (26).

From every lesion in stomach that is suspected of advanced cancer 7-10 samples should be collected, and after receiving the negative result, the examination should be repeated together with sample collection. The collection of samples may be supplemented by gathering endoscopic brush smear (in cases when performing targeted biopsy is more difficult).

In case of cancer presenting with thick folds (linitis plastica), morphological examination of endoscopic biopsy samples and even of larger specimens collected with a diathermic loop is most often negative. In such case ultrasonography and ultrasound endoscopy (EUS) are of help. A typical image in these examinations is thickening of wall with abnormal layering, with main thickening of the submucosal layer. Under the guidance of EUS a biopsy of the changed wall should be performed. The use of truct type needle (EUS-TCB) is a method of choice and gives a chance for stating the diagnosis in 90% of patients (27). When using a thin needle this percentage decreases to 60% (EUS-FNA).

Macroscopically, an early gastric cancer (according to the Japanese endoscopic classification) may be divided into one of the three subtypes. Subtype I is a lesion of an elevated character, above 5 mm, manifesting as a polyp on a short, wide basis, resembling in appearance a thickened fold of mucous membrane. Subtype II is a superficial lesion, less elevated than type I, of an uneven surface, that can be present in the following variants: IIa – flat, slightly elevated, less than 5 mm, IIb – flat lesion, with irregular surface, IIc – flat, with a cavity. Type III is a lesion with a cavity or ulceration. Most of the early gastric cancers can be allocated under type II and III.

An early gastric cancer may take form of a focal change of mucous membrane coloration – including reddening or fair/white discoloration (26). This kind of "non-typical" endoscopic image is present in about 10% of early gastric cancers. The smaller the early lesion, the larger the percentage of cancers in a form of mucous membrane discoloration.

Considering this phenomenon, Yao proposed a new classification of early gastric cancer, with a division into three subtypes: polypoid, ulcerous and gastritis like cancer (22).

Advanced neoplastic changes according to the Borman classification can be macroscopically divided to: I–tumorous, II–ulcerous with clearly separated margin of infiltration, III ulcerous with weakly separated margin of infiltration, and IV– flat and fibrous lesions.

It should be remembered that a neoplastic lesion may seemingly heal under the influence of gastric secretion inhibiting medications.

In the Polish population, where the gastric cancer is still a clinical issue, gastroscopy should be performed for all patients with "dyspepsia". The resignation from endoscopy, initial use of eradication of H. pylori infection and treatment with medications decreasing gastric secretion may cause a delay in diagnostics.

The diagnostic value of endoscopy is determined by the proper training of the physician performing the examination, good preparation of the patient, accurate classical stomach evaluation and targeted biopsy.

In the endoscopic trainings it should be emphasized that while searching for neoplastic lesions in the stomach attention should be paid not only to the concave and convex lesions, but also to the changes in mucous membrane coloration/surface structure and vascular pattern of mucous membrane.

Video recording/photographs taken during the endoscopy make it possible to return to the image if it is needed. They are a foundation for trainings, joint interdisciplinary discussions and the enhancement of the quality of endoscopy.

Technical progress in endoscopic imaging will decrease the number of performed classical biopsies in favor of so-called "optical biopsies".

2.3. Determining gastric cancer advancement stage

In determining the stage of cancer advancement main roles are played by physical examination, classical endoscopy, and computed tomography of abdominal cavity and chest. An evaluation of female genital organs is also routinely performed in females. In chosen cases (cT3, cT4 tumors, suspected intraperitoneal dissemination) diagnostic laparoscopy is recommended. Performing cytological examination of peritoneal washings during laparoscopy and laparotomy is not recommended as obligatory.

Performing EUS in the early and advanced lesions is not routinely recommended due to lack of benefits in terms of treatment planning.

In case of early gastric cancer, initially qualifying for endoscopic treatment, the best method of determining the stage of neoplasm advancement is a pathological examination of the entire removed lesion. The accuracy of determining the depth of infiltration in classical endoscopy is comparable to the evaluation in EUS examination. The results of both methods are abnormal for approximately 20% of the patients (25-30).

3. SURGICAL TREATMENT

For almost three decades there has been an incessant discussion in specialist literature and during international scientific congresses on such aspects of surgical treatment of gastric cancer as:

1. the extent of resection (routine performing of total resection versus subtotal stomach resection)
2. the extent of lymphadenectomy (D1 lymphadenectomy versus D2 versus D2+/D3)
3. spleen resection (routine splenectomy versus resection without splenectomy)
4. the tactics of proceedings in cases of cancers involving esophago-gastric junction (surgical access via chest versus transhiatal resection of esophagus).
5. the separate problem in the age of the development of endoscopic and minimally invasive surgery is the role of these technologies in the treatment of patients with gastric cancer.

3.1. Surgical resection (laparotomy)

Surgical treatment or a resection of a stomach along with the tumor remains the basic method of treatment for patients with gastric cancer. Classical (using access via laparotomy) stomach resection is still the most often performed surgical procedure worldwide in the treatment of patients with gastric cancer.

The intention of the authors of the Consensus was to synthesize the knowledge based on the scientific evidence (EBM) and the results of authors' own studies carried out within the project named "Polish Research on Gastric Cancer" on the surgical treatment of gastric cancer.

The extent of resection

The routine performance of total stomach resection is often recommended by authors from Europe, particularly in the cases of diffuse gastric cancer according to Lauren classification (31-32). Simultaneously, performing total stomach resection was never routinely recommended in the guidelines in Japan and Korea (12). Additionally, at least two randomized clinical studies performed in Europe (33, 34) did not show an improvement of distant follow-up results in the group of patients in whom a total stomach resection was performed. In each case, the overarching aim of surgical treatment of gastric cancer is to obtain oncological radicality with balancing individual decisions regarding the extent of total or partial resection of stomach.

The extent of lymphadenectomy

The recommended extent of the lymph node excision in all cases of treatment of patients with gastric cancer with the intention of performing a potentially radical resection is D2 lymphadenectomy. The necessity for D2 type lymphadenectomy does not concern the patients qualifying for radical endoscopic treatment and patients

in whom the stomach resection surgery does not fulfill the macroscopic criteria of oncological radicality (R2 resection). In D2 lymphadenectomy the rule of removal of specific groups (stations) of lymph nodes applies (as described in chapter 1.3).

The extent of lymphadenectomy smaller than D2 may be performed in special cases of early cancer (T1) patients that do not qualify for a radical endoscopic treatment. It applies to the cases of early gastric cancer with clinical advancement stage cT1 sm2, or cT1 with a diffuse type according to Lauren classification with recommended gastrectomy with type D1/D1+ lymphadenectomy. In cases equivocal in terms of the precise clinical evaluation of the advancement stage of the early cancer, performing D2 lymphadenectomy is justified. (12, 28, 35-37).

In two randomized clinical studies carried out in Japan and in Poland, D2+ lymphadenectomy, though it is not correlated with an increased number of perioperative complications, does not improve the distant follow-up results (38-40).

Splenectomy during stomach resection due to cancer

The concept of performing routine splenectomy (possibly associated with resection of the tail of pancreas) in order to "improve" radicality associated with extension of the lymphadenectomy was criticized. The results of randomized clinical studies carried out in Europe (randomized clinical study on lymphadenectomy conducted as a part of a British, Dutch and Italian study) unanimously indicated that performing splenectomy during stomach resection is correlated with a significantly larger percentage of post-surgical complications. Until the prospective clinical study being continued in Japan (JCOG 0110) is finished, there is lack of unanimous evidence according to which routine splenectomy during a potentially radical stomach resection would be justified (41).

Tactics of surgical proceedings in patients with gastro-esophageal junction cancer

The analysis of available literature makes it possible to state a conclusion that the classification by Siewert (being de facto a topographical classification) is optimal to make a decision about the tactics of surgical proceedings, mainly in the aspect of surgical access. The results of a randomized clinical study that was finished in Japan (42) influenced the decision made by the authors of this Consensus.

SUMMARY

1. Surgical stomach resection due to cancer remains a basic element of treatment of gastric cancer.
2. The authors of the Consensus do not recommend routine total gastrectomy or splenectomy, regardless of the cancer type according to the classification by Lauren.
3. In cases of cancer localized in the peripheral part of stomach a peripheral resection may be performed, provided that at least a 5 cm proximal resection margin is maintained. The classification by Lauren does not influence the margin size.
4. The 5 cm margin does not regard tumors localized near the gastro-esophageal junction and near the pylorus. In case of resection of gastro-esophageal junction cancers it is recommended to perform an intra-operative histopathological examination.
6. Splenectomy and/or resection of the tail of pancreas is justified in cases of macroscopic features of infiltration of the region of splenic hilum and/or tail of pancreas, which concerns in particular the tumors located in the upper part of the stomach and on the greater curvature.
7. The recommended extent of lymph nodes excision during potentially radical resection is D2 lymphadenectomy.
8. If the infiltration of gastric cancer is intraoperatively revealed in the adjacent organs and the patient's general condition makes it possible to perform an extensive operation, a multi-organ resection should be performed provided that this resection would have a radical character.
9. In case of adenocarcinoma of the gastro-esophageal junction, the authors of the Consensus recommend a tactics of surgical proceedings based on the tumor localization according to the classification by Siewert:
    a. type I – laparotomy and right thoracotomy with a removal of lower, thoracic part of the esophagus
    b. type II – total stomach resection with a resection of lower part of esophagus using transhiatal access. When the result of the intraoperative pathological examination is positive it is recommended to extend the extent of the esophagus resection using the access through right thoracotomy. In justified cases it is acceptable to remove both stomach and esophagus.
    c. type III – total stomach resection with the resection of the lower part of using transhiatal access, with intraoperative pathological examination of the resection margin from the side of esophagus. When the result of the pathological examination is positive it is recommended to extend the extent of the esophagus resection using the access through thoracotomy.

3.2. Minimally invasive surgery – laparoscopic surgery and robotic surgery in the treatment of gastric cancer

The number of laparoscopic surgeries or surgeries assisted by laparoscopy systematically increases. This incremental trend regarding the percentage of laparoscopic surgeries is observed not only in Japan or South Korea, but also in the other parts of the world, including Europe.

For obvious reasons, the percentage of laparoscopic stomach resections is highest among the patients with early gastric cancer (T1) localized in the central as well as the distal part of the stomach. Both partial, peripheral and even less extensive wedge stomach resections are acceptable. Laparoscopic stomach resections are also more and more frequently performed in patients with advanced stages of gastric cancer. The standard scope of laparoscopic surgeries in advanced gastric cancer includes both total as well as partial stomach resection with D2 lymphadenectomy.

The majority of the so-far conducted randomized clinical studies indicate that laparoscopic surgeries have a high safety profile in the aspect of perioperative complications and are associated with a shorter time of hospitalization, with a longer surgery time and technical problems accounting for a longer "learning curve".

On the basis of the meta-analyses of the so-far conducted clinical studies, there are no unequivocal recommendations for laparoscopic access as an method equivalent to an open stomach resec-

tion in surgical treatment of patients with gastric cancer. There is no sufficient evidence that would satisfy EBM criteria and confirm the value of laparoscopic techniques as comparable to laparotomy surgeries with respect to 5-year survival rate. The final results and conclusions of two significant randomized clinical studies in Japan (JCOG 0912 study) and South Korea (KLASS study) are still being awaited for (43-45).

The experimental joining of laparoscopic resection with intraoperative biopsy of the sentinel lymph node in patients with an early gastric cancer gives hope for the individualization of therapeutic proceedings, but is still in an experimental stage and as such cannot be a method recommended for routine medical practice.

Surgical treatment of patients with gastric cancer with the use of robots is still a method of low availability, mostly because of the cost of equipment. Nevertheless, further development of this method seems to be a question of time and the number of robot-assisted stomach resections systematically increases. Despite many advantages of robotic surgeries in comparison to laparoscopic surgeries, there is no sufficient scientific evidence which could objectively prove its usefulness in the surgery of gastric cancer.

To conclude, surgical treatment of patients with gastric cancer using laparoscopic access (or a surgical robot assistance) is allowed only in highly-specialized centers that have experience in both advanced laparoscopic procedures and surgical treatment of patients with gastric cancer.

Similarly, a laparoscopic stomach resection with the biopsy of the sentinel lymph node should not decide upon the lymph node excision in patients with gastric cancer. This method is still in an experimental stage. The potential change of the position of the Consensus authors' will be possible after the results and conclusions of JCOG 0912 and KLASS randomized clinical studies as well as other scientific reports regarding robotic surgeries and the importance of the sentinel lymph node biopsy for surgical treatment of gastric cancer are published.

3.3. Endoscopic treatment of early gastric cancer

Endoscopic treatment may be applied in case of early gastric cancer with low probability of metastasis to regional lymph nodes – Type 0. The lesions should qualify for removal as a whole (12, 31, 32).

Indications for endoscopic treatment

There are two types of indications for endoscopic treatment: the so-called absolute indications, which should be treated as a method of choice, and relative, extended indications, reserved for submucosal dissection technique, which are treated as experimental proceedings.

5.1.1. Standard, absolute indications: Highly differentiated type of adenocarcinoma without features of ulceration (UL-) where the infiltration depth does not exceed the mucous membrane (T1a) and the cross-sectional dimension does not exceed 2 cm.

5.1.2. Relative, extended indications: A submucosal dissection method is a proposed technique. Extended indications are proposed for T1a tumors with low probability of metastasis to lymph nodes and that fulfill the following criteria:

- highly differentiated cancer type without features of ulceration (UL-) with diameter larger than 2 cm,
- highly differentiated cancer type of ulcerous character (UL+) with diameter not exceeding 3 cm,
- poorly differentiated cancer type without features of ulceration (UL-) with diameter not exceeding 2 cm.

Methods of endoscopic treatment

Endoscopic mucosal resection (EMR). An operation involving the elevation of the neoplastic lesion with the margin of the surrounding mucous membrane by injecting it with a saline solution and cutting it off with an electrical loop.

Endoscopic submucosal dissection (ESD). After determining the resection margins and injecting the lesion the mucous membrane with a submucosal membrane around the lesion is slit using special electric knives. The kind of tools used depends on the experience of the doctor performing the operation. This technique allows for more radical resection of the lesion, down to the proper muscle membrane.

Evaluation of the effectiveness of treatment

The evaluation of the therapeutic effectiveness of endoscopic treatment includes both pathological evaluation of the resected specimen with respect to radicality as well as the risk of lymph node metastasis.

Endoscopic resection performed according to standard indications is regarded as radical and therapeutic when the following criteria are fulfilled:

- en-bloc resection
- lesion size up to 2 cm
- histologically highly differentiated type of cancer
- pT1a advancement stage
- negative horizontal margin - HM0
- negative vertical margin - VM0
- lack of infiltration of lymph nodes (Ly -) and blood vessels (V -)

Endoscopic resection performed according to extended indications is regarded as radical and therapeutic when the following criteria are fulfilled:

- en-bloc resection
- negative horizontal margin - HM0
- negative vertical margin - VM0
- lack of infiltration of lymph nodes (Ly -) and blood vessels (V -)
- lesion size over 2 cm, histologically highly differentiated type of cancer, pT1a, Ul (-)
- lesion size under 3 cm, histologically highly differentiated type of cancer, pT1a, Ul (+)
- lesion size under 2 cm, histologically poorly differentiated type of cancer, pT1a, Ul (-)
- lesion size under 3 cm, histologically highly differentiated type of cancer, pT1a (SM1, <500 microns from the muscularis mucosa)

Endoscopic resection does not fulfil the criteria of therapeutic operation if any of the above listed criteria is not fulfilled.

The proceedings in case the criteria for therapeutic operation are not fulfilled or in case of a cancer relapse after endoscopic treatment

In case the criteria for endoscopic therapeutic treatment are not fulfilled the patient should undergo surgical treatment.

In cases where the endoscopic resection of an early cancer does not meet the criteria of a therapeutic treatment as defined in chapter 5.3, surgical treatment is indicated. The extent of the resection is determined according to the same rules that apply for more advanced tumors. Depending on the lesion location, total stomach resection and/or peripheral resection are recommended.

The extent of lymphadenectomy depends on the clinical advancement stage of the cancer:

- D1 lymphadenectomy is recommended in case of all T1a tumors and T1b histologically differentiated lesions with a diameter not exceeding 1.5 cm.
- D1+ lymphadenectomy is recommended in the other cases of T1b clinical advancement
- D2 lymphadenectomy is recommended when having doubts about the precise evaluation of the advancement stage of an early cancer or in cases of intra-operative suspicion of metastasis to lymph nodes.

In case of cancer recurrence limited to a mucous membrane after the endoscopic treatment performed in accordance with the standard indications, the treatment may be repeated once again using a submucosal dissection technique. In case of a relapse after the treatment performed according to extended indications the patients should be qualified for surgical treatment with D2 lymphadenectomy.

3.4. Modifications of surgical treatment in patients with gastric cancer (emergency surgery, palliative surgery, extended operations)

In the era of evidence-based medicine (EBM) determining the rules of modification of surgical treatment is a very difficult task. The published and publicly available rules of treating patients with gastric cancer are reduced to the choice of therapeutic proceedings on the basis of different cancer advancement stage. The modifications of these rules are by definition rare and regard only chosen clinical situations (7, 32, 49).

The presence of a neoplasm in the stomach may, in special cases, threaten the patient's life, regardless of the systemic consequences of the neoplastic disease. The exacerbation of the observed complications may be modified by side effects of antineoplastic treatment.

The surgical treatment of emergencies in the course of gastric cancer is limited to the treatment of obstructions, perforations and bleeding to the upper part of gastrointestinal tract. In such cases, the surgeon's actions are most frequently subject to other treatment criteria than the ones used while treating tumor. Radical surgery is rarely possible. Surgical tactics is most often aimed at treating the complication and not the cancer itself. Possible final surgery for the purpose of treating the neoplasm is performed in the second stage after the pathological confirmation of the disease and preparation of the patient. Surgical treatment of complications may involve performing a gastric bypass or palliative stomach resection – its scope depends on the clinical situation resulting from the location and advancement stage of a cancer and on the patient's condition. We chose the treatment which poses lower risk of complications.

Bleeding to the upper part of gastrointestinal tract

Microcytic anemia, being a sign of persistent bleeding to gastrointestinal tract, may be an effect of bleeding from gastric tumor. Relatively rarely – in approximately 5% of patients – bleeding causing hemodynamic effect is observed. The possible occurrence of additional risk factors of bleeding such as taking nonsteroidal anti-inflammatory medications, often encountered in this group of patients, should be kept in mind.

All endoscopic methods of treatment should be used (argon coagulation, endo-clips, injections). Radiologic methods of obliteration of chosen stomach vessels are not very effective due to the specific character of a multi-source blood supply of stomach. Indications for surgery are present only exceptionally and the extent of surgery depends on the clinical situation and the patient's condition.

Obstruction caused by stomach tumor.

The function of surgical proceedings patient with gastric cancer is: location of the lesion in the stomach, determining its local advancement stage, presence of metastases and the patient's general condition. Most often high local advancement makes it impossible to perform a resection. In tumors of the peripheral part of the stomach a palliative resection or a gastrointestinal bypass can be performed. In tumors of the closer part of the stomach and cardia we usually aim to implement prosthesis endoscopically in the place of the constriction.

Stomach perforation during the course of cancer.

In so far as the percentage of perforated gastric cancers is rather small and equals from 0.3% to 3% of cases, gastric cancer is revealed during pathological examination in almost 10% of patients with perforation. It opens a discussion on possibilities of performing a single or two stage operation in patients with regional advancement of the neoplasm. In the opinion of the Gastric Cancer Consensus members the first stage of treatment should involve the control of a perforation and treatment of peritonitis. If there exist technical possibilities after pathological verification and preparation of the patient, we perform resection of the stomach and the appropriate extent of lymph nodes.

"Extended" and palliative resections in patients with gastric cancer.

Routine gastrectomy due to cancer includes a resection of the organ (or its part) and a resection of the lymph nodes within D2 scope. Every operation during which we resect tissues outside the stomach or additional lymph nodes is an extended resection. The results of the definite majority of randomized clinical studies show that there is no purpose in performing extended – exceeding D2 - lymph node excision. The exceptions are cancers of the gastro--esophageal junction where we routinely aim to remove lymph nodes of posterior lower mediastinum. In such localization of the neoplasm - type II according to Siewert – the minimum extent of

the operation is transhiatal resection of the lower part of the esophagus with maintaining of an appropriate margin (the extent of the resection has not been unequivocally determined).

The next problem is a resection of stomach extended with a resection of spleen and / or tail of pancreas tail. In the light of current views (their dominant majority), this type of extended operation can only be considered in cases of direct infiltration of these organs and lack of features indicating the generalization of the neoplastic process. Therefore the resection of spleen and/or the tail of pancreas is not justified only in order to extend the extent of lymphadenectomy.

In the current literature reports on the extension of survival period for selected patients after stomach resection due to cancer can be found as well as after the dissection of single metastatic tumors from the liver. The statistical significance of this type of research does not allow for any recommendations. That is why, based on evidence (EBM), the opinion of the members of the Gastric Cancer Consensus is unequivocal – every resection in patients with IV stage of cancer advancement is a palliative resection.

Performing a non-radical resection (R2) in a patient in whom we have intraoperatively found the presence of non-regional lesions – M1 is acceptable for patients with the symptoms of chronic bleeding from tumor and for patients who may have significant obstruction caused by the tumor. The surgery is not to be extended with the resection of additional lymph nodes except the ones located in the resected part of the stomach. The decision regarding operation in other patients should depend on their positive response to chemotherapy.

Performing extended resections which include neighboring organs in patients with cancer infiltrating the transverse colon still remains an important problem. There is a potential possibility of performing the resections of transverse colon segments as a preventive surgery in case there might be an obstruction that could develop further. According to the authors of the Consensus – both in this and in other cases – performing extended resections is acceptable under the condition that they are potentially radical and patients are in a good general condition.

4. COMBINED TREATMENT

Surgical treatment is still a basic method of treating patients with gastric cancer. However, it is reported that there is a 13-14% increase of five-year survival rate among patients receiving perioperative chemotherapy. Also postoperative radiochemotherapy results in an approximately 11% increase of overall survival rate. Given the more and more numerous reports in the literature it has to be said that the treatment of patients with gastric cancer (apart from early gastric cancer) should be a combined treatment (51-60). Below we present relevant recommendations.

Every patient with potentially resectable gastric cancer in the cT3-4 advancement stage, all N, M0, for whom we assume the possibility of R0 operation should be qualified for perioperative that is pre- and postoperative chemotherapy.

In patients after partial or total resection, in pT3-4 advancement stage NoMo or every pT N(+) Mo and patients with cancer of the gastro-esophageal junction, an adjuvant radiochemotherapy is recommended (unless perioperative chemotherapy started before the surgical treatment)

In patients with advanced, locally nonresectable tumor, but without distant metastases (T4, all N, M0), the use of an induction chemotherapy should be considered with the intention of a re-laparotomy in attempt to remove the organ affected by a neoplasm.

In patients with primarily generalized neoplastic process the use of palliative chemotherapy is recommended, as long as their general condition permits it.

In patients with gastric cancer who have HER2 expression targeted treatment is recommended.

In nonresectable relapses chemotherapy and another attempt of the resection should be considered.

Advanced age of a patient is not a contraindication to a combined treatment; indications for the combined treatment in this group of patients should be determined including all the risk factors related to the patient's general condition.

Qualifying the patient for the appropriate form and a proper regimen of the combined treatment should be done by a highly-specialized team of doctors comprising a surgeon, a radiotherapist and a clinical oncologist.

5. FOLLOW-UP EXAMINATIONS FOR THE PATIENTS AFTER FINISHING OF SURGICAL TREATMENT

Follow up examinations after endoscopic and partial resection due to early gastric cancer

It is recommended to perform a pharmacological eradication of Helicobacter pylori in case the infection is confirmed.
It is recommended to perform a follow-up gastroscopy according to the following regimen:

- 3 months after the treatment
- 6 months after the previous examination
- then in yearly intervals up to 5 years after the treatment

Moreover, it is recommended to perform USG and CT of abdominal cavity once a year (12, 31, 32).

Follow-up examinations in patients after total or partial stomach resection due to advanced gastric cancer

So far no optimal method has been determined for the regimen of follow-up in patients after a radical stomach resection. Probably performing systematic endoscopic and imaging examinations does not result in the extension of patients' survival time in comparison with a method of performing additional examinations in patients reporting various symptoms during follow-up visits (7,12,31,32). Because the largest number of disease relapses take place within 2 years from the completion of treatment, the Panel members are unanimous as to that follow-up examinations (medical interview and physical examination) are recommended every 3 months throughout this period, and afterwards every 6 months for 3 fol-

lowing years. In case the patient reports ingestion disorders it is recommended to perform an endoscopic examination. The USG and CT examinations of abdominal cavity are performed according to individual indications.

Patients after a total resection are advised to have a complete blood count done and blood iron level measured every 3 months. In case of anemia caused by iron deficiency, iron should be supplemented.

REFERENCES

1. Edge S.B., Byrd D.R., Compton C.C. et.al.: AJCC Cancer Staging Manual. 7th ed. New York – Dordrecht – Heidelberg – London: Springer, 2010.
2. Greene F.L. Page D.I. et.al.: AJCC cancer staging manual. 6th ed. New York: Springer Verlag, 2002.
3. McGhan L.J., Pockaj B.A., Gray R.J. et. al.: Validation of the updated 7th edition AJCC TNM staging criteria for gastric adenocarcinoma. J. Gastrointest-surg. 2012; 16: 53–61.
4. Nasierowska-Guttmejer A., Majewski P., Malinowska M.: Czynniki prognostyczne i predykcyjne w raku żołądka. Pol. J. Pathol. 2013; supl 1.
5. Lauwers G.Y., Carneiro F., Graham D.Y. et al.: Gastric carcinoma. In: Bosman F.T., Carneiro F., Hruban R.H., Theise N.D. (eds): WHO Classification of tumours of the digestive system, 4th edn. IARC. Lyon, 2010: 48–58.
6. Dinis-Ribeiro M., Areia M., de Vries A.C. et al.: Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Society of Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Virchows. Arch. 2012; 460: 19–46.
7. Okines A., Verheij M., Allum W. et al.: Gastric cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. On behalf of the ESMO Guidelines Working Group. Annals of Oncology. 2010; 21 (Suppl. 5): 50–54.
8. Fujishiro M.: Perspective on the practical indications of endoscopic submucosal dissection of gastrointestinal neoplasms. World J. Gastroenterol. 2008; 14: 4289–4295.
9. Shen L, Shan YS, Hu HM, Price TJ, Sirohi B, Yeh KH, Yang YH, Sano T, Yang HK, Zhang X, Park SR, Fujii M, Kang YK, Chen LT. Management of gastric cancer in Asia: resource-stratified guidelines. Lancet Oncol. 2013 Nov;14: 535-547
10. Akahoshi K., Akahane H.: A new breakthrough: ESD using a newly developed grasping type scissor forceps for early gastrointestinal tract neoplasms. World J. Gastrointest. Endosc. 2010; 16: 90–96.
11. Probst A., Pommer B., Golger D. et al.: Endoscopic submucosal dissection in gastric neoplasia – experience from a European center Endoscopy. 2010; 42: 1037–1044.
12. Sano T., Aiko T.: New Japanese classification and treatment guidelines for gastric cancer: revision concepts and major revised points. The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2011. Gastric Cancer Treatment Guidelines 2010, version 3. Gastric. Cancer. 2011; 14: 97–100.
13. Washington K.: 7th Edition of the AJCC Cancer Staging Manual: Stomach. Ann. Surg. Oncol. 2010; 17: 3077–3079.
14. Lauren P.: The two histological main types of gastrin carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Microbiol. Scand. 1965; 64: 31–49.
15. Olszewski W.P., Olszewski W.T.: Rola patomorfologa w doborze terapii ukierunkowanej na receptor czynnika wzrostu naskórka (EGFR) u chorych na nowotwory. Onkol. Prak. Klin. 2010; 6: 228–235.
16. Hofmann M., Stoss O., Shi D. et al.: Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008; 52: 797–c805.
17. Ruschoff J., Dietel M., Baretton G. et al.: HER2 diagnostics in gastric cancer – guideline validation and development of standardized immunohistochemical testing. Virchows. Arch. 2010; 457: 2999–2307.
18. Ruschoff J., Wedad H., Michael B. et al.: HER2 testing in gastric cancer: a practical approach. Modern Pathology. 2012, 1–14.
19. Gospodarowicz M., Wittekind Ch., Sobin L.H.: International Union Against Cancer TNM 7th edition. Gastric cancer. (2010). www.uicc.org.
20. Dikken J.L., van de Velde C.J.: The New AJCC/IUAC staging system for adenocarcionoma of the stomach: increased complexity without clear improvement in predictive accuracy. Ann. Surg. Oncol. 2012; 19: 2443–2451.
21. Siewert J.R., Stein H.J.: Classification of adenocarcinoma of the oesophagogastric junction. Br. J. Surg. 1998; 85: 1457–1459.
22. Yao K.: The endoscopic diagnosis of early gastric cancer. Ann. Gastroenterol. 2013; 26: 11–22. 23. Muto M., Yao K., Kaise M. et al: Magnifying endoscopy simple diagnostic algorithm for early gastric cancer (MESDA- G). Digestive Endoscopy. 2016; 28: 379–393 .
23. Uto M, Yao K, Kaise M et al Magnifying endoscopy simple diagnostic algorithm for early gastric cancer (MESDA- G). Digestive Endoscopy 2016;28: 379-393
24. Chai N.-L., Ling-Hu E.-Q., Morita Y. et. al.: Magnifying endoscopy in upper gastroenterology for assessing lesions before completing endoscopic removal. World J. Gastroenterol. 2012; 18: 1295–1307.
25. Nagahama T., Yao K., Imamurs K. et al.: Diagnostic performance of conventional endoscopy in the identification of submucosal invasion by early gastric cancer: the "non-extension sign" as a simple diagnostic marker. Gastric. Cancer. 2016 in press.
26. Ang T.L., Khor C.J., Gotoda T.: Diagnosis and endoscopic resection of early gastric cancer. Singapore Med. J. 2010; 51: 93–100.
27. Dumonceau J.-M., Polkowski M., Larghi A. et al.: Indications, results, and clinical impact of endosopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2011; 43: 897–909 .
28. Lutz M.P., Zalcberg J.R., Ducreux M. et.al.: Highlights of the EORTC St. Gallen International Expert Consensus on the primary therapy of gastric, gastroesophageal and esophageal cancer. European Journal of Cancer. 2012; 48, 2941–2953.
29. Cardoso R., Coburn N., Seevaratnam R. et al.: A systemic review and meta-analysis of the utility of EUS for preoperative staging for gastric cancer. Gastric Cancer. 2012; 15 Supp1: 19–26.
30. Lee H.H., Lee S.-Y., Yoon H.Y. et.al.: Change of mucosal color in early gastric cancer. Journal of Digestive Diseases .2012, 13: 510–516.
31. Siewert J.R., Böttcher K., Roder J.D. et.al.: Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. Br. J. Surg. 1993; Aug.; 80 (8): 1015–1018.
32. Roukos D.H., Paraschou P., Lorenz M.: Distal gastric cancer and extensive surgery: a new evaluation method based on the study of the status of residual lymph nodes after limited surgery. An. Surg. Oncol. 2000 Dec.; 7 (10): 719–726.
33. Piso P., Werner U., Lang H. et.al.: Proximal versus distal gastric carcinoma-what are the differences? Ann. Surg. Oncol. 2000; 7 (7): 520–525.
34. Bozzetti F., Marubini E., Bonfanti G. et.al.: Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. Ann. Surg. 1999 Aug.; 230 (2): 170–178.
35. Sano T., Kodera Y.: The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2011. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric cancer 2011; 14: 101–112.
36. Sano T., Kodera Y.: The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2011. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric cancer 2011; 14: 113–123.
37. Sasson A.R. et al.: NCCN Clinical Practice Guidelines in Oncology. (National Comprehensive Cancer Network, version 2. 2012). Gastric Cancer NCCN Guidelines – including cancer in the proximal 5 cm of the stomach. www. nccn.org.
38. Sasako M., Sano T., Yamamoto S. et al.: D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N. Engl. J. Med. 2008, 359 (5): 453–456.
39. Wang Z., Chen J.-Q. et al.: Systematic review of D2 lymphadenectomy versus D2 with para-aortic nodal dissection for advanced gastric cancer. World J. Gastroenterol. 2010; 16: 1138–1149.
40. Kulig J., Popiela T., Kolodziejczyk P., Sierzega M. on behalf of the Polish Gastric Cancer Study Group: Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial. Am. J. Surg. 2007, 193 (1): 10–15.
41. Sano T., Yamamoto S., Sasako M., Japan Clinical Oncology Group Study LCOG 0110-MF: Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan clinical oncology group study JCOG 0110-MF. Jpn. J. Clin. Oncol. 2002; 32 (9): 363–364.

42. Sasako M., Sano T., Yamamoto S., (JCOG9502) et al.: Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. Lancet Oncol. 2006, 7 (8): 644–651.
43. Hiroshi O., Yutaka T., Kozo N. et al.: A Meta-analysis of randomized controlled trials on the effectiveness of somatostatin analogues for pancreatic surgery: a Cochrane review. Gastrointest. Surg. 2010; 14: 958–964.
44. Byung Hee Kang, Yi Xuan, Hoon Hur et.al.: Comparison of Surgical Outcomes between Robotic and Laparoscopic Gastrectomy for Gastric Cancer: The Learning Curve of Robotic Surgery. J. Gastric Cancer. 2012; 12 (3): 156–163.
45. Yang H.K., Suh Y.S., Lee H.J.: Minimally invasive approaches for gastric cancer--Korean experience. J. Surg. Oncol. 2012 Jul. 17.
46. Rausei S., Dionigi S., Rovera F.: A decade in gastric cancer curative surgery: Evidence of progress (1999-2009). World J. Gastrointest. Surg. 2012; 4.(3): 45–54.
47. Saka M., Morita S., Fukagawa T., Katai H.: Present and Future Status of Gastric Cancer Surgery. Jpn. J. Clin. Oncol. 2011; 41 (3): 307–313.
48. Alonso-Lárraga J.O., Alvaro-Villegas J.C., Sobrino-Cossío S., Hernández-Guerrero A., de-la-Mora-Levy G., Figueroa-Barojas P.: Self-expanding metal stents versus antrectomy for the palliative treatment of obstructive adenocarcinoma of the gastric antrum. Rev. Esp. Enferm. Dig. 2012 Apr.; 104 (4): 185–189.
49. Meyer H., Wilke, H.: Treatment Strategies in Gastric Cancer. Dtsch. Arztebl. Int. 2011; 108 (41): 698–706.
50. Kakeji Y., Morita M., Maehara Y.: Strategies for treating liver metastasis from gastric cancer. Surg. Today. 2010 Apr.;40 (4): 287–294.
51. Cunningham D., Allum W.H., Stenning S.P. et al. and MAGIC Trial Participants: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N. Eng. J. Med. 2006 Jul. 6; 355 (1): 11–20.
52. Ychou M., Boige V., Pignon J.P. et. al.: Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J. Clin. Oncol. 2011, 1, 29.
53. Smalley S.R., Benedetti J.K., Haller D.G. et. al.: SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J. Clin. Oncol. 2012 Jul. 1; 30 (19): 2327–2333.
54. Cunningham D., Starling N., Rao S. et al.: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N. Engl. J. Med. 2008; 358: 36–46.
55. Kang Y.K., Kang W.K., Shin D.B. et al.: Capecitabine/cisplatin versus 5-fluorouracil/ cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann. Oncol. 2009; 20: 666–673.
56. Okines A.F., Norman A.R., McCloud P. et al.: Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann. Oncol. 2009; 20: 1529–1534.
57. 57. van Cutsem E., Chung H., Shen L.: Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC) In ASCO Annual Meeting, Orlando, FL, USA. J. Clin. Oncol. 2009; LBA 4509.
58. Thuss-Patience P.C., Deist T., Hinke A.: Irinotecan versus best supportive care (BSC) as second-line therapy in gastric cancer: a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO) In ASCO Annual Meeting,Orlando, FL, USA. J. Clin. Oncol. 2009; Abstr. 4540.
59. Dank M., Zaluski J., Barone C. et al.: Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann. Oncol. 2008; 19: 1450–1457.
60. Kulig J., Kolodziejczyk P., Kulig P., Legutko J.: Targeted therapy for gastric cancer - current status. Oncol. Pharm. Practice. 19 (1) 75–81.

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