

LETTERS TO THE EDITOR

The role of primary debulking in advanced ovarian cancer patients

Dear Editor,

Ovarian cancer (239,000 cases and 152,000 deaths) is the seventh most common cancer and the eighth cause of death from cancer in women (3.6% of the cases and 4.3% deaths) in the world [1]. In Romania, the incidence of ovarian cancer is continuously increasing and in terms of mortality, this disease is the seventh leading cause of death from cancer in women [2]. Despite many efforts undertaken to detect the disease at an early stage, most cases are diagnosed in stages IIIC and IV, with a long-term prognosis that has not changed significantly over the last decade.

The definition of what can be accepted as "optimal" surgery has varied over time. du Bois et al. showed improved progression-free and overall survival for patients with complete resection (R0=0 mm) compared with patients with suboptimal debulking (1-10 mm, >1 cm), and also the surgical debulking impact on prognosis in advanced ovarian cancer [3]. Today, only complete debulking to no visible tumor residuals can be accepted as "optimal" and was regarded as ultimate goal of any ovarian cancer operation.

Regarding the potential role of lymphadenectomy in advanced ovarian cancer, a recent meta-analysis suggested the possibility that systematic lymphadenectomy can improve overall survival in advanced-stage epithelial ovarian cancer [4], but due to the lack of randomized controlled trials further studies are necessary to elucidate the potential role of systematic lymphadenectomy in advanced ovarian cancer.

Even if primary debulking surgery is considered the standard of care for advanced ovarian cancer, the role of neoadjuvant chemotherapy must not be underestimated. In a recently published randomised trial of the EORTC-NCIC (European Organisation for Research and Treatment of Cancer - National Cancer Institute Canada) in patients with advanced stage IIIC and IV of ovarian cancer, the survival rates were similar in patients who underwent neoadjuvant chemotherapy followed by interval debulking compared to patients who underwent primary debulking surgery, followed by chemotherapy [5].

We have retrospectively analyzed 67 patients with advanced stage IIIC or IV epithelial ovarian carcinoma admitted and treated in the Oncology Institute "Prof. Dr. Ion Chiricută" between 2009 and 2011 that underwent primary debulking surgery. Complete resection (R0) was achieved in 59% of the cases and in the IIIC subgroup the percentage

of complete resection increased to 64%. Compared to the results published in the literature, our patients with any residual tumor had a median survival significantly lower in comparison with patients that achieved complete resection ($p<0.01$). Patients with microscopic (1-10 mm) residual disease had a better survival in comparison to patients with macroscopic (>1 cm) tumor residuals ($p<0.01$).

In conclusion, complete resection should be considered a crucial factor with regard to its prognostic impact in advanced stage ovarian cancer either as primary or interval debulking surgery in patients with bulky disease and a thorough surgical effort is justified by the literature published on this issue.

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Micro-RNAs in p16^{INK4A} (CDKN2A gene) deregulation: A novel molecular approach in cervical and head & neck carcinomas

Dear Editor,

Among tumor suppressor proteins, the p16^{INK4A} encoded by the Cyclin-dependent kinase inhibitor 2A (CDKN2A) gene (9p21.3) plays a critical role in cell homeostasis. p16 negatively regulates the cell cycle by decelerating progression at the level of G1 to S phase. This function is mediated by inhibiting CDK4/CDK6 preventing thus the phosphorylation of retinoblastoma (RB) protein. Mechanisms of p16 gene deregulation in solid malignancies include epigenetic alterations in its promoter methylation (hypermethylation) and also allelic losses due to deletions and point mutations (loss of heterozygosity or homozygosity).

The role of p16^{INK4A} overexpression in human papilloma virus (HPV) related cervical and head & neck squamous cell carcinomas (HNSCC) is significantly under investigation (Figure 1). At the molecular level, HPV E7 oncoprotein deregulates RB/E2F pathway leading to an aberrant p16^{INK4A} overexpression combined also by p53 inactivation due to HPV E6 oncogene overactivation. In these malignancies, p16^{INK4A} elevated protein expression is provided by immunohisto-cytochemistry. Different protein expression patterns have been observed including nuclear, cytoplasmic or diffuse combined nuclear/cytoplasmic localisation. Aberrant overexpression of the marker is considered as a surrogate marker for high risk HPV infection - especially for HPV 16/18/31/33/45/53 subtypes - and also as a prognostic factor [1]. Interestingly, HPV-negative laryngeal SCCs seem to demonstrate a worse prognosis by overexpressing p16^{INK4A} as a result of CDKN2A mutation. Concerning cervical carcinomas, combined p16^{INK4A} and ki-67 (proliferation marker) overexpression seems to correlate with a progressive disease by upgrading cervical intraepithelial neoplasia (CIN) from CIN I to II/III/*in situ* carcinoma [2].

Quite recently, micro-RNAs (miRs) are considered as novel significant markers for discriminating patients based on their molecular characteristics. miRs are short, non-coding RNAs consisting of 20-25 nucleotides located at intra- or intergenic regions. Functional miRs mediate a positive regulation of posttranscriptional gene silencing. Their deregulation in cancer cells due to genetic (mutations, translocations), epigenetic (DNA hypermethylation of tumor suppressor genes, extensive genomic DNA hypomethylation, aberrant histone modification patterns) and transcriptional alterations lead to a loss of miRs-mediated repression of target mRNA. Interestingly, a biphasic role of miRs in cancers of different histogenetic origin has been confirmed. In some of them, their upregulation correlates with an increased oncogenic activity, whereas in others the same miR type acts as a suppressor agent.

Concerning CDKN2A gene deregulation, some studies support the idea that specific miRs modify cell cycle molecules expression in HNSCCs and cervical carcinomas. Upregulation of miR-34a in p16-positive HNSCCs, miR-21/miR-200c overactivation and miR-375 downregulation are potentially significant genetic events affecting prognosis in the corresponding patients [3]. Additionally, elevated miR-150 level - which induces the cell cycle progression from G1/G0 to S - is detected in cervical carcinomas. This specific miR reduces the expression of FOXO4, which regulates the expression of CyclinD1, p27, BIM, and FASL by targeting its 3' UTR [4]. miR-124 in cervical carcinoma, miR-137/ miR-148/ miR-218 in HNSCCs and also miR-9/ miR-34 families in both of them are very promising markers in expanding our molecular knowledge regarding the mechanisms of carcinogenesis in these malignancies [5].

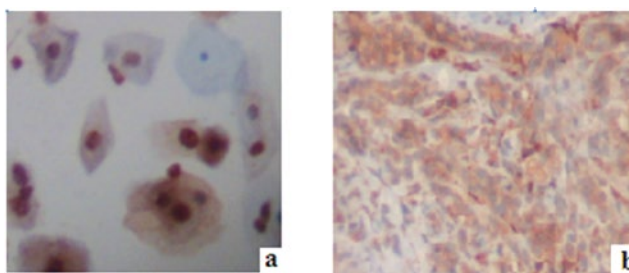


Figure 1. p16^{INK4A} overexpression (anti-p16 staining). **a:** A case of cervical squamous intraepithelial lesion (SIL). Note predominantly nuclear expression (liquid based cytology, DAB chromogen, original magnification 400x). **b:** A case of laryngeal squamous cell carcinoma. Note a diffuse, predominantly cytoplasmic and nuclear expression (tissue section, DAB chromogen, original magnification 100x).

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The association between neutrophil to lymphocyte ratio and survival in metastatic breast cancer patients

Dear Editor,

As cancer patients progress over the course of their illness, knowing what to expect can ease the decision process of care planning. Various prognostic markers are considered while making a decision to choose treatment modality for breast cancer. Stage at initial presentation, histological grade, molecular subtype, tumor size, nodal involvement and lymphovascular invasion are among the most valuable prognostic markers. However, their usefulness to further tailoring breast cancer treatments and predicting breast cancer prognosis remains an open question [1]. Since accurate prognostication is necessary for oncologists in arranging their recommendations, they investigate new prognostic factors due to highly variable treatment responses of individuals [2].

Inflammation has been reported to contribute to the development of many cancers and is now included as a hallmark of cancer [3]. Many recent studies have suggested that an elevated neutrophil-to-lymphocyte ratio (NLR) is associated with poor survival of patients with various types of solid cancers [4]. In addition, association of high NLR with worse overall survival has been shown to be greater in metastatic than in nonmetastatic disease. This may be the result of either greater tumor burden or a more prolonged chronic inflammatory process [5].

In our study, we included 81 patients with metastatic breast carcinoma to evaluate the correlation between NLR and overall survival. According to their calculated NLR values, patients were divided into four quartiles (the lowest being the 1st quartile, the highest being 4th quartile). Survival status was retrieved from our cancer registry.

Median patient age at diagnosis was 47 years (26-83), the majority of them (37%) had grade II and grade III

(29.6%) tumors and were metastatic at the time of their initial diagnosis. ER (+), PR (+) and HER2 (+) percents were 82, 73 and 24%, respectively. Ten percent of the patients were triple negative. Median follow-up time was 26 months and 29 patients died during the follow up period.

When we compared the quartiles, the quartile with the lowest NLR values had longer median overall survival than the quartile with the highest NLR values (212 vs 27 months; $p=0.01$). The second and third quartiles, however, showed no statistically significant difference for overall survival.

In conclusion, a high NLR is shown to be associated with adverse survival in metastatic breast cancer patients. Thus, NLR may serve as a cost-effective prognostic biomarker for therapeutic decision making in these patients.

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Is radiotherapy indicated in the treatment of gastrointestinal stromal tumors?

Dear Editor,

Gastrointestinal stromal tumors (GISTs) originate from the interstitial cells of Cajal and are the most common mesenchymal tumors of the gastrointestinal (GI) tract. They vary from asymptomatic to fast-growing, aggressive tumors and cover about 1% of all GI tumors. The most common site is the stomach (50%) followed by small intestine (25%), colon (10%) and esophagus (5%). Clinical findings are related to tumor localization in the GI tract and its size. Most common presentation is with abdominal pain followed by GI bleeding and obstruction [1,2].

Due to their growing incidence, treatment is more important than before. Treatment varies depending on the patient and tumor characteristics. Despite advances in drug therapy, surgical resection is always essential in the treatment of GISTs [1]. Total surgical resection without rupture of the tumor is still the most successful treatment. Yet, high local recurrence rates are seen despite total surgical resection and negative surgical margins. While 5-year overall survival is 42% for completely resected tumors, it is only 9% for partial resections [1-3].

While surgery alone is adequate in low-grade tumors, it is not sufficient in high-grade cases. In such cases, additional therapies have been proposed, like radiotherapy (RT) and chemotherapy. RT was a therapeutic choice before the launch of imatinib but it didn't contribute much. It is toxic to adjacent organs and has little effect on the tumor. Only a limited number of studies examining the effectiveness of RT exists. Nowadays, receptor tyrosine kinase inhibitors (TKIs) (imatinib, sunitinib, nilotinib, etc.) that are used in the targeted treatment of GISTs have been launched one after another and have contributed significantly to both quality of life and survival of these patients. Although there is no consensus on postoperative adjuvant treatment, some centers administer 12-36-month imatinib 400 mg once daily. Also, it has been stated that TKIs play an important role in patients with recurrent and metastatic disease. There are ongoing trials regarding the use of imatinib as neoadjuvant therapy and promising results have been shown especially in large and metastatic tumors [3-5].

Despite imatinib's beneficial effects on overall and disease free survival, recurrences are an important issue in the postoperative period due to secondary resistance [4]. In the recurrence analysis of the American College

of Surgeons Oncology Group (ACOSOG) Z9000, 5-year relapse-free survival was 40% and local recurrence 33%. There are very few treatment options in patients who develop recurrence [2].

GISTs are unresponsive to RT. According to the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines, RT is not included in the treatment plan other than palliative treatment of bone metastases. However, currently, combination of RT and imatinib is considered as an optimal treatment for selected patients [2-5]. In their review Corbin et al. reported that while RT wasn't used much on the treatment of GISTs, it might be beneficial for the control of symptoms due to locally advanced and metastatic disease [2]. Also in their study Cuaron et al. registered local control in 15 of 17 treated lesions [3]. RT scheme consisted of 30 Gy to 8 patients, 3 Gy/fraction and 5 Gy and higher doses of hypofractionated RT to 9 patients. They didn't report severe toxicity due to RT. In 41% of these cases, TKIs were used concurrently with RT. Six-month PFS and OS were 57% and 57.8%, respectively. While partial palliation rate was 94.4%, complete palliation was 44.4%. As a result, GISTs were proved no radioresistant as known before and in locally advanced and metastatic disease, concurrent use of targeted therapy and RT could have a place for symptom palliation [3]. Crosby and his colleagues reported successful local control in 6 of 10 patients with positive surgical margins after RT with 45-60 Gy [5].

Existing therapeutic protocols for patients who developed resistance to imatinib in the treatment of recurrent and metastatic GISTs cannot lead to successful outcome. Therefore approaches combining new agents are needed and simultaneous application with RT should be preferred [3]. In recent years, intensity modulated RT (IMRT), while delivering higher doses to the target tissue, offers increased protection to normal tissues, thus both acute and chronic side effects are minimized. With higher total and fraction doses, tumors will be easily controlled [4]. However, according to Cuaron et al. [3], RT dose is usually 30 Gy, and the optimal dose should be revised again [3]. Radiation-sensitizing drugs should also be looked at.

In conclusion, the basic treatment of GISTs is surgery and/or targeted therapy. However, in recent years, especially after simultaneous targeted therapy and RT, the latter seems to bear significant importance in controlling symptoms for

tumors which are recurrent, locally advanced or metastatic. One of the most important factors in determining treatment approach is the experience and facility of a center.

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Syringocystadenoma papilliferum with multiple lung metastases and long survival

Dear Editor,

Cutaneous adnexal tumors are rare tumors thought to arise from undifferentiated stem cells rather than mature cells because of their heterogeneity. In general, they develop slowly and they are most seen in head and neck region. Syringocystadenoma papilliferum is a rare adnexal tumor that mostly stems from apocrine sweat glands. It is generally benign with malignant transformation and locoregional metastasis rarely reported [1]. Multiple

lesions that arise outside the head and neck region are rarely seen and according to our knowledge no metastatic patient other than locoregional metastases was reported in the literature until now. Our case is related to a malignant syringocystadenoma papilliferum which causes lung and bone metastasis. To our knowledge, until now, there is no syringocystadenoma papilliferum case with lung and bone metastasis mentioned in the literature.

A 43-year old female admitted to our clinic in July 2013, with a complaint of cough and occasional shortness

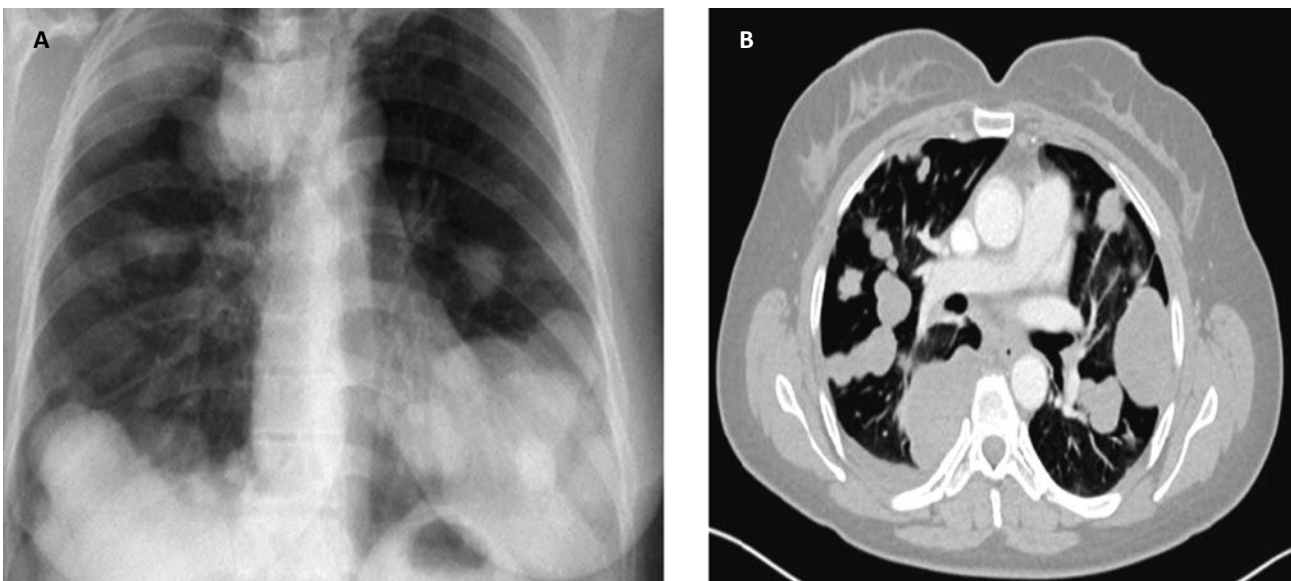


Figure 1. A: Common tumoral infiltrations in postero-anterior chest X ray; B: the largest 6x6 cm multiple bilateral metastatic parenchymal and pleural metastatic masses in thoracic CT.

of breath. She had no additional disease, didn't smoke or drink alcohol and had only a history of 11 x 5.5 x 0.8 cm solid mass excision from scalp 10 years ago. Pathologic examination was reported to be as benign syringocystadenoma papilliferum cutaneous adnexal tumor. Patient's laboratory results were normal and in the physical examination no pathology was detected other than 2x2 cm lesion in the right parietal of the scalp. Gross examination of the lesion showed a greyish-white, soft-tissue piece which was covered with yellowish crustations. In the postero-anterior chest x-ray evaluation, numerous multiple bilateral metastatic masses were found and the largest 6 cm x 6 cm multiple bilateral metastatic parenchymal and pleural metastatic masses and findings compatible with lytic metastasis in sacrum were found in the evaluation of torax-abdominal computed tomography (CT), (Figure 1). In whole body 18-fluoro-deoxy glucose (FDG) positron emission computed tomography (PET-CT) imaging, increased pathologic metabolic activity in the thickening areas of pleural surfaces, bilateral lung and sacrum which were compatible with metastasis to both lung and skeletal system. Tru-cut biopsy of metastases from pleural surface of the patient was performed who had a cutaneous adnexal tumor history, keeping the 2nd primary tumor possibility in mind. Histopathological examination of the tru-cut biopsy of metastatic pleural lesion showed papillomatous epidermis with multiple cystic, papillary, and ductal invaginations with 10% Ki-67 proliferative index, with negative TTF-1, napsin A and chromogranin, which was compatible with malignant cutaneous adnexal tumor metastasis, rather than mesothelioma and lung adenocarcinoma. Histopathological findings were consistent with the transformation of syringocystadenoma to syringocystadenocarcinoma papilliferum. As malignant mesothelioma was excluded, the case was determined to be a metastatic cutaneous adnexal tumor and cisplatin+etoposide per 3 days every 3 week chemotherapy was given. After 4 cycles of chemotherapy, the findings were stable and the observation period without any use of medication started. In the torax-abdomen CT (Figure 2) carried out in April 2015, a significant progression was observed in masses in both lung and in the lytic lesion of sacrum. Due to the symptomatic progression in the sacrum, 45 Gy palliative external radiotherapy was given. Symptoms were relieved with palliative external radiotherapy and after that, due to the lack of evidence of second line palliative chemotherapy the patient was followed without treatment. The patient is still alive for 34 months from the diagnosis of metastases.

Syringocystadenoma or syringocystadenocarcinoma papilliferum mostly benign tumor that shows a slow progress without recurrence or metastasis. Malignant transformation of syringocystadenoma papilliferum was

documented in some cases but no case report such as widespread lung and skeletal metastases was mentioned in the literature before [2]. Locoregional metastases were reported in few cases [3,4]. Though some rare malign cases were reported, lung and bone metastatic cases were not mentioned in the literature so far. Until now, only a 57-year old woman who presented with locally advanced syringocystadenocarcinoma papilliferum of vulva and locoregional failure with feixed large inguinal nodal masses was successfully treated with neoadjuvant chemotherapy with cisplatin and 5-fluorouracil followed with cisplatin based chemoradiotherapy [5]. Palliative chemotherapy and radiotherapy will likely be primary treatment of choice of treatment although there was no clear data like other skin cancers. In conclusion, syringocystadenoma papilliferum should be considered among cutaneous and cutaneous adnexal neoplasia and it should be noted that though they are benign in general, some rare aggressive progress could also be seen. Although rarely, aggressive metastases were seen, the prognosis is good with long survival compared to metastases to lung of metastatic malign melanoma or other skin cancers.

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