Cancer of Unknown Primary Origin (CUPO) is defined by the presence of metastatic lesions, diagnosed by means of cytological or pathological evaluation, for which no primary site can be detected during a thorough examination. The clinical investigation, directed at locating the site of the neoplastic lesion, is determined by the results of laboratory tests, imaging procedures, and pathological examinations. It is also essential to conduct a complete medical history and thorough physical examination. The detection of the primary site allowed to introduce specific therapy, which can offer clinical benefits, considering a favorable prognosis.

The aim of the study was to assess the range of diagnostic procedures performed in patients with CUPO and efficacy in identifying the primary lesion.

Material and methods. Retrospective analysis comprised a group of 29 patients with CUPO, operated between January, 2002 and December, 2011, at the Department of Surgical Oncology, Medical University in Łódź. The study group comprised 16 male and 13 female patients; median age at presentation was 58.3 years (ranging between 30-79 years).

Results. Detailed diagnostic management depending on the location of metastatic lesions and their histological type was performed in 20 of the 29 study patients (69%). Considering the remaining 9 (31%) patients detailed diagnostics was not performed, due to the patients' poor general condition. In 55% (11/20) of patients subject to detailed diagnostics, the primary neoplastic lesion was determined.

Conclusions. Considering the study group, most patients with cancer of unknown primary origin were characterized by a favorable prognosis, which justified thorough diagnostics, in order to establish the primary neoplastic lesion. The introduction of diagnostic examinations enabled to identify the primary site of the tumor in more than 50% of patients. With the development of imaging methods one can expect improvement of unsatisfactory results, considering the detection of primary neoplastic foci.

Key words: cancer of unknown primary origin, diagnostics

Metastasis and generalized neoplastic disease are consecutive stages of a primarily diagnosed neoplastic lesion. In the presence of neoplastic metastases, and lack of identification of the primary site of the tumor, one may define the above-mentioned as Cancer of Unknown Primary Origin (CUPO) (1, 2). Depending on the accepted definition and scope of investigations CUPO diagnosis ranges between 1.5 and 5% of malignant tumors (2, 3). Cancer of unknown primary origin is observed in both sexes at a similar rate. Mean age of patients at diagnosis is approximately 60 years (1, 4). Metastases from an unknown primary site are mainly located in the lymph nodes, lungs, bones, liver, and brain (4).

There are several hypotheses explaining the difficulties in determining the primary site of the tumor. The first assumes that the primary lesion after disease generalization is subject to complete immunological regression, thus, upon metastases detection, its determination is not possible (5, 6). The second theory assumes that some tumors may have a genetic
ability to metastasize, without simultaneous local progression. In consequence, the primary foci may remain clinically undetected (5, 7). The small size of the primary tumor may also result from the inhibiting effect of metastatic lesions on the primary neoplastic site (8). Additionally, difficulties in detecting the primary foci may be associated with the insufficient accuracy or poor choice of diagnostic methods.

Most CUPO metastases are of epithelial character, with more than 80% being adenocarcinomas of varying differentiation, and the remaining are squamous cell carcinomas. Non-epithelial malignant tumors associated with CUPO metastases include neuroendocrine and germ cell tumors, as well as sarcomas and melanomas (1, 4, 9).

Immunohistochemical investigations using monoclonal antibodies against cellular proteins are an essential complement to the microscopic evaluation. They facilitate the differentiation of epithelial tumors, lymphomas, sarcomas, and melanomas. In selected cases they may also be helpful in locating the primary site of the tumor (1, 9, 10).

Prognosis in case of cancer of unknown primary origin is unfavorable. The mean survival time ranges between five and ten months (11, 12, 13). Unfavorable prognostic factors include male sex, adenocarcinoma diagnosis, presence of multiple metastases, neoplastic lesions located in the liver, lungs, bones, poor general condition of the patient, and elevated lactate dehydrogenase activity (11, 13, 14, 15). Prognosis seems more favorable in case of squamous cell carcinoma metastases to cervical lymph nodes, adenocarcinoma cells to axillary lymph nodes in female patients, and neoplastic metastases from undifferentiated cells (potentially chemosensitive) and germ cell tumors (9, 13).

The study presented the analysis of patients operated at the Department of Surgical Oncology, due to metastases from cancer of unknown primary origin, at the Department of Surgical Oncology, Medical University in Łódź. Complete documentation was obtained from 29 patients, being subject to analysis. The study group comprised 16 male and 13 female patients. Median age amounted to 58.3 years (ranging between 30-79 years).

Preoperative diagnosis of CUPO metastases was based on the presence of cancer cells in cytological examinations obtained by means of fine-needle biopsies, in the absence of the primary lesion on medical and physical examinations, as well as basic imaging investigations (chest X-ray, abdominal ultrasound).

Twenty-eight planned operations were performed. One patient was subject to emergency surgery, due to bleeding from an ulcerated cutaneous tumor in the axillary area. Eight patients were subject to surgical biopsy of the lymph nodes. Complete lymph node excision (cervical, axial, inguino-iliac) was performed in 14 patients. In 2 of 3 patients with liver metastases there was a need for palliative intestinal stoma, due to threatening gastrointestinal obstruction (abdominal cancer dissemination). One patient required explorative laparotomy. In case of all patients histopathological samples were collected. Table 1 presented the different surgical procedures that were performed.

**RESULTS**

Of the 29 analysed patients, 22 (75.9%) presented with metastatic involvement of the lymph nodes. Post-lymph node location concerned 7 (24.1%) patients. In three (10.3%) patients the lymph nodes were subjected to surgical biopsy. One patient was subject to explorative laparotomy.

### Table 1. Type of surgical procedures performed in patients with cancer of unknown primary origin metastases (n=29)

<table>
<thead>
<tr>
<th>Type of procedure</th>
<th>Number of patients</th>
<th>%</th>
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<tbody>
<tr>
<td>Surgical biopsy of the lymph node</td>
<td>8</td>
<td>27.6</td>
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<tr>
<td>One-sided radical dissection of the cervical lymph system</td>
<td>4</td>
<td>13.8</td>
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<tr>
<td>Axillary lymphadenectomy</td>
<td>5</td>
<td>17.2</td>
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<tr>
<td>Inguino-iliac lymphadenectomy</td>
<td>5</td>
<td>17.2</td>
</tr>
<tr>
<td>Surgical excision of the skin tumor</td>
<td>4</td>
<td>13.8</td>
</tr>
<tr>
<td>Explorative laparotomy</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>Occlusion surgery – stoma formation</td>
<td>2</td>
<td>6.9</td>
</tr>
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<td>29</td>
<td>100</td>
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patients metastases were located in the liver, in 4 (13.8%) within the skin or subcutaneous tissue. Considering the subgroup with metastases to the lymph nodes, 19 (65.5%) comprised one group of lymph nodes, while 2 (6.9%), two lymph node groups (supraclavicular and axillary, and cervical and axillary). One (3.4%) patient was diagnosed with generalized lymphadenopathy. Table 2 presented detailed data concerning the location of CUPO metastases in the investigated group.

Considering the histopathological examination of postoperative samples, 21 (72.4%) patients were diagnosed with epithelial lesions, including high/medium differentiated adenocarcinomas in 9 (31%) cases, 6 (20.7%) cases with low-differentiated adenocarcinomas, and 6 (20.7%) with squamous cell carcinomas. In the remaining 8 (27.6%) cases non-epithelial tumors were diagnosed. One (3.4%) patient was diagnosed with a neuroendocrine tumor and seven (24.1%) with melanoma metastases. Table 3 presented histopathological/immunohistochemical postoperative sample results.

**DISCUSSION**

The determination of the primary site of the tumor enables targeted therapy, therefore, more effective treatment. In the presented study the majority of patients (20/29) were characterized by a favorable prognosis, which justified the need for extended diagnostics. Considering patients in poor general condition

<table>
<thead>
<tr>
<th>Table 2. Location of metastatic lesions from CUPO</th>
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<tr>
<td>Site of metastasis</td>
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<tr>
<td>Lymph node location:</td>
</tr>
<tr>
<td>cervical</td>
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<tr>
<td>axillary</td>
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<tr>
<td>inguinal</td>
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<td>general lymphadenopathy</td>
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<td></td>
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<tr>
<td>Post lymph node location:</td>
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<tr>
<td>liver</td>
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<tr>
<td>skin and subcutaneous tissue</td>
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<table>
<thead>
<tr>
<th>Table 3. Postoperative sample histopathological/immunohistochemical results</th>
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</thead>
<tbody>
<tr>
<td>Cervical lymph nodes</td>
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<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Adenocarcinoma highly- or medium-differentiated</td>
</tr>
<tr>
<td>Adenocarcinoma or low-differentiation cancer</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
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<tr>
<td>Melanoma or neuroendocrine tumor</td>
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</tbody>
</table>

29 (100)
or with advanced neoplastic disease, one may withdraw from the implementation of thorough diagnostics, in favor of optimal symptomatic treatment (1). The above-mentioned was observed in 9 (31%) patients.

The determination of the primary cancer lesion proved effective in more than 50% of patients subject to thorough diagnostics (11/20-55%). Briasoulis et Pavlidis, analysed 2114 of patients with cancer of unknown primary origin demonstrating that the primary foci remained undetermined in 68% of cases (4). One should not forget that in case of an autopsy of a CUPO patient the primary lesion remains undetermined in 15-30% of patients (16, 17, 18). Analysis of 884 patients subject to post-mortem examinations showed that the primary foci was most often located in the lungs (27%) and pancreas (24%), less frequently in the liver and bile ducts, kidneys, suprarenal glands, colon, genital organs and stomach (18).

In the presented analysis, neoplastic metastases from an unknown primary site were most often diagnosed in lymph nodes (75.9%). Additionally, metastatic lesions were observed in the liver (10.3%), skin and subcutaneous tissue (13.8%). The investigated group did not include metastatic lesions to the lungs, and mediastinal, bone, and cerebral lymph nodes. This stems mainly from the profile of the organ center in which the study was conducted.

In case of CUPO metastases to lymph nodes it is important to know the direction of lymph outflow, as well as pathomorphological and immunohistochemical sample results.

In the presented material, CUPO metastases diagnosed in cervical lymph nodes concerned 8 (27.6%) patients. In 3 (10.3%) patients the histopathological diagnosis was squamous cell carcinoma, in yet another three (10.3%) – undifferentiated nasopharyngeal carcinoma. Adenocarcinomas were diagnosed in two (6.9%) patients. Detailed diagnostic procedures enabled to determine the primary site of the tumor in 4 (13.8%) cases. Weber et al. showed that the source of metastatic cells to the cervical lymph nodes was attributed to malignant mucous membrane tumors of the head and neck in 70-80% of cases (19). During the histopathological examination squamous cancer cells are most commonly observed, followed by undifferentiated cancer and adenocarcinoma (19, 20). When detecting cervical lymph node metastases the otorhinolaryngological examination seems most essential. Computer tomography and MR imaging of the head and neck also seems to be of significant diagnostic value (3, 21, 22). The primary lesion of squamous cell carcinoma is mostly located in the nasopharynx, palatine tonsils, base of the tongue, or laryngeal part of the pharynx (19, 23). In the presented study the primary tumor located in the base of the tongue was diagnosed in two patients. In the former case during a consecutive laryngological consultation, and in the latter case following CT of the head and neck.

Recommended management in case of CUPO metastases to cervical lymph nodes is to perform endoscopic examinations under general anesthesia with histopathological sampling (3, 21, 22). It is recommended to perform direct laryngoscopy and esophagoscopy, determining the piriform recess, posterior wall of the pharynx and retro-ring area (3, 21, 22). Tracheobronchoscopy is justified in the presence of pathological x-ray lesions or respiratory system symptoms indicating the possible presence of the primary site within the above-mentioned (2).

It is advisable to collect samples from the nasopharynx and base of the tongue, as well as perform bilateral tonsillectomy (3, 21). Routine tonsillectomy in patients with a diagnosed cervical CUPO allows to locate the primary tumor in 18-26% of cases (24, 25). In consequence, this enables to protect the pharyngeal and laryngeal area from irradiation. Diagnostic management depends on the area of cervical lymph node involvement and histopathological type of tumor.

The location of the primary lesion outside the head and neck might be evidence of lower neck or supraclavicular lymph node metastases. Adenocarcinoma diagnosis after exclusion of primary head and neck lesions might be evidence of the possibility of gastrointestinal, lung, breast, prostate, testicular, thyroid, and ovarian involvement (21). In our study, considering patients with CUPO metastases to cervical lymph nodes, lung (chest CT) and breast cancer were diagnosed.

PET (positron emission tomography) with the use of 18-fluorodeoxyglucose in combination with the CT examination is considered by many authors as the method of high efficacy, both in the determination of the primary lesion
(40-60%), and staging of the neoplastic process (26, 27, 28). Greven et al. pointed to the limited specificity of 18-FDG PET: the primary lesion was diagnosed in 1 of 13 analysed cases with a high percentage of false positive results (29).

In Poland, PET-CT is fully funded by the National Health Fund in case of cancer of unknown primary origin, when determining the primary lesion, and when other available examinations are not possible to perform (30). PET-CT is recommended especially in case of malignant tumors of the head and neck, as well as chest (1, 22, 31). The above-mentioned examination detects primary lesions within the head and neck, lungs, breasts, and pancreas with great specificity and sensitivity (32, 33).

In the presented study PET-CT was not performed in any of the cervical lymph nodes metastases, due to the limited availability of the above-mentioned.

Isolated metastases to axillary lymph nodes from an unknown primary lesion concerned three of our female and two male patients (17.2%). All three female patients presented with adenocarcinoma metastases. The primary lesion within the breast was diagnosed in 2 (6.9%) cases. In the first case the lesion was visualized during breast ultrasound, in the second-following MRI. Mammography (performed in all patients with adenocarcinoma metastasis) did not allow to determine the primary lesion in any of the cases.

The detection of neoplastic cells (adenocarcinoma or undifferentiated) obliges to undertake thorough breast diagnostics (34). Immunohistochemical examinations determining the expression of estrogen (ER), progesteron (PR) and HER-2 receptors is of diagnostic, prognostic and therapeutic value.

Mammography is the basic examination which should be performed in case of adenocarcinoma metastases (especially to the axillary lymph nodes) (1, 2, 3, 34). Diagnostics in young female patients should be supplemented by breast ultrasound. Suspicious lesions should be subject to fine- or thick-needle biopsies.

The situation when axillary lymph node metastases are diagnosed and the primary lesion is not found, both following the clinical examination and mammography, is described as occult breast cancer. The diagnosis of cancer of unknown primary origin with axillary lymph nodes involvement is an indication for MRI (1, 3, 22, 31, 34). Analysis of the efficacy of the above-mentioned was performed in 22 female patients diagnosed with axillary lymph nodes metastases, where palpation and mammography did not reveal the primary lesion. The study showed the high diagnostic efficacy of the method: in 86% of patients the primary lesion was located within the breast (35).

Inguinal lymph nodes metastases were observed in 6 (20.7%) patients. In three cases melanoma metastases were diagnosed. Additionally, neoplastic cells originated from ovarian and prostatic cancer. To the inguinal lymph nodes, lymph flows from all lower limb lymphatic vessels, external genitalia, perineum, gluteal and the lower abdomen area. Most efferent inguinal lymph node vessels flow to the iliac lymph nodes, which also receive minor pelvis lymph.

In the retroperitoneal space one may observe lymphatic drainage from the abdominal cavity organs, pelvis, abdominal wall, perineum, and lower limbs. Lymph nodes located in the area might be diagnosed with metastases from ovarian, cervical, fundus, pudendal, prostatic, testicular, urinary bladder, and rectal cancer.

Analysis of 56 patients with inguinal lymph node metastases from an unknown primary lesion was undertaken by Guarischi et al. showing that five-year survival amounted to 27%. Anaplastic cancer (43%), squamous cell cancer (20%), adenocarcinoma (16%), melanoma (16%), and other (5%) metastases were diagnosed (36).

In case of detection of metastatic lesions to inguinal lymph nodes it is necessary to perform a thorough physical examination of the perineum, rectum, anus, and in case of female patients, a gynecological examination. Significant diagnostic value is attributed to abdominal and pelvic CT (1, 2, 3). Diagnosis of adenocarcinoma within the inguinal lymph nodes and other locations in a 40-year old male patient obliges to perform a per rectum examination of the prostatic gland and PSA level evaluation (1, 2, 3). When suspecting neoplastic growth it is advisable to perform transrectal ultrasonography combined with prostate biopsy.

Metastatic lesions within the skin and subcutaneous tissue were in three cases metastatic foci of a melanoma. A similar texture
was diagnosed in the axillary lymph nodes of one patient and inguinal lymph nodes in three patients. The physical examination of the skin and mucous membranes revealed no primary lesion in any of the seven patients.

In studies on a large group of patients, amongst all subjects with diagnosis of a melanoma, in 2-3% of cases, the primary lesion remains unidentified (37, 38). Analysis of 65 patients with diagnosis of MUPO (Melanoma of Unknown Primary Origin) performed by Katz et al. showed that metastases most often concern the lymph nodes (46%), less often the skin and subcutaneous tissue (19%), with 35% of patients diagnosed with organ metastases (38). Cormier et al. noted that MUPO metastases most often concerned the axillary (76%), inguinal (20%) and cervical (4%) lymph nodes (37). Based on both studies melanoma metastasis is more common in male patients (38, 39).

The basis of diagnosis is a detailed history and physical examination. One should not forget that the primary lesion of a cutaneous melanoma (91%) might be located in the orbital cavity and mucous membrane (oral cavity, nasopharynx, sinuses, larynx, gastrointestinal tract, anus, rectum, genitalia, and urinary ducts) (37, 40). All the above-mentioned should be subject to diagnostic evaluation. One should underline the necessity of histopathological evaluation of all removed cutaneous lesions.

In conclusion, nearly one third of operated patients did not qualify for thorough diagnostics in search of the primary lesion, due to the advanced stage of the disease or disease progression. In case of patients subject to thorough investigation the primary lesion was diagnosed in more than 50% of cases. The introduction of more and more sophisticated imaging methods and their proper selection might be one of the factors increasing the diagnosis of primary lesions in case of rare tumors.

REFERENCES


Diagnostic imaging efficacy in metastases from unknown primary site – own material