IMAGING OF THE CERVICAL AND ABDOMINAL LYMPH NODES IN A COMBINED TREATMENT OF SQUAMOUS CELL OESOPHAGEAL CARCINOMA

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The presence of lymph node metastases in esophageal cancer is one of the most principle prognostic indicators. The aim of the study was the assessment of cervical and abdominal lymph nodes (N/pN) by ultrasound (US) examination in patients with squamous cell carcinoma of the thoracic esophagus referred to esophagectomy.

Material and methods. The analyzed study population consisted of 110 patients who underwent a combined-modality treatment (neoadjuvant chemotherapy – 74 patients or chemoradiotherapy – 36 patients). The results of US lymph node assessment were compared to the results of histopathological evaluation of lymph nodes harvested during surgery and diagnostic value of cervical and abdominal US in terms of sensitivity, specificity, positive and negative predictive value were determined.

Results. The complete metastatic regression was shown by US in 14.3-22.2% of patients depending on the node location and mode of neoadjuvant treatment. There was no significant difference in the assessment of lymph nodes between chemotherapy and chemoradiotherapy patients.

Conclusions. US investigation is a method recommended for the assessment of metastatic lymph nodes in squamous cell oesophageal carcinoma, especially – for cervical nodes, where its specificity amounted to 96% and sensitivity – 100%. When positive nodes are suggested by US of the neck esophagectomy should be combined with 3-field lymphadenectomy.

Key words: Squamous cell oesophageal carcinoma, lymph nodes metastases, US of cervical lymph nodes

Squamous cell carcinoma (SCC) of the esophagus is one of the most malignant gastrointestinal neoplasms (1, 2, 3). Yet unsatisfactory results of surgical treatment of advanced SCC of the esophagus have inclined researchers to inquire and investigate a combined modality treatment (CMT) with neoadjuvant chemotherapy or chemoradiotherapy (4-9).

In Poland the majority of patients with esophageal cancer are diagnosed in advanced stage with prominent dysphagia (4). Early lymph node involvement is a common finding in the course of esophageal cancer – even in cancer infiltrating the submucosa lymph node metastases are found in 34-40% of the patients (1, 10, 11, 12). Positive lymph nodes usually indicate poor prognosis (1, 4, 5, 13). Five-year survival after curative esophagectomy can be achieved in 53-67% of the patients without lymph node invasion and only in 9-15% of the patients with positive nodes (11, 13, 14, 15).

The rate of lymph node involvement in esophageal cancer has been reported as 65-80%. Positive nodes most frequently are found in the mediastinum, then in the upper abdomen, within the upper aperture of the thorax and in the neck (4, 9, 14, 16, 17).

The suspicion of lymph node involvement results in the extension of the resection range
about the dissection of lymphatic tissue of the mediastinum and the upper abdomen. In some cases a 3-field lymphadenectomy including the dissection of lymphatic tissue of the neck and the upper aperture of the thorax could be a recommended surgical approach (1, 10, 14, 16, 18, 19). Esophagectomy with 3-field lymph node dissection is the most radical and extensive surgical procedure associated with numerous complications and increased postoperative mortality risk (2, 3, 10, 11, 13). In many Japanese centers this approach is performed as a recommended therapy for esophageal cancer (10, 14, 16, 18). A more selective application of 3-field lymphadenectomy has been lately advocated (1, 2, 3, 10, 19). The authors of the current report conditionate a surgical approach based on lymph node status of the neck and abdomen.

The aim of the present study was to establish the role of ultrasound (US) in the assessment of cervical and abdominal lymph nodes in patients with SCC of the thoracic esophagus referred to esophagectomy who underwent preoperative chemotherapy or chemoradiotherapy. The accuracy and sensitivity of ultrasound in the assessment of metastatic lymph nodes were additionally estimated.

MATERIAL AND METHODS

Two-hundred and ninety-seven patients with SCC of the thoracic esophagus were operated on at Second Department of General Surgery, Medical University of Lublin, Poland between 1992 and 2009. In this study we analyzed a series of 110 patients who underwent a combined modality treatment with neoadjuvant chemotherapy – 74 patients (SCSR 440149102) or neoadjuvant chemoradiotherapy – 36 patients followed by esophagectomy or chemoradiotherapy (SCSR 4P05C01611) (multicenter, prospective randomized trials).

The clinical staging was established based on radiology, endoscopy, US (percutaneous cervical and abdominal, endoscopic – EUS) and computed tomography (CT) performed before and after the neoadjuvant treatment. The depth of tumor infiltration – T category, the regional lymph nodes status – N category and distant metastases – M category were determined (V and VI UICC/TNM staging classification system). Metastases to cervical and/or celiac lymph node stations were determined as M1a and distinguished from distant organ metastases (M1b). T3 N0-N1 M0 or T4 N0-N1 M0 cancers were diagnosed in all 110 patients.

The 21-day combination chemotherapy regimen consisted of a continuous infusion of cisplatin at 20 mg/m²/day on days 1-5, 17-21 and 5-fluorouracil at 300 mg/m²/day on days 1-21. The patients who underwent chemoradiotherapy received fractionated radiation of 2 Gy on days: 1-5, 8-12, 15-19 to a total dose of 30 Gy with the concurrent combination chemotherapy regimen described above.

The US examination was performed using sonograph HITACHI EUB-410. The evaluation of abdominal lymph nodes was carried out with the Convex head at 3.5 MHz. The following abdominal lymph node stations were evaluated: paracardiac, lesser curvature, celiac trunk, left gastric artery, common hepatic artery nodes. The evaluation of cervical lymph nodes was carried out with the linear head at 7.5 MHz and included deep cervical nodes with recurrent nerve lymphatic chain, paratracheal and supraclavicular nodes. The overall US evaluation was performed before and after the neoadjuvant therapy. The results of US examination were compared and supplemented by CT. A combined analysis of both studies determined a clinical staging and lymph node status. The US assessment of lymph node metastases in esophageal cancer was made based on the criteria proposed by the Japanese Society for Esophageal Diseases (17). A lymph node was regarded as metastatic when a distinct lymph node boundary with internal inhomogeneous echo pattern were found, when a long diameter exceeded 5 mm in the neck and 10 mm in the abdomen or when a short/long diameter ratio was higher than 1:2.

The reconstruction after esophagectomy was performed with gastric tube formation in 98 patients (89.1%). The jejunum was used as the esophageal subsitute in 4 patients (3.6%) and the colon in the remaining 8 patients (7.3%). The esophageal substitute was traversed through the posterior mediastinum in 61 patients (55.4%) and through the anterior mediastinum (retrosternal route) in 49 patients (44.6%).

The principal surgical procedure was a subtotal transthoracic esophagectomy with the anastomosis in the neck and two-field extended lymph node dissection (19).
patients, in whom cervical lymph node metastases were suspected on cervical ultrasound, esophagectomy was accompanied with three-field lymph node dissection. The mean number of lymph nodes harvested was 22, range 8-64 (median ±SD: 33.4 ±13.7).

A detailed histopathological evaluation (HP) of the entire removed specimen enabled a pathological staging and establishing a true lymph node involvement (N/pN).

In a statistical analysis the results of US lymph node assessment were compared with the results of HP of lymph nodes harvested during surgery and diagnostic value of cervical and abdominal US in the assessment of lymph node status was determined using sensitivity, specificity, positive and negative predictive value tests.

RESULTS

In the assessment of lymph node status in patients who underwent a combined modality treatment an US complete and partial response to the neoadjuvant treatment were defined according to the criteria provided by the Japanese Society for Esophageal Diseases (17). An US complete response (US CR) was defined when previously regarded as metastatic lymph nodes were undetectable. An US partial response (US PR) to the neoadjuvant treatment was defined when at least 50% decrease in lymph node diameter or changes in lymph node US presentation (boundary, shape, internal echo pattern) were found.

A pathological complete response (CR) was defined when no cancer cells were found within the esophageal wall and lymph nodes harvested. A partial pathological response (PR) was defined when fibrosis with only few cancer cells were found.

HP of the specimen revealed that preoperative chemotherapy resulted in CR in 6/74 (8.1%) and in PR in 18/74 (24.3%) patients. In patients who underwent preoperative chemoradiotherapy CR was found in 4/36 (11.1%), and PR in 15/36 (41.6%) patients (tab. 1).

US performed at presentation (before any treatment) suggested lymph node metastasis in 17/74 patients. On US re-evaluation after neoadjuvant treatment, US CR and US PR was found in 3/17 (17.6%) and 5 (29.4%) patients; respectively. In the remaining 9 patients US lymph node presentation was not altered by the neoadjuvant treatment. HP did not reveal cancer cells in lymph nodes in 2 patients. The detailed analysis of lymph node status and their US presentation before and after neoadjuvant chemotherapy or chemoradiotherapy has been show in tab. 1.

For cervical US, no false negative results (not detected by US metastatic nodes) were observed and false positive results (positive nodes on US not confirmed by HP) were found in 4 patients (4/26). More distinct differences were evident for abdominal US. False negative (overlooked nodes) and false positive results were observed in 8 and 6 patients, respectively. The detailed analysis has been show in tab. 2.

In overall analysis, the sensitivity and specificity of cervical US in detecting lymph node involvement were 96% and 100%, respectively. A very high positive predictive value of cervical US – 100% – suggests, that US of the

Table 1. The assessment of lymph node (LN) metastases in the neck and abdominal cavity in the course of a combined therapy for esophageal cancer

<table>
<thead>
<tr>
<th></th>
<th>Initial US</th>
<th>US CR</th>
<th>US PR</th>
<th>HP positive LN</th>
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<tbody>
<tr>
<td>Neck LN Chemotherapy</td>
<td>17/74</td>
<td>3/17 (17.6%)</td>
<td>5/17 (29.4%)</td>
<td>10/74</td>
</tr>
<tr>
<td>Neck LN Chemoradiotherapy</td>
<td>9/36</td>
<td>2/9 (22.2%)</td>
<td>2/9 (22.2%)</td>
<td>7/36</td>
</tr>
<tr>
<td>Abdominal LN Chemotherapy</td>
<td>28/74</td>
<td>4/28 (14.3%)</td>
<td>7/28 (25%)</td>
<td>24/74</td>
</tr>
<tr>
<td>Abdominal LN Chemoradiotherapy</td>
<td>14/36</td>
<td>2/14 (14.3%)</td>
<td>5/14 (35.7%)</td>
<td>14/36</td>
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Table 2. The comparison of ultrasound (US) and histopathology (HP)

<table>
<thead>
<tr>
<th>Chemotherapy + Chemoradiotherapy</th>
<th>US positive LN after treatment</th>
<th>HP positive LN after treatment</th>
<th>US negative / HP positive LN</th>
<th>US positive / HP negative LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck LN</td>
<td>22/26</td>
<td>17/26</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal LN</td>
<td>38/42</td>
<td>38/42</td>
<td>8</td>
<td>6</td>
</tr>
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neck is sufficient to rule out metastases of esophageal cancer to cervical lymph nodes. The sensitivity and specificity of abdominal US in detecting lymph node involvement were 94% and 82%, respectively. The detailed analysis has been shown in tab. 3.

DISCUSSION

Surgical resection is the method of choice in majority cases of regional advanced oesophageal carcinoma (4, 5, 7, 14, 18). In patients who undergo resection regional and distant lymph node metastases are regarded as one of the most significant prognostic factors (1, 3, 5, 13, 18). The appropriate assessment of lymph node involvement can indicate the necessity of neoadjuvant treatment or determine the extent of lymph node dissection before planned surgery (4, 6, 7, 8).

The simplest method of the detection of metastases in cervical lymph nodes is palpation currently performed as a preliminary gross-assessment. A low precision estimated at the rate of 12.5-24% and a high probability to miss nodes less than 12mm in size make this examination only preliminary diagnostic procedure (19,20,21,22). Imaging techniques such as US, CT or NMR significantly increase the efficacy of the examination with the accuracy of 78-99% (6, 12, 18, 20, 23). In presented data that was 100% and 82.6%. The high specificity of the US assessment of lymph node involvement reaching in our series 95.9% for cervical and 92.1% for abdominal lymph node stations is worth of note finding. The comparable results have been also reported by other investigators with the specificity of US assessment of 86-96% for cervical and 78-94% for abdominal nodes (9, 18, 23, 24).

Currently available diagnostic techniques can deeply penetrate into the internal structure of lymph node. The presentation of lymph node hilum, Doppler spectrum parameters of flow within the lymph node vasculature have been lately available for investigation. A promising results has been expected from imaging techniques visualizing architecture of lymph node vasculature and allowing to establish abnormal patterns of blood supply, specially with utilizing of contrast media (25). The accurate assessment of such detailed structures, however, requires a highly advanced equipment and diagnostic experience.

EUS is strongly recommended diagnostic method for imaging of lymph nodes specifically pericardiac, mediastinal and nodes on the boundary of the neck and superior mediastinum. Its accuracy has been reported as 70-90% with the specificity estimated slightly below 78-87 (13, 19, 24). The accuracy of EUS is predominantly related to a node size, reaching 93% when the lymph node diameter exceeds 10 mm (13).

The peculiar anatomy of the esophagus with respect to its lymphatic drainage (rich net of lymphatic channels within particular esophageal wall layers, numerous lymphatic channels spreading along the longitudinal axis of the esophagus) results in more frequent and early manifestation of lymph node involvement (10, 11). When the primary tumor is situated above or at the level of the tracheal bifurcation lymph node metastases are seen most often in cervical lymph node stations and in recurrent nerve lymphatic chain. Location of the primary tumor below the tracheal bifurcation is associated with the increased risk of abdominal lymph node involvement (10, 14). Cervical lymph node involvement in carcinoma of the thoracic esophagus is observed in 15-30% of patients (11, 13, 14, 16, 20, 21). The most common sites of nodal metastases in the neck are nodes of the right recurrent nerve lymphatic chain and supraclavicular nodes (6, 12, 15). Most frequent lymph node involvement in the neck, even in 50% of patients, is observed when a tumor is located in the upper part of the esophagus (26). Our data revealed positive lymph nodes in the neck in 46% of the patients. Among abdominal lymph nodes most frequently involved are pericardiac nodes. Lesser

<table>
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<tr>
<th>Statystics</th>
<th>Neck US</th>
<th>Abdominal US</th>
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<tr>
<td>Sensitivity</td>
<td>17/(17+0) x100% = 100%</td>
<td>38/(38+8) x100% = 82.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>93/(93+4) x100% = 95.9%</td>
<td>70/(70+6) x100% = 92.1%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>17/(17+1) x100% = 81.0%</td>
<td>38/(38+6) x100% = 86.4%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>93/(93+0) x100% = 100%</td>
<td>70/(70+8) x100% = 89.7%</td>
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</table>
curvature, celiac or common hepatic artery nodes are the rarer sites of lymph node metastases (10, 14, 16, 18, 27). The source of metastases is usually a tumor of the lower esophagus than of the middle esophagus – in our data in 48% and 27%, respectively (26). Akiyama et al. (14) reported lymph node involvement of the epigastric lymph node stations in 70% of patients with carcinoma of the lower part of the esophagus.

Metastatic nodes may show extracapsular infiltration beyond lymph node capsule into surrounding fat tissue what additionally may result in worsening of the prognosis (27). Most frequently in such cases cancer represents specific biological pattern with aggressive and prone to spreading behavior.

The US findings indicating metastatic character of enlarged lymph nodes are a distinct node boundary, poor, inhomogeneous internal echo pattern and a size exceeding 10 mm (17, 23, 25). A more precise criterion is a shorter/longer node diameter ratio. The ratio higher than 1:2 usually suggests (19) and approximating 1:1 is almost a certain evidence of metastatic nature of enlarged nodes (20). The next indicator of metastatic nature is a short diameter of a node and its value higher than 6 mm may suggest metastasis (12, 20, 23), in other reports this diameter has been established as 10 mm (6, 22, 24), particularly for abdominal nodes. A round, hypoechoic node, 10 mm in size, with clear distinct margin should always be regarded as metastatic. This presentation was established in our unit as a diagnosis of metastatic peripheral lymph node. Findings delivered by US solely can not confirm positive nodes, is should be done by cytological and particularly histopathological assessment of a taken specimen (1, 11, 20, 21, 27). An internal nodal architecture, neoplastic rearrangement, infiltration of nodal structures and surrounding tissues should be assessed in detail.

A histopathologically proven lymph node involvement in esophageal cancer patients results in a dramatic decrease of a long-term survival (1, 5, 13, 18). A five-year survival rate for patients without lymph node metastases after a curative resection has been reported to be 53-67% as compared to 9-15% for patients with lymph nodes involved (11, 13, 14, 15). Moreover, metastases found in distant lymph node stations in the neck and along celiac trunk (M1a) are still associated with the higher 3- and 5-year survival rates after the curative resection with three-field lymph node dissection than in patients in whom distant hematogenous metastases (M1b) are observed and thus the curative resection cannot be achieved (10, 11). An important prognostic factor is a number of positive nodes, involvement of 5 and more lymph nodes results in a decrease of 5-year survival rate after esophagectomy to less than 10% (15). Much better prognostic indicator is a lack lymph node involvement or small number of positive node between 1 and 3 (28) with 5-year survival rates of 34 and 27%, respectively.

The appropriate extend of lymph node dissection in esophageal cancer surgery has still remained a matter of debate. en block esophagectomy with two-field lymph node dissection is a principle surgical procedure in the treatment of carcinoma of the thoracic esophagus is carried out in Europe and in the United States whereas in Japan three-field lymph node dissection is routinely performed (10, 14, 16, 18). Fujita (18) and Ōkuma (13) recommend removal of the recurrent nerve lymphatic chain nodes in all cases and three-field dissection when a tumor is located in the upper or middle third of the thoracic esophagus because of a high rate of cervical lymph node involvement, its specific distribution and a frequent nodal recurrence pattern. Lymph node involvement indicates a high biological activity and dynamic of a tumor. The crucial issue is what optimal number of lymph nodes should be dissected irrespective of their metastatic status. Herrera (29) recommends, that the number of harvested lymph nodes should be as high as it possible and it should increase with the stage of cancer. In T1 tumor at least 10, in T2 more than 20 and in T3 and T4 cancer more than 30 lymph nodes should be removed.

However, a prophylactic lymph node dissection in the neck in every esophageal cancer patient is not commonly advocated. The body of evidence questioning the appropriateness of three-field lymph node dissection has been accumulating. Siewert and Stein (3) as well as Law and Wong (2) do not advocate this method as a standard procedure due to an increased morbidity and mortality rate, a difficulty in selection of patients who could benefit from this kind of the treatment, and also due to the
increased local recurrence rate approximating the rate after two-field lymph node dissection. Taking into account the high specificity and accuracy of cervical US in the assessment of lymph node involvement Igaki (1), Matsubara (10) and Tachimori (19) proposed carrying out three-field lymph node dissection only in patients with positive cervical lymph nodes on US. This is also a strategy incorporated into the management of esophageal cancer at our department. Moreover, like many others, when metastatic nodes are suspected we refer patients with esophageal cancer to combined modality therapy (6, 27-31).

A combined therapy for esophageal cancer is expected to improve the outcome of treatment. An anticipated effect of chemotherapy or chemoradiotherapy is a reduction of response rates (including CR) and thus an increase of curative resection rates (4, 6, 7, 8). In our series a CR and PR with respect to lymph node involvement was found in 14.3-22.2%, and 22.2-35.7% of the patients, respectively. That was no statistically significant difference between chemotherapy and chemoradiotherapy settings. A beneficial effect of neoadjuvant treatment in esophageal cancer has been discussed in 2 large reports summarizing results achieved in many institutions presented by Roul and panel of experts (9) and Medical Research Council Oesophageal Cancer Working Party (7). A 5-year survival in patients who underwent a combined treatment with complete response to chemotherapy or chemoradiotherapy and followed by curative resection reached a rate of 60% (31). This approach appears to improve respectability and local control of a tumor and also prevent local recurrence. In patients with good response to neoadjuvant treatment as compared to patients treated by surgery alone a longer survival and improved quality of life were clearly notified. (9, 27, 30, 31). When preoperative chemotherapy or chemoradiotherapy is used one may expect an increased postoperative morbidity and mortality rates as well as a delayed resection of a tumor. Early complications of a combined therapy include respiratory failure resulting from irradiation induced injury of the lungs, compromised healing of anastomoses (increased leakage rates) and compromised immune response with septic complications (30). Currently, it is believed that outcome of treatment and longer survival of patients with potentially respectable esophageal cancer result from advances in preoperative assessment of tumor staging and an optimal selection of appropriate treatment option, advances in operative techniques and application of a combined modality therapy (10, 27, 28, 30, 31). Nevertheless, the authors of cited above reports conclude that the evaluation of a combined therapy still requires further detailed investigation and objective assessment in large settings of esophageal cancer patients.

CONCLUSIONS

1. An ultrasound is a highly valuable and recommended diagnostic technique in the assessment of lymph node involvement in patients with SCC of the esophagus.
2. An ultrasound is specifically useful and accurate for neck lymph nodes with specificity of 96% and sensitivity of 100%.
3. In patients with cancer of the upper or middle esophagus in whom confirmed metastatic lymph nodes are found on cervical ultrasound it seems to be a rational to carry out a 3-field lymph node dissection.

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