6. The role of cytoreductive surgery for non-genital tract metastases to the ovary

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Abstract. Approximately 6-7% of all adnexal masses found during physical examination are actually metastatic ovarian tumors, which often masquerades as the primary ovarian tumor. The circumstances leading to the discovery of these metastatic lesions depends on the site of the primary tumor. The ovaries may be only slightly enlarged or measure 10 cm or more. Ovarian metastases are bilateral in approximately 70%. The routes of tumor spread to the ovary are variable. Lymphatic and haematogenous metastasis to the ovaries is the most common form of dissemination for the vast majority of cases of carcinoma of the breast, stomach, as well as lymphomas and leukemias. Direct extension is a common manner of spread from colorectum and retropritoneal sarcomas. The ovaries can be reached by the transperitoneal route by cancers from abdominal organs, such as the appendix. Carcinoma of the breast, stomach, colon, and endometrium, as well as lymphomas and leukemias account for the vast majority of cases of metastatic ovarian tumors. In cases, when both ovarian and extraovarian involvement is extensive, determination of the origin of the metastatic ovarian tumor may be impossible.

The distinction of metastatic ovarian neoplasm from a primary one is crucial to its subsequent management, and diagnostic misinterpretation may have important adverse consequences for the patient. Although intraoperative frozen-section evaluation is useful

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for the diagnosis of metastatic tumors of the adnexa, in some cases it is difficult to distinguish primary ovarian tumors from metastatic ones even by histological examination. In such patients the treatment the treatment should be the same as in primary ovarian carcinoma. The treatment of choice is bilateral salphingo-oophorectomy, hysterectomy, omentectomy and appendectomy. If there is no gross evidence of abdominal metastasis, pelvic lymph node sampling should be done to determine the extent of disease; In cases when complete resection of the adnexal tumor is impossible, cytoreductive surgery reducing tumor mass before chemotherapy is considered the optimal treatment. The cytoreductive surgery is optimal if the diameter of the largest residual tumor is ≤ 1.0 cm, which is assessed by the maximum tumor in the pelvis and abdomen.

In metastatic breast cancer patients ovarian metastases are present in 10-40% of cases, but rarely is the ovarian metastasis evident before the primary tumor is detected. Signs and symptoms of an ovarian tumor are rarely present in patients with breast cancer metastases to the ovaries and microscopic ovarian metastases are occasionally diagnosed at prophylactic oophorectomy by laparoscopy or laparotomy. Ovarian metastases of breast cancer usually are accompanied by other foci of abdominal spread, and the most common treatment modality in such cases is systemic chemotherapy or hormonotherapy. Isolated ovarian metastases occasionally are encountered, and in these cases laparotomy should be performed for optimal cytoreduction.

In patients with gastrointestinal cancer the ovarian metastatic tumor is discovered before, or more frequently, at the same time as the gastrointestinal primary. Most of the literature on metastatic ovarian carcinomas from the gastrointestinal tract has concentrated on mucinous, signet-ring cell adenocarcinomas, called Krukenberg tumors. The Krukenberg tumor is almost always secondary to the gastric carcinoma, but may occasionally originate in the large intestine, appendix, breast or other sites. In 35% of patients with a Krukenberg tumor, the diagnosis of the digestive primary precedes the diagnosis of the ovarian metastasis. In these cases the choice of treatment is difficult and prognosis is worse in most cases with fatal outcome in one year. Early diagnosis and complete resection is the only possible hope. Radical operation such as pelvic exenteration can improve survival only in cases of recurrent solitary ovarian metastasis or local extended disease.

Colonic adenocarcinomas account for 11-45% of all metastatic ovarian tumors. The addition of prophylactic bilateral oophorectomy as routine in peri-menopausal and post-menopausal women undergoing abdominal surgery for bowel cancer was postulated by many authors. On the contrary, another authors indicated no benefits in survival of these patients. In cases of direct invasion of the contiguous ovary from the colorectal cancer (pT4) or macroscopic metastases (M1) found during the abdominal surgery for bowel cancer the radical resection of ovarian metastases with a curative aim seems to improve overall survival. Women with isolated ovarian metastasis with a long interval between initial diagnosis of colon cancer and recurrence, and women with limited disease that appears amenable to facile surgical resection would seem to be the preferred candidates to cytoreductive surgery. For patients with isolated ovarian metastases from colon cancer the optimal cytoreduction can confer a significant

survival advantage compared with those patients who are left with bulky residual disease.

Primary tumors of the appendix are rare and most of them are unrecognized preoperatively, presenting as appendicits, pelvic masses or with atypical abdominal pain. The ovarian and appendiceal tumors are histologically similar; usually it is difficult to distinguish in intraoperative frozen-section primary ovarian mucinous tumors from metastatic ones, and surgical procedures due to primary epithelial ovarian cancer are treatment of choice.

Other rare primary tumors reported in the literature are: malignant lymphoma, malignant melanoma, carcinoid tumors, extragenital sarcomas, tumors of the pancreas, gallbladder and bile ducts, pulmonary and mediastinal tumors, renal tumors, adrenal gland tumors, mesothelioma, and peritoneal tumors. Metastases to the ovary other than those already described are of great rarity. In cases of such tumors surgery in the form of a diagnostic laparotomy for the ovarian mass and for symptom relief is often necessary, but the further management of patients depends upon the site of extent of the primary disease. Numerous studies suggest that resection of metastatic ovarian tumors and cytoreductive surgery play a significant role in improving the survival time in patients with no distant metastasis other than to the adnexa. The benefitial role of cytoreductive surgery in malignant melanoma, as well as malignant lymphoma metastatic to the ovary is not confirmed.

Introduction

Since the establishment of the metastatic nature of most Krukenberg tumors by Schlagenhaufer in 1902, it has been demonstrated that many carcinomas, including that of thyroid breast, stomach, gallbladder, pancreas, colon, rectum, and malignancies arising from the female genital tract, may metastatize to the ovaries [1]. Approximately 6-7% of all adnexal masses found during physical examination, and 10-30% of all ovarian malignancies are actually metastatic ovarian tumors. The metastatic origin of these tumors is frequently not suspected by gynecologists [2,3,4]. Carcinoma of the stomach, colon, breast and endometrium, as well as lymphomas and leukemias account for the vast majority of such cases [5,6]. Many reports on metastatic ovarian tumors described the most often primary sites of neoplasms in gastrointestinal tract 36-74% (stomach 8-61%; colon 11-45%), breast 13-31%, and gynecologic organs 18-40% [2,5-10]. Women with solid metastases to the ovary of non-genital origin usually have worse prognosis than women with metastatic cancers of genital origin. Their overall five year survival reaches only 10% [11,12]. In cases, when both ovarian and extraovarian involvement is extensive, identification of the origin of the metastatic ovarian tumor may be impossible.

The metastasis often masquerades as the primary ovarian tumor. The circumstances leading to the discovery of these metastatic lesions

depends on the site of the primary tumor. The metastatic tumors are bilateral in approximately 70%. Macroscopically the ovaries may be normal, may be only slightly enlarged or may measure 10 cm or more [5,6,12]. The routes of tumor spread to the ovary are variable. Lymphatic and haematogenous metastasis to the ovaries is the most common form of dissemination for the vast majority of cases of carcinoma of the breast, stomach, as well as lymphomas and leukemias. Direct extension is a common manner of spread from colorectum and from retroperitoneal sarcomas. The ovaries can be reached by the transperitoneal route by cancers from abdominal organs, such as the appendix [12,13]. Regional lymph node or liver involvement, and abdominal spread frequently occurred in patients with ovarian metastatic cancers [14].

Surgical treatment for primary ovarian cancer is well defined, and cytoreduction to a low residual tumor volume has arbitrary been shown to offer a survival benefit [15]. In the presence of metastatic ovarian tumors, however, diferent guidelines may apply and an aggressive surgical procedures may be less beneficial [16]. Despite of that, the treatment of choice in most such patients remains surgery, which is usually indicated in the form of explorative laparotomy for adnexal mass, and for relief of symptoms [14]. The optimal cytoreductive surgery has an advantage on survival time in selected patients with nongenital metastatic tumors of the ovary, especially of colorectal origin without abdominal dissemination [14].

The distinction of metastatic ovarian neoplasm from a primary one is crucial to its subsequent management, and diagnostic misinterpretation may have important adverse consequences for the patient. The intraoperative frozen-section evaluation is useful for the diagnosis of metastatic tumors of the adnexa with the reported by an 81-98% accuracy rate in detecting metastatic character of the ovarian tumors [10,12,17]. When surgeons encounter metastatic ovarian tumor and it is confirmed by frozen-section evaluation, and the diagnosis of primary disease is not made previously, an intensive search for primary site should be performed [6]. Unfortunately, in some cases it is difficult to distinguish primary ovarian tumors from metastatic ones even by histological examination. In such patients the treatment should be the same as in primary ovarian carcinoma. The treatment of choice is bilateral salphingo-oophorectomy, hysterectomy, omentectomy and appendectomy. If there is no gross evidence of abdominal metastasis, pelvic lymph node sampling should be done to determine the extent of disease. In cases when complete resection of the adnexal tumor is impossible, cytoreductive surgery reducing tumor mass before chemotherapy is considered the optimal treatment. The cytoreductive surgery is optimal if the diameter of the largest residual tumor is ≤ 1.0 cm, which is assessed by the maximum tumor in the pelvis and abdomen [14].

Ovarian metastasis is a late reprezentation of generalized disease and therefore it is accepted that the prognosis is generally poor. Most patients die within 1 year of the diagnosis of ovarian tumor [2]. Patients with gynecologic tumors have significantly better prognosis than patients with non-gynecologic tumors metastatic to the ovary [3]. The reported 5-year survival after resection of ovarian metastatic tumors from genital tract and from non-genital organs is 47% and 10-36% respectively [2,3]. It is worth to recall that generally reported 5-year survival of patients with primary ovarian cancer is about 40% [3]. Therefore the prognosis of patients with metastasis to ovary from genital tract organs is better, and with metastasis from non-genital organ is worse than prognosis of patients with primary cancer of ovary.

Breast cancer

In metastatic breast cancer patients ovarian metastases, ascites, and carcinomatosis are present in 10-40%, 5.4%, and 2.6% of cases, respectively. It was confirmed by numerous clinical and anatomopathological reports [5,18,19]. Although the risk of breast cancer recurrence diminishes over time, late metachronous ovarian metastases well into the second decade following the initial diagnosis can occur [11,18]. In women treated previously for breast cancer when non-funcional ovarian tumor is detected and the patient is qualified for surgical removal of this tumor, the risk that the tumor is malignant is 50%. Primary ovarian cancer develops in these patients three times more often than metastases of breast cancer to ovary [11,20,21]. Lobular carcinomas, including those of signet-ring cell type, spread to the ovary more frequently than those of ductal type [5,13].

Only in 1.0-2.0% of patients the ovarian metastasis is diagnosed before the diagnosis of primary breast carcinoma [5,22]. Signs and symptoms of an ovarian tumor are rarely present in patients with breast cancer metastases to the ovaries. Ovarian metastases are rather occasionally diagnosed at prophylactic oophorectomy. Indications for prophylactic oophorectomy are well defined in BRCA1 or BRCA2 germline mutations carriers [21,23]. Many authors suggest that in BRCA1/BRCA2 mutation carriers adnexectomy instead of simple oophorectomy should rather be performed. It is because of the increased risk of the fallopian cancer in such women [23]. Moreover adnexectomy is in fact a simple and effective technique which does not increase the risks of complications and ureteral injuries. Moreover, adnexectomy avoids the risk of ovary remnants being left in the mesovarium during the oophorectomy. The procedure can be easily performed using a laparoscopic approach [23]. Bilateral oophorectomy, commonly with peritoneal

cytology, is proposed by some authors as a therapeutic option in premenopausal patients with localized or advanced breast cancer [19]. Ovarian metastases are found in 15% to 40% of these breast cancer patients undergoing prophylactic surgery [19]. Most of cases of adnexal tumor found at the time of prophylactic oophorectomy are not recognized at the time of surgical procedure itself, because 29-66% of these patients have only microscopic ovarian metastases. Such metastases are found at final histological examination [12,23]. Generally, in breast cancer patients the indications for prophylactic oophorectomy are not well defined and there are no consensus expert statements about its role and beneficial effect on survival in these patients. However, it should be also remembered that oophorectomy may be used as a form of treatment of selected breast cancer patients. Surgical oophorectomy is regarded as an therapeutic option which can be used in premenopausal breast cancer patients, classified as high risk or intermediate risk patients, with highly endocrine responsive or incompletely endocrine responsive breast cancer [24].

Macroscopically the metastatic ovarian tumor in breast cancer patients is usually smooth-surfaced or bosselated mass, and only exceptionally the cystic elements are found. Metastatic tumors are usually small. In one large study, in only 15% of patients the size of the metastatic tumor was larger than 5 cm [22]. The metastases are bilateral in approximately 80% of cases [22], and in almost 75% of cases ovarian metastases are accompanied by other foci of abdominal spread [22,25]. The presence of ovarian metastases from breast cancer is usually a sign of general dissemination of the disease and the involvement of the ovary is not clinically significant. The most common treatment modality in such cases is systemic chemotherapy or hormonal therapy.

The accuracy of intraoperative frozen-section diagnosis of breast carcinoma metastasis to adnexa is 81% [10]. When the intraoperative frozen-section diagnosis is breast cancer metastasis, the surgical resection of metastatic tumors should be considered in patients with prolonged time after initial breast cancer diagnosis and with resectable disease [14,20]. Occasionally isolated ovarian metastases are encountered. In these cases laparotomy should be performed and metastatic tumor should be resected. Abdominal disease outside the pelvis apparently influences the extent of the surgical intervention and most of the patients with disease outside the pelvis cannot be optimally cytoreduced. The extent of surgery should be individualized and balanced against the morbidity of the offered treatment [20]. The prognosis in cases of ovarian metastases of breast cancer is generally poor with the five-year survival 0-27%, and median survival between 12 and 36 months [7,19-21].

Gastrointestinal tumors

The ovary is a common site for spread of carcinomas from the gastrointestinal tract, and ovarian metastases are present in 8-16% of cases. In patients with gastrointestinal cancer the ovarian metastatic tumor is discovered before, or more frequently, at the same time as the gastrointestinal primary [26]. Among all metastatic ovarian tumors, colon, appendiceal, and upper gastrointestinal tract primary tumors have been shown to be the most common primary malignancies associated with clinical findings suggestive of a primary ovarian cancer [27]. The incidence of ovarian metastases from gastrointestinal tumors seems to be higher in young menstruating women [28]. In some patients even long interval between initial diagnosis of gastrointestinal cancer and ovarian recurrence is observed.

Carcinoma of the stomach, including Krukenberg tumor

Most of the literature on metastatic ovarian carcinomas from the gastrointestinal tract has concentrated on Krukenberg tumors, first described by Friedrich Krukenberg in 1896 [4,29]. The World Health Organization reports that following features should be present when making the diagnosis on Krukenberg tumor: 1) the presence of stromal involvement, 2) the presence of mucin-producing neoplastic signet-ring cells, and 3) ovarian stromal sarcomatoid proliferation [30]. The Krukenberg tumor is almost always secondary to the gastric carcinoma, but the large intestine, appendix, breast, pancreas, urinary system, biliary system and uterine cervix have also been reported as primary sites [4,12,13].

In 35% of patients with a Krukenberg tumor, the diagnosis of the digestive primary preceded the diagnosis of the ovarian metastasis [25,31-33]. The gastric primary focus can be small, asymptomatic, or can be present as *linitis plastica*. In these cases the choice of treatment is difficult and prognosis is worse in most cases with fatal outcome in one year. The Krukenberg tumors usually form white masses that may be bosselated and may attain a large size [29,34]. In ultrasound / computer tomography Krukenberg tumor more frequently is presented as a solid mass with an intratumour cyst, when compared to predominantly cystic primary ovarian malignancies [35]. Eighty percent or more of patients with a Krukenberg tumor had bilateral ovarian metastases [22,25,29,34].

Early diagnosis and complete resection is the only possible hope, but most surgeons do not attempt to remove ovarian tumors when Krukenberg tumors are diagnosed preoperatively [36]. In the literature patients survived more than 4 years after resection of metachronous Krukenberg tumors and

the absence of residual disease after treatment and limited disease extent were reported [37]. Radical operation such as pelvic exenteration can improve survival only in cases of recurrent solitary ovarian metastasis or locally extended disease [37]. However, no optimal treatment strategy for Krukenberg tumors from gastric cancer has been clearly established, and the prognosis in patients with Krukenberg tumors remains generally poor [36].

Intestinal carcinoma

Most metastatic ovarian tumors of intestinal origin are from the large intestine, with occasional examples of small intestinal derivation [38,39]. Seventy five percent of these metastatic ovarian tumors are adenocarcinomas of sigmoid and rectal origin. Ovarian metastasis from a duodenal and jejunal cancer is extremely rare with only several cases described, and it is difficult to detect a small bowel lesion preoperatively [39,40]. The rarity of metastatic tumor of small intestine origin should not be surprising as primary adenocarcinoma of the small bowel accounts for only approximately 1-3% of all gastrointestinal malignancies, even though the small bowel constitutes 75% of the length and 90% of the mucosa surface of the alimentary tract.

Colonic adenocarcinomas account for 11-45% of all metastatic ovarian tumors, and in colorectal cancer patients ovarian metastases are present in 28-35% of cases [2,5,7-9]. At the time of initial laparotomy 3.4-10.3% of patients with colon carcinoma have synchronous ovarian metastases [41]. Transcoelomic dissemination and retrograde lymphatic flow are likely to be common metastatic routes for ovarian tumor of gastric and colorectal origin.

The addition of prophylactic bilateral oophorectomy as routine in peri-menopausal and post-menopausal women undergoing abdominal surgery for bowel cancer is postulated by many authors [3,42]. Becker et all. recommended that the performance of adjunctive bilateral oophorectomy should be strongly considered at the time of initial laparotomy due to rectal cancer in the following situations: 1) as therapy when there in gross evidence of benign or malignant ovarian disease, when there is extensive serosal, peritoneal, or regional lymph node invasion of the rectal cancer, and when one or both ovaries or the uterus are adherent to the bowel adjacent to the primary tumor; 2) as prophylaxis in all postmenopausal women, mainly to prevent primary ovarian carcinoma; 3) as prophylaxis in premenopausal women with the confirmed high risk or strong family history of breast, ovarian, endometrial or bowel cancer, and those with stage IV rectal cancer [42]. On the contrary, another authors indicated lack of survival benefit in these patients.

In patients with gastrointestinal cancer the ovarian metastatic tumor is discovered before, or more frequently, at the same time as the gastrointestinal primary [26]. The tumors can be discovered during surgery for primary ovarian tumor by gynecologists, or by surgeons at the time of initial surgery for newly diagnosed colon cancer [43]. In approximately 60% of cases metastatic ovarian carcinoma of intestinal origin are bilateral, solid, but more often predominantly cystic, frequently large above 10 cm in largest dimention [28,44]. When malignant ovarian tumors encountered at the time of operation are considered, metastases from intestinal carcinomas are almost five times as frequent as those from gastric carcinomas [45,46].

Metastatic colonic carcinomas may simulate clinically, radiologically, and histologically primary ovarian endometrioid or mucinous carcinomas. In some cases it is difficult to distinguish primary ovarian cancers from metastatic tumors derived from colon cancer, even by histological examination [9]. It was reported that 45% of metastatic ovarian tumors from colon cancer were misdiagnosed as primary ovarian cancers [2,12,41]. The extrapelvic spread is a helpful feature in the distinction of ovarian metastasis from colorectal carcinoma. The omental, hepatic parenchymal metastases, a prominent involvement of the peritoneal surface and the involvement of mesenteric lymphnodes favor an intestinal primary tumor rather than primary ovarian carcinoma [9]. Metastatic colonic carcinomas may simulate primary endometrioid or mucinous ovarian carcinomas on gross and histologic examination [9]. In histologic assessment subgrups of cytokeratins (CKs) have been used to differentiate primary ovarian metastatic carcinomas. CK7 has been shown to be ubiquitously present in primary ovarian carcinomas, and CK20 is well expressed in colorectal carcinomas and their metastases [9]. The problem has practical importance for choice of therapy. Given the maximal cytoreduction as treatment of choice of primary ovarian cancer and inability to guarantee intraoperative pathologic distinction of primary ovarian carcinoma from metastatic colon carcinoma to the ovary even *via frozen section* examination, many cases of metastatic colon cancer are submitted to cytoreductive surgery [43]. Misdiagnosis may also lead to inappropriate therapy, because in adjuvant chemotherapy colorectal cancer is generally treated with 5-FU, and primary ovarian cancer is generally treated with paclitaxel and platinum agent.

An isolated ovarian metastasis from colorectal cancer is very often an unexpected finding at laparotomy or laparoscopy and it requests an immediate decision about how to proceed. Women with isolated ovarian metastasis with a long interval between initial diagnosis of colon cancer and recurrence, and women with limited disease that appears amenable to facile surgical resection would seem to be the preferred candidates to cytoreductive

surgery [28,43,47]. Management of colorectal cancers metastatic to the ovary should include: 1) resection of the primary tumor with the 5 cm surgical margin on either side, 2) the ovarian metastasis, and 3) bilateral salphingo-oophorectomy in the absence of extensive peritoneal spread or liver metastasis. The incidence of bilateral ovarian involvement is significant, thus, even if only one ovary is grossly involved with metastatic cancer, a bilateral oophorectomy should be performed [28]. Pelvic lymphadenectomy should be considered in the absence of peritoneal or hepatic metastasis [41,43,47]. In cases of direct invasion of the contiguous ovary from the colorectal cancer (pT4) or isolated macroscopic metastases (M1) found during the abdominal surgery for bowel cancer the radical *en block* resection of the primary lesion and all pelvic organs with metastatic disease with a curative aim seems to improve overall survival [16,41]. For patients with isolated ovarian metastases from colon cancer the optimal cytoreduction can confer a significant survival adventage compared with those patients who are left with bulky residual disease [43,47].

Only when surgical expertise to remove all visible evidence of cancer within the abdomen and pelvis is available should definitive cancer resection occur in association to peritonectomy and perioperative intraperitoneal chemotherapy. For patients with bulky ovarian disease, the aim of cytoreductive surgery with the removal of the pelvic tumor is to provide symptomatic pain relief and may relieve obstruction. The cytoreduction also for colon cancer patients who are et high risk for the development of local-regional recurrence and carcinomatosis, such as patients with perforated cancers or with adjacent organ involvement can be take into consideration [41,47,48]. In patients with extensive metastatic disease and peritoneal surface dissemination, aggressive tumor reduction with increased risk of surgical morbidity, however, contributes little and systemic therapy is of greater importance. In these patients systemic therapy is treatment of choice [16,47].

Patients with optymally cytoreduced isolated ovarian metastases from colon cancer have a better prognosis than patients with colon cancer metastases elsewhere. Patients with metastases limited to the ovaries who received optimal cytoreduction had a median disease-free survival of 14.5 months and an overall median survival of 61 months and therefore 50% 5-year survival. The optimal cytoreduction can confer a significant survival adventage compared with those patients who are left with bulky residual disease [41,43]. Rayson reported median survival of 31 months in patients who underwent complete metastatectomy compared to those patients with residual disease with median survival of 14 months. The median 5-year survival in patients without optimal cytoreduction ranged 5-23% [7].

Carcinoid tumors and tumors of the appendix

The primary carcinoid of the ovary is a rare malignancy. It represents approximately 0.1% of ovarian neoplasms. Metastatic carcinoid tumors to the ovary typically originate from primary distal ileal tumors, may be even more uncommon; less than 70 cases were reported in medical literature [49]. They are commonly associated with disseminated abdominal disease. Synchronous metastases involve typically peritoneal surfaces – mesentery, omentum and peritoneum, and liver. Patients typically present with adnexal mass, and only minority develop the carcinoid syndrome consisting of flushing and/or diarrhaea, due to secretion of serotonin directly into the systemic circulation [49].

Primary tumors of the appendix are rare with the most common being carcinoid. Primary appendiceal adenocarcinoma account for less than 0.5% of all gastrointestinal tumors, and 5-8% of primary appendiceal neoplasms. The reported incidence of ovarian metastasis from appendiceal tumors varies from 59% to 88%, and in cases of diagnosed primary appendiceal malignancy the addition to the right hemicolectomy bilateral oophorectomy is recommended in good surgical candidates [50,51]. Prolonged survival may be associated with cytoreductive surgery and octreotide treatment [49].

Most of appendiceal tumors are unrecognized preoperatively, presenting as appendicits, pelvic masses or with atypical abdominal pain. Rarely is the diagnosis of primary appendiceal malignant tumor made preoperatively. It is because neither ultrasonography and computer tomography can differentiate between appendiceal tumor and more common malignancies, including colonic as well as ovarian carcinoma [51]. The metastatic appendiceal tumors to ovary are typically cystic, often bilateral, average about 10 cm or more in diameter, usually multilocular. In cases of unilateral tumor, the right ovary is more often involved when compared to the left ones, due to its proximity to the appendix [38].

Acute appendicitis with periappendiceal abscess is the clinical presentation in 70% of patients with appendiceal adenocarcinoma. With appendiceal adenocarcinoma there is often associated pseudomyxoma peritonei, characterized by the presence of abundant mucinous material within the abdomen and peritoneal cavity. It is clear, that most cases of pseudomyxoma peritonei are of appendiceal, or more rarely colorectal origin, and that ovarian mucinous tumors are secondary to direct spread and implantation from the appendiceal neoplasms [52]. If a mass of mucoid or fibrous material is removed, this should be carefully examined to identify the appendix. In cases of pseudomyxoma peritonei the surgeon should always remove the appendix, even if the coexistent ovarian tumor is present. In some cases the appendix is grossly normal and a small adenocarcinoid or adenocarcinoma may be identified in histological examination [52].

Inspection of the appendix should be a part of the initial exploration at the beginning of abdominal procedures, because the primary appendiceal neoplasms in most cases when ovarian metastatic tumors are present, are minimal and show only thickening, induration or firmness. Additionally, usually it is difficult to distinguish in intraoperative frozen-section primary ovarian mucinous tumors from metastatic appendiceal ones. It makes the correct diagnosis difficult, and in these cases the surgical procedures should be the same as in primary epithelial ovarian cancer. Therefore, when frozen section examination of an ovarian tumor reveals metastatic ovarian neoplasm, and obvious primary lesion is apparently absent, routine appendectomy should be recommended, because the neoplastic appendix may appear macroscopically normal. In numerous cases, primary appendiceal tumors have been diagnozed only at second laparotomies. The data from the literature suggest, that right hemicolectomy confers a survival benefit versus simple appendectomy for primary tumor even in advanced disease. Aggressive debulking, oophorectomy and omentectomy are recommended when ovarian metastatic tumors are present [50].

Pancreatic cancer and biliary tract tumors

Pancreatic adenocarcinoma uncommonly metastatizes to ovary. The reported incidence of ovarian metastasis from pancreatic adenocarcinoma at autopsy of pancreatic adenocarcinoma patients is 4-6% [52]. In several studies of nongenital cancers metastasized to the ovaries, pancreatic carcinoma was diagnosed as a primary malignancy in 2-19% of patients [14,52].

Adenocaricnoma of pancreas may present as ovarian metastasis in the absence of the known primary [52]. Large, cystic, multiloculated unilateral mucinous ovarian tumor, or bilateral tumors, usually dominate the clinical presentation of the primary disease. In such cases the primary tumor can be missed [34,52,53] and most of patients initially present with advanced disease.

The impact of cytoreductive surgery on survival in metastatic cancer of the pancreas is difficult to assess. Observations by Falchook et al. suggest longer median survival duration in patients who had undergone metastatectomy followed by chemotherapy than patients who had undergone chemotherapy alone (16.5 months *vs*. 8.5 months). Surgical intervention can be often necessary to remove the large pelvic tumor, to provide symptomatic pain relief and relieve obstruction. Generally, the resection of ovarian metastatic tumors from pancreatic carcinoma plays a palliative role, and may increase the survival time of symptomatic patients [53].

Ovarian metastatic carcinoma of gallbladder and extrahepatic bile ducts is a very rare disease, and less than 10% of patients are found to have peritoneal carcinomatosis. The cases of ovarian metastases from cholangiocarcinoma are extremely rare. It should be considered when ovarian tumors with widespread carcinomatosis accompanies biliary obstruction. In such cases the prognosis for patients is poor. Surgery in the form of a diagnostic laparotomy for the ovarian mass, and for symptom relief is often necessary, but when diagnosis is confirmed, palliation remains the mainstay of therapy [54].

Malignant lymphomas and leukaemias

Involvement of the ovary by malignant lymphoma can present either as a primary lesion, or more frequently as a focus of involvement in cases of disseminated malignancy [55]. Lymphomas represent 2.6-17.1% of metastatic ovarian tumors [12]. The ovaries are most common site of metastatic tumors from malignant lymphoma in genital organs. Ovarian involvement as a manifestation of clinically occult or overt lymphomatous malignancy is well recognized with frequency as high as 26%.

The haematological secondary ovarian tumors, both lymphomatous or leukaemic, are usually bilateral, solid, and in most cases of the large diameter [56,57]. The presence of ovarian involvement by malignant lymphoma or leukaemia usually is the late manifestation of disseminated nodal disease, and the involvement of the ovary can be not clinically significant [58]. Exploratory surgery due to an ovarian tumor is common treatment method to confirm the diagnosis. The bilateral ovarian involvement, peritoneal implant, and ovarian involvement at the time of surgery may be used as an agrument of a secondary character of ovarian haematologic malignancy [58].

The radical surgery is not associated with improved survival of patients, but the removal of ovarian metastasis palliates symptoms and facilitates the response to systemic treatment [14]. Surgical debulking of the tumors is not considered to be related to improved prognosis, and the treatment of choice of lymphomas and leukemias remains systemic chemotherapy [58]. In young women, when the intraoperative diagnosis by frozen-section from the ovarian tumor biopsy confirmes malignant lymphoma metastatic to ovary, the ovaries should be preserved, to allow the possible preservation of ovarian function as well as preservation of fertility in some these patients after systemic treatment [59]. The 47% overall five-years survival in patients suffering from malignant lymphoma and coexistant synchronic ovarian metastastatic tumors is described.

Considering the role of surgery in patients with haematologic malignancies, the problem of fertility sparing surgical procedures in young patients without synchronous ovarian metastases should be discussed. Over the last years cryopreservation of ovarian tissue is currently practiced in an attempt to preserve fertility before commencing potentially sterilizing chemotherapy, but clinical and laboratory guidelines are needed to standardize the procedure. The indications and timing of ovarian tissue banking should be individualized. Patients previously exposed to chemotherapy can consider ovarian tissue freezing. The extent of tissue removed should take into account the large number of follicles lost and the risk of future sterilization. Tissue handling should enable further investigation of primordial follicles and identification of cancer cells. In these patients harvesting of ovarian tissue should be performed during surgery following previous exposure to chemotherapy or shortly after the chemotherapy. Partial oophorectomy on the way of laparoscopy or laparotomy is the preferred surgical procedure [56].

Malignant melanoma

Metastatic ovarian malignant melanomas are more common than primary ovarian malignant melanomas. The melanoma metastatic to ovary arise usually from a cutaneous melanoma, but the secondary ovarian tumors can be discovered many years after the diagnosis of the primary lesion. The diagnosis of malignant melanoma metastatic to the ovary is uncommon in living patients, but approximately 20% of patients dying of malignant melanoma have ovarian metastases at postmortem examination [60]. Most of these patients have abdominal dissemination of melanoma disease, and the involvement of the ovary is not clinically significant. It is rare for melanoma to present clinically as an solitary ovarian tumor [61].

Malignant melanoma metastatic to the ovary should be suspected in any patient who presents with an adnexal mass and has a history of malignant melanoma. Pathologically the ovaries are usually enlarged and the unilateral or bilateral lesions are et last partially cystic with a smooth capsule. Only a minority exhibit conspicuous amounts of melanin pigment [61]. The findings from ultrasonography and computer tomography can be nonspecific in these cases, but magnetic resonance imaging allow detection melanin in the melanoma, which can differentiate to produce this substance [61].

The optimal surgical management of metastatic ovarian malignant melanoma is a challenge and it has been not established to date. Some authors suggest, that if the one ovary is the only site of relapse and there is no evidence of involvement of contralateral ovary, unilateral oophorectomy or salphingo-oophorectomy may contribute to long-term survival. When the

contralateral ovary can be suspected of metastasis, even without frozen section examination, the bilateral oophorectomy or salphingo-oophorectomy should be performed. Another authors recommend the total abdominal hysterectomy and bilateral salphingo-oophorectomy as treatment of choice in malignant melanoma metastatic to the ovary without abdominal dissemination. Unfortunately, the vast majority of cases of malignant melanoma metastatic to the ovary reported in the literature were associated with other, both abdominal and extraabdominal sites of relapse. In these cases surgical treatment can be necessary to provide symptomatic pain relief and relieve obstruction. For these patients chemotherapy should be considered. However, there is no definitive evidence that it is beneficial, and the patients with multilocular relapse usually die within 2 years from diagnosis of ovarian metastasis [60,61].

Tumors from the urinary tract

Renal carcinoma and carcinoma of the urinary bladder uncommonly metastasize to the ovary [62]. The reported rate of ovarian metastases from renal cancer and bladder cancer to ovary are about 0.5% and 4-12.4% respectively [63,64]. Sometimes there is no history of a primary urinary tract neoplasm, and the ovarian metastatic tumor is the first presentation of the disease. The most common histology of the renal cancer metastatic to the ovary is clear cell carcinoma, and metastatic ovarian cancers from urinary bladder are usually of transitional cell subtype. Bilaterality is an favour of a secondary tumor, but some ovarian metastases from primary tumors arising from urinary tract are unilateral [13,52,62,63,65]. Macroscopically, the predominant features of these metastases are tumors without exophytic growth and mixed yellowish solid and cystic areas [64]. Only isolated examples of ovarian metastasis of ureteral or urethral cancer have been reported in the literature [13].

The treatment of choice in most patients with ovarian metastases from urinary system remains surgery. Unfortunately, very often only explorative laparotomy is possible. In cases with solitary adnexal metastases without abdominal dissemination, the resection of metastatic tumors should be performed. Because of rarity of such cases, the indications for cytoreductive surgery should be individualized [65].

Primary peritoneal tumors

Primary peritoneal serous carcinoma is a tumor which was first reported by Swerdlow in 1959. It is the most common peritoneal malignancy, clinically and morphologically identical to primary ovarian serous adenocarcinoma

[52,66,67]. There appears to be no significalt epidemiological differences between cancers arising primarily within the ovary or the peritoneum [68].

Primary peritoneal serous carcinoma is a tumor that diffusely involves the peritoneal surface whilst there is no or minimal involvement of the ovaries. The peritoneal tumor is generally bulky and widespread, showing extensive peritoneal carcinomatosis. The omentum is almost always involved [68]. The criteria for diagnosis of primary serous peritoneal adenocarcinoma proposed by GOG (Gynecological Oncology Group) are: 1) the ovaries are normal in size or are enlarged by a benign process, 2) the extraovarian site of carcinoma are of significantly greater volume than the tumor present in either ovary, 3). The ovarian tumor components is neither non-existent, confined to the ovarian surface with or without stromal invasion measuring in aggregate less than 5 mm x 5 mm, or within the ovarian substance and measuring less than 5 mm x 5 mm, d) the histologic characteristics indicate serous carcinoma of any grade [69].

This is not a crucial distinction to make since management of both neoplasms is identical, treatment is based on surgical resection associated with adjuvant chemotherapy [52,67]. In surgical treatment the succesive procedures are: the laparotomy via midline vertical incision, peritoneal washings, total abdominal hysterectomy and bilateral salphingooophorectomy, omentectomy, sampling of pelvic / paraaortic lymphnodes when enlarged, maximal cytoreduction [67,68]. Some of the factors that may prevent optimal cytoreduction include extensive nodular infiltration of the mesenteric, visceral and peritoneal surfaces, and involvement of the porta-hepatis, liver, higher paraaortic nodes and stomach [68]. Very little is known about the role of lymphadenectomy in patients with primary peritoneal serous carcinoma, and only few series have adressed the issue of nodal spread in those patients. Lymphadenectomy should include all pelvic and para-aortic chains up to the level of the right renal vein. The procedure has both a diagnostic and prognostic value. The therapeutic value of lymphadenectomy remains unproven [70]. Although most of investigators reported the optimal cytoreductive surgery as a favourable prognostic factor in patients with primary peritoneal carcinoma, some authors did not found a significant prognostic value for optimal cytoreductive surgery in these cases [67]. In the adjuvant setting the combination of paclitaxel and platinum is a standard of chemotherapy in patients with primary peritoneal carcinoma [15,67]. The value of secondary cytoreductive surgery in patients suffering from primary peritoneal carcinoma is not clearly defined [67].

Ovaries can be even reached by diffuse malignant peritoneal mesothelioma. Usually in these cases there is widespread peritoneal disease with only minimal involvement of the surface of the ovaries. Rarely there is

prominent ovarian involvement, mimicking a primary ovarian carcinoma, and occasional cases of primary ovarian mesothelioma have been described [52]. Over the past decade, the management of these patients has evolved similarly to ovarian cancer treatment and now involves cytoreductive surgery, heated intraoperative intraperitoneal chemotherapy (HIIC) with cisplatin and doxorubicin, and early postoperative intraperitoneal paclitaxel. These perioperative treatments are followed by adjuvant intraperitoneal paclitaxel and second-look cytoreduction [71].

Another extragenital tumors metastatized to ovaries

A variety of other neoplasms rare metastatize to the ovaries and present as an ovarian tumor in a patient with a known extra-ovarian malignancy. Uncommon cases of ovarian metastasis from the liver, lung, thyroid glands, extragenital sarcomas, adrenal gland tumors, pulmonary, mediastinal and vascular tumors were described [13,34,72,73]. Metastases to the ovary other than those alredy described are of great rarity. In 2.6-16.9% of cases the primary tumor remains unidentified [12,27].

In cases of such tumors surgery in the form of a diagnostic laparotomy for the ovarian mass and for symptom relief is often necessary, but the further management of patients depends upon the site of extent of the primary disease, histopathology of the tumor and general condition of the patient [72]. Numerous studies suggest that resection of metastatic ovarian tumors and cytoreductive surgery play a significant role in improving the survival time in patients with no distant metastasis other than to the adnexa.

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