POLISH CONSENSUS ON TREATMENT OF GASTRIC CANCER; UPDATE 2013

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The project „Polish Research on Gastric Cancer” has been carried out since 1986. The main aim of this project, which is a multi-centre and cross-functional research, is enhancing the treatment results of gastric cancer patients by means of developing and encouraging the use of optimal methods for diagnosis, as well as both surgical and combined treatment.

One of the most important achievements of the project is the development and publishing of a document named ‘Polish Consensus on Treatment of Gastric Cancer Patients’, whose first version was published in 1998. Another versions were updated in accordance to the changing trends in the treatment of patients with gastric cancer. The current issue of the Consensus, that is, the 2013 update, was created in a particularly important time. Firstly, in 2010-2011 various new classifications of stomach cancer advancement were adopted and, most importantly, the “Japanese” and “Western” classifications were for the first time similar to each other.

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The publication partially used the results of research projects financed by KBN (State Committee for Scientific Research), MNiI (Ministry of Scientific Research and Information Technology), MEiN (Ministry of Education and Scientific Research), MNiSW (Ministry of Science and Higher Education) (grants no. PRVI, 3 P05 C 067 23 p01, 2 P05 C 024 29, N 403 069 31/3255, N N403 038839)
ondly, the new classification by Japanese scientific research societies which regarded the definition of topography and the extent of lymph node removal was largely simplified and became “friendly” for the surgeon community worldwide. Thirdly, based on EBM results, an agreement was reached in the 30-year-old discussion on surgical treatment (extent of resection, extent of lymph node removal, splenectomy) and combined treatment (perioperative chemotherapy, chemoradiotherapy, adjuvant chemotherapy). Fourthly, the current Consensus version discusses the role of endoscopic treatment of the early stomach cancer and the role of less invasive methods (laparoscopy and robotics). Both methods are becoming a very important part of stomach cancer patient treatment.

To sum up, the current version of the Consensus is both an analysis and a synthesis of current knowledge on gastric cancer treatment, and takes into account both reports from the world literature and the experience of centres which actively participate in the project „Polish Research on Gastric Cancer”.

The contents of this publication was prepared by authors based on basic rules of creating a consensus. A plenary panel session with the Consensus authors took place during the 9th International Symposium on „Esophagus and stomach diseases” in Lublin, on 6-7 December 2012. During the session, 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 should be emphasized that the directions included in the Consensus are not arbitrarily assumed rules of conduct in a legal aspect, which means that every doctor/team of doctors is entitled to make their own decisions as long as they are beneficial to a gastric cancer patient.

1. CLASSIFICATIONS

1.1. Classification of gastric cancer advancement stage

An accurate assessment of the tumour advancement stage is a basis for introducing the appropriate illness treatment and prognosis. It is also a standard in reporting new tumours and treatment results.

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

In 2010 American Joint Committee on Cancer (AJCC) published a new, modified 7th issue of TNM classification on gastric cancer. The previous classification had been widely applied since 2002. Even though only a few changes were introduced, they proved to be very significant ones (1, 2).

The new classification is used only for stomach cancer, it doesn’t concern other stomach neoplasms. Cancers with mixed glandual and neuroendocrinal pattern are classified the same way as stomach cancer.

It should be emphasized that in the new edition, neoplasms that include 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 parameters has been changed. Five new T parameter groups have been designated, which made it similar to the one used for other gastrointestinal cancers, that is T1, T2, T3 T4a and T4b (tab. 1). There have been certain changes introduced for tumours with T2 parameters, where the neoplasm may infiltrate the muscle layer of stomach wall and spread by gastrocolic and gastrohepatic ligament, as well as a larger or smaller omentum.

In case of tumours classified as T3, the Tumour infiltrates connective tissue located under the serous layer but does not infiltrate the visceral peritoneum and the surrounding structures

In T4 tumours, the tumour infiltrates the peritoneum or the neighbouring structures. Neighbouring structures include: spleen, transverse colon, liver, diaphragm, pancreas, abdominal cavity wall, adrenal gland, kidney, small bowel and retroperitoneum. Intramural spread of a neoplasm to duodenum and esophagus is classified taking into account the greatest depth of infiltration on the listed gastrointestinal tract sections, including stomach. In the previous, 6th edition, the criteria T, T2a and T2b (specifying the infiltr-
tration on muscular submucosal layer) had been reclassified to T2 and T3. This change introduced a significant difference in a five year survival rate of patients with tumours that infiltrate the muscular layer, as compared with the ones with the infiltration of a submucosal layer.

The previous T3 category was changed to T4a and T4b the moment the neighbouring structures were included in infiltration. From now on, T4b tumours do not necessarily mean the 4th group of neoplastic disease by definition.

The new classification also proposes another approach in case of setting the degree of spread to lymph nodes N (tab. 2). The latest classification of TN7 7th edition divided the so-far used N1 category (1 to 6 positive nodes in the region) onto N1 (1-2 nodes) and N2 (3-6 nodes), with parameter N3a currently meaning 7-15 nodes which shown spread (replaced N2), and the N3b property meaning 16 or more positive nodes (replaced N3) (tab. 3).

Notice that in order to adequately assess the advancement stage of lymph node 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 the ones in the region (mesenteric, retroperitoneal, para-aortic) is classified as presence of distant metastasis (M1 property). Microscopic metastatic focus of stomach cancer in the fat layer adjacent to the stomach cancer, without changes in lymph node pattern should be classified as metastasis in lymph node. Similar focus on the peritoneum surface is classified as distant metastasis (M1). M1 property is currently accepted only for distant metastases. It is particularly important in case of total resection en block for T4 tumours, which may become a medical therapy (tab. 3).

\[ \text{Table 3. Distant metastases – M property} \]

<table>
<thead>
<tr>
<th>M0</th>
<th>no distant metastases present.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>distant metastases present.</td>
</tr>
</tbody>
</table>

Stages of clinical advancement for gastric cancer are presented in the table (Tab. 4). In the current 7th edition very important changes were introduced. First of all, because the stage II is divided into A and B, it includes cases previously classified as group III. The highest advancement stage IV is only for cases of distant metastases, but very advanced
local tumours were degraded from IV to the newly formed IIIC stage. Thus, there is a visible tendency to lower the advancement stage with regard to the changes in classification of T property. Only stages 0 and I are the same.

Table 4. Clinical advancement stages of a neoplasm

<table>
<thead>
<tr>
<th>Clinical advancement stage of a neoplasm</th>
<th>T property</th>
<th>N property</th>
<th>M property</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T4a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Every T</td>
<td>Every N</td>
<td>M1</td>
</tr>
</tbody>
</table>

1.2. Patomorphologic examination standards and histopathological classifications

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

The purpose of gastric cancer patomorphological diagnostics is to determine the neoplasm diagnosis, specify its advancement stage and research the forecast and predictive factors which are a basis for choosing the optimal treatment method.

Diagnostic materials include:
1. A small endoscopic biopsy (excision) gathered during endoscopic examination.
2. Lesion extracted locally using EMR – endoscopic mucosal resection, or an EST – endoscopic submucosal dissection.
3. Frozen specimens examined during intra-operative examination.
4. Surgical specimen of the entirely or partially removed stomach along with the tumour and surrounding tissue (lymphatic system, omentum, neighbouring organs, for instance: spleen, pancreas etc.).

In each case, the lab that performs examination should receive both the tissue material and a referral that includes patient information, clinical diagnosis, place and method of obtaining material and the results of earlier examinations with the necessary clinical information on the course of the illness. In case of a specimen of lesions removed endoscopically, the description of the endoscopic examination that includes the macroscopic assessment of a lesion should be attached.

In case of tissues examined in a normal mode, a fixative (after submerging in paraffin) is a 10% buffered formalin. Endoscopic specimens should be immediately submerged in formalin (and not the other way round), and the topography of the specimen location should be specified. Information about the location and number of obtained samples from suspicious lesions and the way the biopsy specimen lies on the blotting paper (to enable the assessment of the whole mucous membrane cross-section) are 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 lab fresh and not submerged in formalin. In case surgical specimen needs to be secured during transport, surgeon cuts the stomach open along the greater curvature of the front wall, stretches it on a cork, wooden or paraffin board and pours it over with formalin. In each case it is recommended for the operating surgeon to separate lymph nodes into groups and send each of them in a separate container with the description of their topography.

The material obtained for intra-operative examination should be sent for examination fresh and poured over neither with fixative, nor with saline.

Necessary pathomorphological data included in the description of examination

Small endoscopic biopsy

In the endoscopic biopsy we specify a histological type of gastric cancer according to WHO and Lauren classification (colon type,
diffuse or mixed), as well as its maturity grade (Grading – G). In the age of molecular targeting therapies, endoscopic biopsy of stomach cancer has become a useful material for examination of aberrations of \( \text{HER2} \) gene, both using immunohistochemical and molecular methods. However, you should notice that a small tumour sample may not be representative for the entire neoplasm mass because of microscopic heterogeneity of stomach cancer. The final diagnosis may only be made after a histopathological examination of the entire tumour.

Difficulties in interpreting a small endoscopic biopsy regard the interpretation of precancerous conditions (exacerbation of atrophic colitis and colic metaplasia) and precancerous lesions (endoepithelial dysplasia/neoplasia), inflammations with regeneration of mucous membrane that imitates cancer infiltration and telling apart chronic inflammation, lymphomas and undifferentiated, small cell carcinoma. In the examples listed above it is recommended to perform immunohistochemical staining using an antibody panel (1 to 6 antibodies).

Lesions extracted locally using endoscopic methods (EMR, ESR)

The histopathological report additionally includes additional 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 assessment of foci of micro-invasions, we can detect single diffused cancer cells using an immunohistochemical method that utilises keratin antibodies.

Frozen sections examined on intra-operative basis

An intra-operative examination of proximal or distal margin is recommended in resection of primary stomach cancer in cases where there is doubt as to the radicality of resection. If in a diffuse cancer there is a presence of little diffused groups or single diffused cells infiltrating perivascular parenchyma, it is easy to miss them in a frozen sample. That is why the examination of frozen samples from surgical margin has its limitations in microscopic interpretation. Histopathological preparations sometimes require a confirmation of an immunohistochemical examination with the use of one antibody (keratin). Another indication for inter-surgical examination is a microscopic evaluation of cancer metastasis to lymph nodes or the lymph network in order to determine the primary diagnosis and/or assess the tumour advancement stage. Inter-surgical obtaining of stomach wall samples from the side of serous membrane is contraindicated, because it breaks the natural protective barrier against cancer infiltration and may result in a dissemination of the neoplasm.

Surgical specimen of stomach with a tumour

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

Macroscopic examination consists of defining the following parameters:

a) surgical specimen size: stomach length (along the greater and lesser curvature), esophagus and/or duodenum length, if these organs are delivered for examination;

b) location of the tumour in the stomach near:
   – stomach cardia, fundus, body, pyloric part,
   – greater curvature, lesser curvature,
   – anterior wall and posterior wall;

c) largest tumour size.

d) macroscopic tumour type, taking into account the classification for early and/or advanced gastric cancer;

e) the approximate depth of neoplastic infiltration of stomach wall with the specification of stomach wall layers affected by infiltration and decision whether the infiltration involves the tissue surrounding the stomach;

f) the state of proximal and distal margins, describing whether the margins are affected by neoplastic process and providing the distance between the margin and a neoplastic infiltration;

g) the description of lesions on the surface of serosa and marking them with ink;
h) state, location and number of lymph nodes with specification of a number of enlarged lymph nodes suspected with metastasis.

i) Condition of lesser omentum, greater omentum as well as the neighbouring tissue;

j) the description of the spleen, if it is present in surgical specimen.

Microscopic examination includes the following parameters:

a) histological type acc. to the WHO classification (2010) (tab. 5) and Lauren (obligatory) as well as according to Goseki (conditionally). Lauren classification involves types: colic, diffuse and mixed;

b) cancer histological maturity grade according to grades G1 – well differentiated, G2 – moderately differentiated, G3 – poorly differentiated;

c) cancer advancement stage according to the 7th edition of pTNM (AJCC/UICC) classification is presented in chapter 1.

It should be emphasized that gland cancers that include gastro-esophageal junction are included in the TNM classification as esophagus cancer.

In case there are less than 16 lymph nodes, N property is specified as pNX (however, it is necessary to provide the number of excised lymph nodes and the number of lymph nodes with metastasis).

d) surgical margins according to R-UICC classification that specifies the radicality of tumour resection, where:

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

R1 degree – means cancer infiltration confirmed only microscopically, not macroscopically in the proximal and/or distal and/or radial margin

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

e) angioinvasion,

f) infiltration of nerve trunks,

g) assessment of HER2 expression.

**Warning:** In case of cancers that include the gastro-esophageal junction, radial margin is assessed for (not covered with serosa, margin constituted by adventitia tissues)

Assessment of HER2 expression is not a routine examination and should be performed each time a referring physician assumes that marking HER2 has its clinical justification (15-18).

Assessment of HER2 receptor expression using immunohistochemical method and amplification of HER2 gene using in situ hybridization (IHS) is recommended in pathomorphological diagnostic of stomach cancer. It is included in the histopathological report, according to the guidelines of American Pathology Society, which is presented in the tab. 6 and 7.

### 1.3. Classification of lymph node topography and the scope of lymph node resection

The consensus recommends using a topography classification and nomenclature of the separate stations (groups) as well as the definition of the resection scope in accordance with the latest recommendations of International Gastric Cancer Association and Japanese Gastric Cancer Association from 2011, taking into account the current TNM classification discussed above (7, 12, 13, 19, 20).

**Table 5. Histopathological classification acc. to WHO, 2010**

<table>
<thead>
<tr>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Papillary adenocarcinoma</td>
</tr>
<tr>
<td>Tubular adenocarcinoma</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Poorly cohesive carcinoma including signet ring cell carcinoma and other variants</td>
</tr>
<tr>
<td>Mixed adenocarcinoma</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
</tr>
<tr>
<td>Carcinoma with lymphoid stroma (medullary carcinoma)</td>
</tr>
<tr>
<td>Hepatoid adenocarcinoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
</tr>
</tbody>
</table>

**Table 6. Criteria of assessment for HER2 immunohistochemical staining with interpretation**

<table>
<thead>
<tr>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1+</td>
<td>negative state</td>
</tr>
<tr>
<td>2+</td>
<td>border state (requires further diagnostic action – assessment using in situ hybridization method)</td>
</tr>
<tr>
<td>3+</td>
<td>positive state</td>
</tr>
</tbody>
</table>
Table 7. Assessment of HER2 gene amplification and interpretation of the result

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Amplification present</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=1.8</td>
<td>No HER2 gene amplification</td>
<td>negative state</td>
</tr>
<tr>
<td>&lt;1.8 &lt; 2.2</td>
<td>amplification uncertain</td>
<td>border state – requires the amplification to be reassessed</td>
</tr>
<tr>
<td>&gt;2.2</td>
<td>HER2 gene amplification</td>
<td>positive state</td>
</tr>
</tbody>
</table>

In the repeated examination performed using FISH method > 2.0

FISH — fluorescent in situ hybridization

Lymph node topography classification

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

Table 8. Gastric cancer lymph node topography

1. Right cardia lymph nodes, including the ones along the esophagus-cardia branch, the highest ascending branch of left gastric artery.
2. Left cardia lymph nodes, including the ones along the esophagus-cardia branch of left subdiaphragmatic artery.
3. a. Lymph nodes of lesser curvature along the left gastric artery branch.
   b. Lymph nodes of lesser curvature along the distal part of right gastric artery and its branches.
4. sa. Lymph nodes of greater curvature (left) along the gastric short vessels (perigastric area)
   sb. Lymph nodes of greater curvature (left) along the left gastro-omental artery (perigastric area)
   d. Lymph nodes of the lesser curvature (right) along the distal part of right gastro-omental artery and its branches.
5. Pyloric lymph nodes along the proximal part of right gastro-omental artery and its branches.
6. Retropyloric lymph nodes along the first branches and a proximal section 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 left gastric artery trunk from branching from the Celiac artery to the division into ascending branches.
8. a. Anterior-superior lymph nodes along the common hepatic artery.
    p. Posterior lymph nodes along the common hepatic artery.
9. Lymph nodes near the celiac artery
10. Lymph nodes of the splenic hilum and the end section of spleen artery, along the pancreatic tail and short gastric vessels over the junctions with branches of left gastro-omental artery.
11. p. Lymph nodes along the proximal part of the splenic artery from its branching from celiac artery to the half of the pancreatic tail length.
    d. Lymph nodes along the distal part of the splenic artery from half of its length to the end of pancreatic tail.
12. a. Lymph nodes of hepatoduodenal ligament, along the hepatic artery proper from the pancreatic head to the height of junction between left and right hepatic duct
    b. Lymph nodes of hepatoduodenal ligament along the common bile duct to the pancreatic head to the height of a junction between left and right hepatic duct.
    p. Lymph nodes of hepatoduodenal ligament along the portal vein from the height of pancreatic head to the height of a junction between left and right hepatic duct.

Nomenclature and definitions regarding the extent of lymphadenectomy

Current definitions of the extent of lymphadenectomy in gastrectomy operations differ with regard to the resection extent (total or peripheral stomach resection).

In terms of total stomach resection the following nomenclature applies:

D0: lymphadenectomy at the extent lesser than D1.

D1: resection of lymph nodes, stations from 1 to 7.

D1+: resection of lymph nodes within the D1 extent, and additionally stations no. 8a, 9, 11p.

D2: resection of lymph nodes within the D1 extent, and additionally stations no. 8a, 9, 10, 11p, 11d, 12a. Moreover, for tumours that infiltrate esophagus, lymph nodes from stations no. 19, 20, 110 and 111 should be removed.

D2+: resection of lymph nodes in D2 extent, and additional resection of lymph nodes from stations no. 16, 19, 20, 110, 111.
For peripheral (subtotal stomach resection the following nomenclature applies:

D0: lymphadenectomy at the extent lesser than D1.
D1: resection of lymph nodes from stations 1, 3, 4sb, 4d, 5, 6, 7.
D1+: resection of lymph nodes within the D1 extent, and additionally stations no. 8a, 9.
D2: resection of lymph nodes within the D1 extent, and additionally stations no. 8a, 9, 11p, 12a.

1.4. Classification regarding gland cancer of gastro-esophagal junction

The consensus recommends routine using of topography classification according to Siewert for patients with adenocarcinoma that includes gastro-esophagal junction, which is a basis for surgical treatment tactics (21).

Moreover, in accordance with the 7th edition of TNM/AJCC classification, you should use the TNM classification for esophagus cancer to assess the advancement stage of gastrointestinal neoplasms for patients with adenocarcinoma that involves gastro-esophagal junction.

2. DIAGNOSIS OF STOMACH CANCER AND CLINICAL EVALUATION OF ADVANCEMENT STAGE

2.1. History and the examination in question

Most gastric cancer patients report symptoms already in the early stage of the illness. They are non-specific symptoms, most often niggling pain, pain in the abdomen, feeling full after eating, nausea. Symptoms subside or lessen after using medication that inhibits gastric secretion. With respect to the patients with early stage stomach cancer, the examination in question most often shows a correct result with no traces of illness. Basic blood test results are also correct.

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

2.2. Endoscopic examination

The basic examination in the diagnostics of stomach cancer is a „classic endoscopy” with obtaining a sample for morphological assessment. The examination should be documented with photographs/videos.

The first and most important stage of the examination is a very careful visual inspection of stomach mucous membrane, with performing the so-called inversion (additional assessment of stomach cardia and fundus), after initial removal of mucus/foam or a liquid that makes it harder to assess the mucous membrane. During endoscopy, stomach peristalsis needs to be assessed, as well as the behaviour of gastric folds after giving air. In Japan, in order to enhance the quality of endoscopy, parents routinely receive 100 ml of water with mucus and foam reducing agent before the gastroscopy (Gaston and Pronase) (22).
In case of finding a suspected focal lesion with early diagnosed cancer, it is necessary to use indigo carmine/methylene blue staining (making lesion boundaries visible, choosing the optimum place for biopsy). In new generation endoscopes instead of classic staining, light „staining” (narrow band imagining, NBI) and enhancing the image are used. NBI with image magnification makes it possible to assess the vascular pattern. Based on the vascular pattern and the surface structure of focal lesion it is possible to perform an initial differential diagnosis (the so-called optical biopsy) and specify with great precision the infiltration boundaries and the optimum place for biopsy.

The last stage of diagnostic endoscopy is obtaining material for morphological examinations. The material is obtained using biopsy forceps. In case of advanced cancer, obtaining samples may be supplemented by gathering endoscopical brushing (in case targeted biopsy is more difficult).

If a lesion in the stomach is suspected to be early cancer, the number of biopsies is limited to gathering 1-2 samples, best performed using NBI and image magnification (23, 24, 25). Obtaining a greater number of samples may cause lesion fibrosis and make it harder to remove with the use of an endoscopic method. In subject literature (mostly the Japanese one), we find guidelines according to which biopsy should not be performed in such cases, the lesion should be solely carefully inspected (magnification, NBI), later removed and assessed microscopically in its entirety (26).

For every stomach lesion suspected of advanced cancer, gather 7-10 samples, if the result is negative, repeat the examination with obtaining the material. In case of cancer presented as thick folds (linitis plastica), morphological examination of endoscopic biopsy, and even of larger sections gathered with a diathermic loop are most often negative. In such cases, USG and an endoscopic ultrasound (EUS) prove very useful. A typical image in such examinations is a wall thickening with incorrect layers with main thickening of the submucous layer. Under the EUS guidance, perform a biopsy of the wall with lesion. Trucut type needles (EUS-TCB) is a method of choice and gives a 90% chance to determine the diagnosis in patients (27). When using a thin needle, this percentage decreases to 60% (EUS-FNA).

Macroscopically, early gastric cancer (according to the Japanese endoscopic classification) can be included into one of the three subtypes. Subtype I is a lesion with a salient character, 5 mm over the surface, manifesting itself as a polyp on a short, wide basis, looking like a thickened mucous membrane fold. Subtype II is a surface layer, less salient than type I, with uneven surface that may be present in the following variants: IIa – flat, slightly salient, less than 5 mm, IIb – flat lesion with irregular surface, IIc – flat, with a hollow. Type III is a lesion with a hollow, or ulceration. Most early stomach cancers can be counted among types II and III.

Early gastric cancer may take form of a mucous membrane discoloured focal lesion – including a redness or light/white discolouration (26). This type of „non-typical” endoscopic image is present in about 10% of early stomach cancers. The smaller the early lesion, the larger the percentage of cancers in a form of mucous membrane colour change.

Advanced neoplastic changes according to the Borman classification may be divided on a macroscopic level on to: I – tumourous, II – ulcerous with clearly separated infiltration boundary, III ulcerous with weakly separated infiltration boundary, and IV – flat and fibrous lesions.

It should be kept in mind that a neoplastic lesion may apparently heal under influence of medication that inhibits gastric secretion.

In the Polish population, where stomach cancer is still a clinical issue, gastroscopy should be performed for all patients with dyspepsia. The resignation from endoscopy, initial using of eradication of H. pylori infection, as well as giving medications that lower gastric secretion may cause diagnostics delay.

The diagnostic value of Endoscopy depends on the proper training of the physician performing the examination, good preparation of the patient, accurate ordinary stomach assessment and targeted biopsy.

In the endoscopic trainings it should be emphasized that when searching for neoplastic lesions in the stomach one should pay particular attention not only to concave and convex lesions, but also to the change in mucous membrane colour.

Video recording/photographs performed during endoscopy make it possible to return to the image if there is a need to do so. They are
a basis for trainings, interdisciplinary discussions as well as the quality enhancement of endoscopy.

Technical progress in endoscopic imaging will decrease the number of performed classical biopsies in favour of „optical biopsies”.

2.3. Defining stomach cancer advancement stage

Several types of examinations play a great role in defining stomach cancer advancement stage, namely the examination in question, classic endoscopy, tomography of abdominal cavity and chest. Routinely in females, an assessment of reproductive organs are performed. In chosen cases (cT3, cT4 tumours, suspected intraperitoneal spread) diagnostic laparoscopy is recommended. Performing cytological examination of peritoneal washings during laparoscopy and laparotomy is not recommended to be obligatory.

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

In case of early stomach cancer, initially qualified for endoscopic treatment, the best method of determining a neoplasm advancement stage is a histopathological examination of the entire removed lesion. Accuracy of classical endoscopy in terms of determining infiltration depth is comparable to the assessment in EUS examination. The results of both methods are incorrect for 20% of the patients (26-30).

3. SURGICAL TREATMENT

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

1) the extent of a resection (routine performing of total vs versus subtotal stomach resection),
2) the extent of limphadenectomy (D1 limphadenectomy versus D2 versus D2+/D3),
3) spleen resection (routine splenectomy versus resection without splenectomy,
4) the tactics of conduct in cases of esophageal-gastric junction (surgical access via chest, versus transhiatalesophagectomy),
5) as the endoscopic and minimally invasive surgery methods undergo a constant development, the main issue is the role of these technologies in treatment of stomach cancer patients.

3.1. Surgical resection (laparotomy)

Surgical treatment, that is a resection of a stomach along with the tumour remains the basic method of treatment for stomach cancer patients. Classic (available via laparotomy) stomach resection is still the surgical operation most often used in treatment of gastric cancer patients.

The intention of the Consensus authors was to synthesize knowledge based on scientific evidence (EBM) and taking into account own studies carried out within the project named „Polish research on stomach cancer” devoted to surgical treatment of stomach cancer.

The extent of resection

Routine performance of total stomach resection is often recommended by various European authors, particularly in cases of diffuse stomach cancer, according to Lauren classification (31, 32). Simultaneously, performing total stomach resection was never recommended in Japanese and Korean guidelines (12). Moreover, at least two randomized clinical studies carried out in Europe (33, 34) did not show the improvement in follow-up results in the group of patients with a total stomach resection performed. In each case, the main aim of surgical treatment of stomach cancer is obtaining oncological radicality with balancing individual decision so as to the extent of total, or partial gastrectomy.

The extent of limphadenectomy

The recommended scope of removal for lymph nodes in all cases of stomach cancer treatment with the intention of performing a potentially radical resection is D2 limphadenectomy. The need for D2 type lymphadenectomy does not concern patients qualified for radical endoscopic treatment and patient for which gastrectomy operation doesn’t fulfil
the macroscopic criteria of oncological radicality (R2 resection). In D2 lymphadenectomy the principle of removal of specified 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 don’t qualify for a radical endoscopic treatment. It applies only to cases of early stomach cancer with clinical advancement stage cT1 sm2, or cT1 with a diffuse type according to Lauren classification with recommended gastrectomy with lymphadenectomy type D1/D1+. In cases when there is any doubt as to the accurate clinical evaluation of the early cancer advancement stage, performing D2 lymphadenectomy is justified. (12, 28, 35, 36, 37).

In two randomised clinical studies carried out in Japan and in Poland, lymphadenectomy D2+, despite the fact that it wasn’t correlated with an increased number of perioperative complications, did not enhance follow-up results (38, 39, 40).

Splenectomy during stomach resection brought about by cancer

The concept of routine performing of splenectomy (possibly connected with resection of pancreatic tail) in order to „improve“ radicality related to extending the lymphadenectomy was received critically. The results of randomised clinical examinations carried out in Europe (randomised clinical study on lymphadenectomy carried out as a part of a British, Dutch and Italian study) unanimously indicated that performing splenectomy during stomach resection is related to a significantly larger percentage of post-surgical complications. Until the prospective clinical study continued in Japan (JCOG 0110) is finished, there is no unanimous evidence according to which routine splenectomy would be justified during a potentially radical stomach resection (41).

Surgical tactics in gastro-esophageal junction cancer patients

The analysis of available literature makes it possible to draw a conclusion that Siewert classification (which is de facto a topographical one) is optimal to make a decision about the surgical tactics, mainly in the aspect of surgical access. Results of a randomised clinical study that was concluded in Japan (42) influenced the decision of the Consensus authors.

Summary

1. Surgical stomach resection due to cancer remains a basic element of stomach cancer treatment.
2. The authors of the Consensus do not recommend routine total stomach resection or splenectomy, regardless of the cancer type according to the classification by Lauren.
3. In cases of cancer localised in the peripheral part of stomach peripheral resection may be performed, provided that at least a 5 cm proximal resection margin is maintained. Lauren classification does not influence the margin size.
4. 5 cm margin does not regard tumours localised 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. Resection of spleen and/or pancreatic tail is justified in cases of macroscopic evidence of infiltration of splenic hilus and/or pancreatic tail, which regards in particular the tumours located in the upper part of the stomach, and on the greater curvature.
7. The recommended extent of lymph nodes removal during potentially radical resection is lymphadenectomy D2.
8. If stomach tumour infiltration is intraoperatively revealed in the neighbouring organs and the patient’s condition makes it possible to perform an extensive operation, a multi-organ resection should be performed, provided that this resection is radical in its character.
9. In case of gastro-esophageal adenocarcinoma, the Consensus authors recommend a surgical tactic depending on the tumour location according to the Siewert classification:
   a) type I – laparotomy and thoracotomy with a removal of lower thoracic esophagus section);
b) type II – total stomach resection with a resection of lower esophagus section using preforaminal access. If the result of histopathological examination is positive, it is recommended to extend the esophagus resection extent using access gained by right thoracotomy. In justified cases, the removal of both stomach and esophagus is accepted;

c) type III – total stomach resection with resection of the lower esophagus section using preforaminal access, with intraoperative histopathological examination of the resection margin from the esophagus side. If the result of histopathological examination is positive, it is recommended to extend the esophagus resection extent using access gained by thoracotomy.

3.2. Minimally invasive surgery – laparoscopic surgery and robotic surgery in treating stomach cancer

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

For obvious reasons, the percentage of laparoscopic stomach resections is highest among patients with early stomach cancer (T1) located in the central as well as distal part of the stomach. Both partial, peripheral and even less extensive wedge stomach resections are allowed. Laparoscopic stomach resections are more and more often performed in case of patients diagnosed with advanced cancer. The standard scope of laparoscopic surgeries in case of advanced cancer includes both full and partial gastrectomy and D2 lymphadenectomy.

The majority of the so-far conducted randomized clinical studies indicate that despite a longer surgery and technical problems accounting for a longer „learning curve”, the laparoscopic method is very safe with respect to perioperative complications and a shorter hospitalization period.

Given the meta-analyses of the so-far conducted clinical research studies, there are no definite recommendations of laparoscopic approach as an equivalent method to open stomach resection when surgically treating patients with stomach cancer. There is no sufficient evidence that would satisfy EBM criteria and prove that laparoscopic techniques are as valuable as laparotomic surgeries with respect to 5-year survival rate. We are still awaiting the final results and findings of two relevant randomized clinical studies in Japan (JCOG 0912 study) and South Korea (KLASS study) (43-45).

Laparoscopic resection experimentally joined with intraoperative biopsy of the sentry ganglion in case of patients with an early stage of stomach cancer makes it possible to individualize therapeutical proceedings, however is still in an experimental stage and as such cannot be a method recommended for routine medical practice.

Robotic surgery for treating patients with stomach cancer is still rather an inaccessible method, mostly because of the equipment expense. However 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 over laparoscopic treatment, there is no sufficient scientific evidence which could objectively prove its usefulness in stomach cancer surgery.

To conclude, surgical treatment of stomach cancer patients with the use of laparoscopic or robot-assisted procedures is allowed only in highly-specialized centres that have experience in both advanced laparoscopic procedures and surgical treatment of patients with stomach cancer. Both laparoscopic procedures and robot-assisted stomach surgeries are treated as a medical experiment and require the patient’s informed consent as well as the positive opinion of the Bioethical Commission.

Similarly, a laparoscopic stomach resection with biopsy of the sentry ganglion should not decide upon lymph node dissection among patients with stomach cancer. This method is still in an experimental stage. The change of the Consensus authors’ opinion will be possible after publishing the results and findings of JCOG 0912 and KLASS randomized clinical research studies, as well as other scientific reports regarding robotic surgeries and the importance of biopsy of the sentry ganglion for stomach cancer surgical treatment.
3.3. Endoscopic treatment of early stomach cancer

Endoscopic treatment may be applied in case of early stomach cancer with low risk of regional lymph node metastasis – Type 0. The neoplastic lesions should qualify to be removed in one fragment (12, 31, 32).

Recommendations for endoscopic treatment

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

5.1.1. Standard / absolute recommendations: Highly differentiated type of adenocarcinoma without ulceration features (UL-) where the infiltration depth does not exceed the mucous membrane (T1a) and the horizontal section does not exceed 2 cm.

5.1.2. Relative / extended recommendations: A submucous dissection method is proposed. Extended recommendations are proposed for T1a tumours with low probability of metastasis to lymph nodes that fulfil the following criteria:
– highly differentiated cancer type without ulceration features (UL-) with diameter larger than 2 cm,
– highly differentiated cancer type with ulcerous character (UL+) with diameter smaller than 3 cm,
– poorly differentiated cancer type without ulceration features (UL-) with diameter no larger than 2 cm.

Methods of endoscopic treatment

Endoscopic mucosal resection. An operation that raises the neoplastic lesion with the margin of the surrounding mucous membrane by injecting it with a saline solution, and shearing it off with an electrical loop.

Endoscopic submucosal dissection. After setting the resection boundaries and injecting the lesion, the mucous membrane with a submucous membrane around the lesion is slit using special electric knives. The kind of tools used depends on the experience of the physician that performs the operation. This technique enables more radical resection of the lesion, down to the proper muscle membrane.

Evaluation of the therapy effectiveness

The evaluation of the effectiveness of endoscopic treatment includes both histopathological evaluation of removed preparation with respect to radicality as well as the risk of lymph node metastasis.

Endoscopic resection performed according to standard recommendations is regarded a radical therapy if it fulfils the following criteria:
– en-block resection,
– lesion size up to 2 cm,
– well differentiated cancer type from histological point of view,
– pT1a advancement stage,
– HM0 – negative horizontal margin,
– VM0 – negative vertical margin,
– no infiltration of lymph nodes (Ly-) and blood vessels (V-).

Endoscopic resection performed according to extended recommendations is regarded a radical therapy if it fulfils the following criteria:
– en-block resection,
– HM0 – negative horizontal margin,
– VM0 – negative vertical margin,
– no infiltration of lymph nodes (Ly-) and blood vessels (V-),
– lesion size over 2 cm, well differentiated cancer type from histological point of view, pT1a, Ul (-),
– lesion size under 3 cm, well differentiated cancer type from histological point of view, pT1a, Ul (-),
– lesion size under 2 cm, poorly differentiated cancer type from histological point of view, pT1a, Ul (-),
– lesion size under 3 cm, well differentiated cancer type from histological point of view, pT1a (SM1, <500 microns from the mucous membrane muscularis).

Endoscopic resection does not fulfil the criteria of medical treatment if any of the criteria listed above is not fulfilled.
The procedure in case the criteria for endoscopic treatment are not fulfilled, or there is a cancer relapse after endoscopic treatment

In case the criteria for endoscopic treatment are not fulfilled, the patient should be subjected to surgical treatment.

In case the endoscopic resection of an early cancer does not meet the criteria of a medical treatment as defined in section 5.3, surgical treatment is recommended. The range of resection is specified according to the same rules that apply in case of more advanced tumours. Depending on the lesion location, total stomach resection and/or peripheral resection are recommended.

The extent of lymphadenectomy depends on the cancer clinical advancement stage:
- D1 lymphadenectomy is recommended in case of all T1a tumours and T1b lesions differentiated from the histological point of view with a diameter that does not exceed 1.5 cm,
- D1+ lymphadenectomy is recommended in the other cases of T1b clinical advancement,
- D2 lymphadenectomy is recommended when in doubt about the accuracy of the advancement stage assessment of early cancer, or in cases of intra-operative suspected metastasis to lymph nodes.

In case of cancer recurrence limited to a mucous membrane after the endoscopic treatment performed in accordance with the primary recommendations, a treatment may be repeated once again using a submucous dissection technique. In case of a relapse after the treatment is performed due to patient’s extended recommendation, the patient is qualified for surgical treatment with D2 lymphadenectomy.

3.4. Modifications of surgical treatment of stomach cancer patients (sudden condition surgery, palliative surgery, extended operations)

In the era of evidence-based medicine (EBM) it is very difficult to posit rules that would regard the modification of surgical treatment. The available published rules of treating patients with stomach cancer condition the choice of therapeutical proceedings on the basis of cancer 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 burden of noticed complications may be modified by undesired effects of cancer treatment.

The surgical treatment of sudden conditions in case of stomach cancer is limited to treatment of obstructions, perforations and bleeding to the upper section of gastrointestinal tract. In such cases, the surgeon’s actions are subject to other treatment criteria than the ones for treating tumours. Radical surgery is possible very rarely. Surgical tactics aims at treating the complication and not the cancer itself. Possible final operation for the purpose of treating the neoplasm is performed in the second stage, after the histopathological 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 location and advancement stage of a cancer and on the patient’s condition. We chose the treatment which has the lowest complication risk.

Bleeding to the upper esophagus section

Gastric tumour bleeding may cause microcytic anaemia, which results from chronic bleeding to gastrointestinal tract. Bleeding that causes hemodynamic effect is fairly scarce – about 5% of patients experience it. One has to bear in mind additional risk factors regarding bleeding, such as receiving steroid anti-inflammatory medication, often encountered in this patient group.

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

The surgical procedure in stomach cancer patients is: locating the stomach lesion, specifying its local advancement stage, presence of metastases and the patient’s general condition. Most often, large local advancement makes it impossible to perform a resection. In tumours on peripheral stomach part we can perform a palliative resection or a gastroenterostomy. In tumours of the closer stomach section and cardia we usually aim to implement prosthesis endoscopically in the tighter place.

Stomach perforation during the course of cancer

Even though the percentage of perforated stomach cancers is rather small and equals from 0.3% to 3% of cases, stomach cancer is diagnosed during histopathological examination in almost 10% of patients with perforation. It opens a discussion on possibilities of performing a single or two stage operation for patients with regional neoplasm advancement. In the opinion of the Gastric Cancer Consensus members, the first treatment stage should involve perforation control as well as peritoneum inflammation treatment. If there are such technical possibilities in the second stage, after histopathological verification and preparation of the patient, we perform resection of the stomach and the appropriate extent of lymph nodes.

„Extended” and palliative resections in stomach cancer patients

Routine gastrectomy due to cancer includes resection of the organ (or its part) as well as resection of lymph nodes within D2 scope. Every operation during which we resect tissue outside the stomach or additional lymph nodes is an extended resection. The results of the majority of randomised clinical studies show that there is no purpose in performing extended lymph node removal – more than D2. The exceptions are gastro-esophageal junction cancers where we routinely aim to remove lymph nodes of posterior lower mediastinum. At such a neoplasm location – type II according to Siewert – the minimum extent of the operation is transthiatalesophagectomy with maintaining a correct margin of the lower esophagus section (the extent of resection not being definitely specified).

The next problem is gastrectomy extended with splenectomy and/or pancreatic tail resection. In the light of current views (the dominant ones), this type of extended operation can be considered only in cases of direct infiltration on these organs and lack of features that might demonstrate generalization of the neoplastic process. That is why the splenectomy and/or removal of pancreatic tail are not justified only in order to extend the extent of lymphadenectomy.

In the current subject literature, we can find reports on extending survival period for selected patients after cancer-related gastrectomy and removal of single metastatic tumours from a liver. The statistical significance of this type of examination does not enable any recommendations. That is why, based on evidence (EBM), the opinion of the members of the Gastric Cancer Consensus is definite – every resection for patients in IV advancement stage is a palliative resection.

Performing a non-radical resection (R2) on a patient for whom we intraoperatively determined the presence of lesions outside the region – M1 is acceptable for patients with symptoms of chronic bleeding from tumour, and for patients who may have significant obstruction caused by a tumour. It does not extend the treatment with resection of additional lymph nodes apart from the ones located in the resected stomach part. The decision regarding operating other patients should depend on the positive response to chemotherapy.

Performing extended resections which include neighbouring organs on patients with cancer infiltrating the transverse colon still remains an issue. There is a possibility of performing resections of transverse colon segments as a preventive surgery in case there is an obstruction which might develop further. According to the Consensus authors – both in this and other cases – performing extended resections is accepted provided they are potentially radical and patients are in a good general condition.
4. COMBINED TREATMENT

For the time being, surgical treatment is still a predominant method of treating patients with gastric cancer. However, it has been 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 numerous articles in subject literature, we should decide that patients with gastric cancer (except for early gastric carcinoma) should receive combined treatment (51-60). Relevant recommendations are presented below.

Perioperative chemotherapy should be considered for every patient with potentially resectable gastric cancer in advancement stage cT3-4, all N, M0 for whom we assume the possibility of R0 operation.

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

For patients with advanced, locally non-resectable tumour, but without distant metastasis (T4, all N, M0), we should consider using an induction chemotherapy with the intention of a repeated laparotomy in attempt to remove the organ affected by a neoplasm.

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

For patients with generalized neoplastic disease who have HER2 expression we should consider targeted treatment.

Consider chemotherapy and another attempt of a resection in case of unresectable relapses.

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

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

5. FOLLOW-UP EXAMINATION FOR PATIENTS AFTER CONCLUDING 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.

Performing a follow-up gastroscopy is recommended according to the following regimen:
- 3 months after the treatment,
- 6 months after the previous examination,
- next, in yearly intervals up to 5 years after the treatment.

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

Follow-up examination for patients after total or partial stomach resection due to advanced gastric cancer

As of now, the is no optimal method determined for observing patients after a radical stomach resection. Probably performing systematic endoscopic and imaging examinations does not extend patient survival as compared with other method of performing additional examinations in patients that report discomfort during follow-up visits (7,12, 31, 32).

Because the largest number of disease relapses take place within 2 years from the end of the treatment, the Panel members are unanimous as to that follow-up examinations (interview and medical evaluation) should take place every 3 months throughout this period, and next every 6 months for 3 years. In case the patient reports ingestion disorders, it is recommended to perform an endoscopic examination. USG and CT examinations of abdominal cavity are performed in accordance with 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 anaemia caused by iron shortage, iron should be supplemented.
REFERENCES


