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EGFR expression in liver metastases in patients with colorectal cancer EGFR positive primary tumor and response to systemic chemotherapy and targeted therapy

KEYWORDS: Receptor, Epidermal Growth Factor; Colorectal Neoplasms; Neoplasm Metastasis

Background: EGFR and its ligands play a critical role in over 70% of all cancers. The enhanced activity of this receptor is a hallmark of many human malignancies - breast, lung, prostate, head and neck, ovary, stomach, kidney, brain, pancreas. In many of these tumor types, EGF receptor is expressed 100-times higher than on the surface of the normal cells. Aim: To evaluate expression of epidermal growth factor receptor (EGFR) in liver metastases in patients with colorectal carcinoma EGFR immunohistochemistry (IHC) positive primary tumor and to evaluate response to systemic chemotherapy in this group of patients.

Methods: A group of 19 patients with IHC positive EGFR in primary tumor with synchronous liver metastasis were analyzed. All patients received irinotecan and/or oxaliplatin based chemotherapy regimen in combination with oral fluoropyrimidines - capecitabine.

Results: 10 patients had EGFR IHC positive expression in liver metastases. EGFR IHC negative liver metastases were present in 9 patients. In patients with EGFR IHC positive liver metastases 2 patients had partial response, 1 patients had stable disease and 6 patients had progressive disease after chemotherapy. In patients with EGFR IHC negative liver metastases 3 patients had PR, 2 patients had SD and 5 patients had PD after chemotherapy. All patients with PD received cetuximab with previous systemic chemotherapy. Progression free survival in this group of patients was 4.1 month.

Conclusion: This study is ongoing. At this moment, results do not support routine determination of EGFR status on distant metastatic sites in patients with colorectal carcinoma and its predictive role.

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Does retroperitoneal lymphadenectomy represent the best treatment option in patients with clinical stage A of nonseminomatous testicular tumors and normal values of serum tumor markers relapsed after orchiectomy?

KEYWORDS: Testicular Neoplasms; Lymph Node Excision; Antineoplastic Agents

Background: We previously reported that patients in clinical stage A (CS-A) of nonseminomatous testicular tumors (NSTT) who underwent retroperitoneal lymphadenectomy (RPLA) are more likely relapse if their preorchiectomy alpha-feto protein (AFP) was > 80 ng/ml, if they have $> 80\%$ of embryonal carcinoma component or if there was vascular invasion. The aim of the present study is to analyze experience with only surveillance in comparison to primary RPLA and cisplatin (CDDP)-based chemotherapy (CHT) according to risk factors in CS-A NSTT with normal values of serum tumor markers (STM) relapsed after orchiectomy.

Methods: 195 patients entered a prospective but non-randomized study, from January 1981 to December 2003. Patients were divided into 3 groups according to primary risk adapted treatment: arm A (n=60) - surveillance, arm B (n=65) - "nerve sparing" RPLA with 2 cycles of adjunctive CDDP-based CHT in PS-B1/B2, and arm C (n=70) - only 2 cycles of CDDP-based CHT in high risk (HR) group.

Results: Arm A - 9/21 patients (42.9%) with HR relapsed (4 RPLN, 2 RPLN+lung, 1 inguinal lymph nodes (LN)+lung, 2 only elevated STM) within interval of 12.3 months (range 3-46) with complete response (CR) following applied therapy in 6 patients (66.6%) (8 patients necessitate surgery). Alive and free of disease are 18 patients (85.7%) at follow-up of 12.3 years (range 3.5-20.6). Six out of 39 patients (15.4%) with low risk (LR) relapsed within of 6.8 months (range 3-10) (3 RPLN, 1 lung, 2 only elevated STM) with CR following applied CHT ($p < 0.05$). All pts are free of disease after follow-up of 9 years (range 1.9-18.7). Arm B - Relapses following RPLA in HR PS-A occurred in 7/35 patients (20%) within 8.3 months (range 2-23) (5 lung, 1 RPLN, 1 only elevated STM) with CR following CHT +/- surgery in 4 patients (57.1%). Patients with LN metastasis (11) had universal survival. Overall, relapses occurred in 10/46 pts (21.7%) with survival in 41 pts (91.1%) at follow-up of 14.6 years (range 8.75-17.25). Among 19 patients with LR, only 2 patients (10.5%) had LN metastasis, whereas relapse rate was null in 17 fully available patients after follow-up of 10.8 years (range 8.6-15.8) (1 lost of follow-up at 26 months, 1 died of other malignancy at 90 months). 18 out of 46 patients (39%) in HR received adjunctive CDDP-based CHT versus 2/19 (10.5%) in LR group of patients ($p < 0.05$). Arm C - 1/70 HR patients treated with primary CHT relapsed at 12 months (lung) and died despite salvage CHT+surgery. Alive and free of disease are 69 patients (98.6%) at follow-up of 5.5 years (range 1.5-13.7).

Conclusion: We conclude that patients in CS-A NSTT are not necessarily helped by initial RPLA. According to results of present study optimal therapy for HR patients are 2 cycles of CDDP-based CHT. Surveillance policy is acceptable mode of treatment in strictly selected group of LR patients.



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The role of *Helicobacter pylori* infection in gastric cancer etiology

Thyroid lymphoma

KEYWORDS: Stomach Neoplasms; Risk Factors; Helicobacter Infections

KEYWORDS: Thyroid Neoplasms; Lymphoma

Background: Neoplasms are among the main causes of the death today. One of the leading cancers at the rate of occurrence at either sex is gastric cancer. Appearance of gastric cancer varies in different parts of the world and among different nations. Nutrition habits, exposure to cancerous elements and in last two decades *Helicobacter pylori* play significant role in gastric cancer etiology. The aim of the study was to examine prevalence of *Helicobacter pylori* infection in gastric cancer patients, and compared it with control group.

Methods: The examination was carried out in The Clinic Center of Banja Luka, Republic of Srpska. Eighty patients were included, divided into two groups. In a control group, there are 40 people without gastric problems, and the other group consists of patients with histopathological verified gastric cancer. Methodology used was serological evidence of IgG and IgA antibodies against *Helicobacter pylori* by ELISA techniques.

Results: *Helicobacter pylori* infection appeared at 27.5 % of examined healthy population. *Helicobacter pylori* infection has been found at 72.5% of examined gastric cancer patients. There was a significant difference between number of positive patients and examinees from the control group ($p < 0.05$). *Helicobacter pylori* infection odds ratio in relation with healthy population was significant OR=6.95 (95% CI=2.60-18.55).

Conclusion: Results of this study indicate that *Helicobacter pylori* infection contributes as significant factor in etiology of gastric cancer.

Background: Thyroid lymphoma is a systematic disease, which can be present in a thyroid gland. Thyroid lymphoma accounts 2% of all lymphomas. It is usually detected in Hashimoto's thyroiditis, in women aged 60 years and more. At the beginning of the disease, there is a similarity between thyroid lymphoma and anaplastic thyroid carcinoma. The aim of the paper is to review diagnostics, therapy, follow up and survival of patients with thyroid lymphoma and to point out difference between thyroid lymphoma and thyroid anaplastic carcinoma.

Methods: Ten patients, three men and seven women, mean age 54.7 years, were presented. All of them were diagnosed and treated at the Institute of Oncology, Sremska Kamenica.

Results: Diagnosis was done according to the clinical image: prolonged dyspnea and enlarged thyroid: diffuse, nodular and partially substernal. Thyroid was medium hard on palpation. Positive thyroglobulin or peroxidase antibodies and increased thyreo-stimulating hormone value were found. Ultrasound of thyroid showed hypoechogen image and scintigraphy showed nonfunctioning and hypo functioning areas. Cytological finding indicated sings of Hashimoto's thyroiditis and suspected lymphoma. In 50% of patients, the diagnosis was based on the histopathological verification and in 71% of the patients cytological finding was also pathological. Survival time for all patients was from 3 to 36 months. Therapy was done according of the protocol that included radiotherapy and chemotherapy for all patients and total thyroidectomy in 5 patients only.

Conclusion: Only a rational, prompt diagnostics with a precise therapy according to the protocol can influence better survival and quality of life of patients with thyroid lymphoma. Thyroid lymphoma can be easily differentiated from anaplastic thyroid carcinoma if we stick to diagnostic protocol.



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Sensitivity of ultrasound characteristics of lymph nodes in metastatic skin melanoma - preliminary report

Inflammatory myofibroblastic tumors - lung neoplasms with unpredictable behavior

KEYWORDS: Melanoma; Neoplasm Metastasis; Lymph Nodes; Ultrasonography

KEYWORDS: Plasma Cell Granuloma, Pulmonary; Lung Neoplasms

Background: Analysis of ultrasound characteristics of regional lymph nodes provides more accurate diagnosis of the presence of melanoma metastasis in lymph nodes. Early identification of lymph nodes involvement and their surgical removal are crucial steps in patient treatment. We tried to determine sensitivity and specificity of following characteristics of lymph nodes: echogenicity of lymph node center, type of lymph node vascularization, intranodal lymph node vascularization and resistance index.

Methods: Twenty-two patients with stage III melanoma were subjected to this study in our clinic. Ultrasound examination was performed with ACUSON SEQOIA 2000 ultrasound device. Multifrequent probe, with frequency level from 5 to 8 Hz was used. All lymph nodes were examined in B-real time mode, pulse Doppler and power modem settings. Sensitivity and specificity of method was determined with histopathological examination.

Results: Sensitivity of the ultrasound lymph nodes characteristics was shown as follows: echogenicity of lymph node - 81.8%, type of lymph node vascularization 90.9%, intranodal lymph node vascularization - 77.2 with resistance index sensitivity of 81.8%.

Conclusion: The data shown are obtained in the early phase of the study. The research is still being performed in our institution.

Background: IMTs are mesenchymal neoplasms with benign or locally invasive, malignant growth pattern. They appear mostly in immunodeficient patients (infections and malignancy). IMTs were referred before as an inflammatory pseudotumor, but according to a recent, 2004, WHO classification of lung tumors, inflammatory myofibroblastic tumor (IMT) is a mesenchymal lung neoplasm.

Methods: We analyzed biological behavior of 20 IMTs diagnosed in last ten years on operated tissue obtained as segmental resection, lobectomy or pneumonectomy.

Results: Macroscopically, IMTs were presented as solid, yellowish, endoluminal mass. 17 IMTs were solitary nodules without necrosis and 3 IMTs were multinodular with one central, necrotic and large nodule. It was surrounded by a few smaller, necrotic, "satellite" nodules, involved mediastinal pleura and penetrating in mediastinal fat tissue. Morphologically, tumor contained spindle cells arrayed in fascicles with or without mild nuclear pleomorphism and seldom mitoses. Spindle cells showed myofibroblastic differentiation, histochemically by van Gieson, Masson - trichrome, Retikulin (Gordon-Sweet method) and Periodic-Acid-Shiff (PAS) and immunohistochemically by vimentin, desmin and α -smooth muscle actin positivity. Ki67 was applied for determination of tumor proliferation capability. After surgery, all 17 solitary IMTs did not recidivate. Three benign form of IMTs were associated with tuberculosis or tuberculoma and two with lung adenocarcinoma. One malignant form of IMT even with involvement of mediastinal lymph nodes was diagnosed in HIV positive patient.

Conclusion: The criteria for IMTs malignancy, despite cellular pleomorphism, mitoses and necrosis, are their multinodular, aggressive growth pattern. It still remains a question whether aggressive IMT, as truly mesenchymal neoplasm, not pseudotumor, should be oncology treated as malignant neoplasm or frequent, postsurgery examinations are enough for their follow up.



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First experiences in the treatment of painful bone metastasis

Lung cancer frequency in registry of oncology dispensary Gornji Milanovac in the period January 2001 - September 2005

KEYWORDS: Neoplasm Metastasis; Bone and Bones; Pain; Radiopharmaceuticals

KEYWORDS: Lung Neoplasms; Incidence; Smoking

Background: Bone metastases are a common complication in patients with prostate, breast, lung and kidney cancer. The therapeutic approach is currently based on pain palliation.

Methods: We report our first experience in the treatment of painful bone metastasis with Strontium-89 (^{89}Sr) and Samarium-153 (^{153}Sm). Five patients were treated with ^{89}Sr , while six doses of ^{153}Sm were administered to 4 patients. Before therapy bone, scintigraphy was made with Tc-99m- DPD in order to verify number, localization and the extent of bone metastasis.

Results: The results showed that we achieved lowering of pain, improved quality of life and reduced the need for analgesics. The effects lasted from 1-3 months after therapy.

Conclusion: The use of radiopharmaceuticals in the treatment of painful bone metastasis is simple, well tolerated and can be combined with other forms of therapy.

Background: Lung cancer is the most frequent malignant disease in males, and one of the most frequent in females, in our country and worldwide. The incidence of the disease in EU countries is 52.5/100 000 (in males 79.3 and in females 21.6). Standardized incidence rate in Serbia is 80.9. There is a lot of evidence that smoking plays the central role in the pathogenesis of lung cancer, both in males and females. An important role in the pathogenesis of lung cancer is also attributed to air pollution, working in uranium mines and working with asbestos. WHO histological types of lung cancer are squamous cell, small cell, adenocarcinoma, large cell carcinoma, adenosquamous cell type, neuroendocrine tumors, bronchioalveolar carcinoma and others. The aim of the study was to present the number of lung cancer patients in the municipality of Gornji Milanovac between January 2001 and September 2005 and to establish the incidence of lung cancer according to age, sex, histological type, and the main risk factor- smoking. All patients have been registered at the Oncology Dispensary of Gornji Milanovac.

Methods: Between January 2001 and September 2005, 76 lung cancer patients were registered at the Oncology Dispensary of Gornji Milanovac, 58 male and 18 female. Thirteen patients were registered in 2001, 10 in 2002, 16 in 2003, 17 in 2004, and 20 until September 2005. Average age for male patients at presentation was 61, and 53 for female patients.

Results: Forty patients were diagnosed with squamous cell carcinoma, 20 with small cell carcinoma, and 16 with adenocarcinoma. Among 53 male patients, 33 had squamous cell carcinoma, 17 had small cell carcinoma and 8 had adenocarcinoma; among 18 female patients, 7 had squamous cell carcinoma, 3 had small cell carcinoma and 8 adenocarcinoma. 61 out of 78 patients were heavy smokers (long term smoking habits and over 25 cigarettes per day) and 15 nonsmokers (9 male and 6 female). In nonsmokers, 8 had squamous cell carcinoma and 5 had adenocarcinoma.

Conclusion: The number of lung cancer patients in the municipality of Gornji Milanovac increased between 2001 and 2005. It is more frequent in male patients than in females (3:1). The most frequent histological type in males is squamous cell and in females adenocarcinoma. Most of the patients are heavy smokers.



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Role of ^{99m}Tc-MIBI in the evaluation of single pulmonary nodules - our first experience

KEYWORDS: Lung Neoplasms; Diagnosis Differential; Technetium Tc 99m Sestamibi

Background: Evaluation of single pulmonary nodules might be a problem in cases when invasive procedures (such as bronchoscopy) are not available for different reasons. In those cases application of ^{99m}Tc-MIBI as noninvasive procedure might be useful diagnostic modality in management patients with single pulmonary nodules. The purpose of the study was to assess the possibility of using ^{99m}Tc labeled 2 -methoxy isobutyl isonitrile (MIBI) to differentiate benign from malignant single pulmonary nodules.

Methods: Our study was done in 11 patients with single pulmonary nodules (9/11 were malignant and 2/11 benign lesions). Before definitive diagnosis (bronchoscopy and histopathologically report) all patients were completely evaluated by their physicians (anamnesis, examination, chest X-ray, CT) and by ^{99m}Tc-MIBI SPECT scanning. Early SPECT scan was done 10 minutes after the intravenous injection of 740 MBq ^{99m}Tc-MIBI using Gama-camera 'Siemens-Orbiter' and low energy high-resolution colimator. Delayed scan was performed 60 minutes after the application of radionuclide. Sixty scans (each 10 sec.) were made during the Gama-camera rotation and saved in 64x64 matrix. Assessment of MIBI uptake in solitary pulmonary nodules was done qualitatively, by visual analyzing of increased accumulation in pulmonary nodule or equal with surrounding tissue.

Results: Increased uptake of ^{99m}Tc-MIBI corresponding to the location of the nodule was found in 7/9 (78%) patients with malignant lesions. Histologically, there were 5/9 adenocarcinomas, 2/9 large cell carcinomas, 1/9 squamous cell Ca and 1/9 was the metastases of colon adenocarcinoma in the lung. Two patients with benign lesions had negative MIBI scans.

Conclusion: This preliminary study shows that ^{99m}Tc-MIBI might be an useful noninvasive diagnostic procedure in the evaluation of malignant single pulmonary nodules.

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Postoperative complication after regional node dissection in melanoma patients

KEYWORDS: Melanoma; Lymph Node Excision; Postoperative Complications

Background: Surgical treatment of melanoma patients has been so far ultimate treatment option. Dissection of regional lymph nodes can be performed simultaneously with excision of primary lesion or can be delayed and performed or without sentinel lymph node biopsy (SNB). Removing metastatic lymph nodes provides secondary metastases of melanoma. Elective dissection has been replaced with SNB, which became a standard in treatment and diagnostics. The number of postoperative complication is decreased due to the appropriate surgical procedure (S incision for inguinal dissection).

Methods: At the Institute of Oncology and Radiology of Serbia we had average 180 patients per year during 2002/2003.

Results: In average 59 patients have dissection of regional lymph nodes (axillary 28, inguinal 21, neck 5, retroperitoneal 5) per year. In 53 patients (90%), we performed dissection with positive clinical status. In 6 patients (10%), we performed dissection after positive SNB status. In 3 patients, we performed transposition of sartorius muscle. The most common postoperative complication was prolonged voluminous seroma - 39 patients (70%), wound infection (opaque to purulent seroma): inguinal 5-25% (4 out of 5 patients had dehiscence), axillary 2-7%, postoperative hemorrhage 1 - 0.5%. Seroma, infection and dehiscence are more common in inguinal dissection due to weak vascular network in that region, contact with scrotal and peranal region and thin skin flaps. All patients had at least 5 day antibiotic therapy in postoperative course. Patients who had dissection after SNB + had fewer number of postoperative complication because dissection was not as extensive.

Conclusions: Correctly done and on time, dissection of regional lymphatic in melanoma patients, significantly increase prognosis. The most common postoperative complication in our patients was prolonged voluminous seroma with or without infection. Incidence can be reduced using meticulous surgical technique and performing careful lymph stasis. Inguinal dissections have significantly higher number of complication in comparison to other regions.