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## Monitoring serum levels of different aminoglycosides during febrile neutropenia caused by nephrotoxic therapy

**KEYWORDS:** Fever; Neutropenia; Antineoplastic Agents; Drug Toxicity; Kidney; Aminoglycosides; Cisplatin

**Background:** With the progress of cytotoxic therapy, fever in cancer patients has been closely linked with infection, especially when the patient is granulocytopenic. Since fever can be the only sign of infection in neutropenic patients, its appearance commands a series of diagnostic and therapeutic measures to be taken empirically, without the precise knowledge of the nature and cause of the infection. It should be emphasized that the beneficial effect of aminoglycoside-containing combinations with broad spectrum beta-lactam has been used primarily in severely neutropenic patients. Beside the aminoglycosides marked therapeutic efficacy, their main drawback has been occurrence of nephrotoxicity and ototoxicity in a significant number of patients. However, nephrotoxicity has been a major side-effect in many of chemotherapeutic combinations which include cisplatin. The aim of this work was to investigate the possible existence of increased nephrotoxicity caused by once daily aminoglycosides in febrile neutropenic patients who were previously treated with nephrotoxic chemotherapy.

**Patients and methods:** Thirty one patients with metastatic tumors received standard chemotherapy and, as a result, developed febrile neutropenia. Patients were randomized in regard to treatment with cisplatin chemotherapy (n=15) or chemotherapeutic regimen without cisplatin (n=16). Both groups received intravenous empiric treatment which included combinations of once daily aminoglycosides (amikacin 15 mg/kg or gentamicin 4 mg/kg) with beta-lactams (ceftriakson 2 g).

**Results:** An analysis of the heightened and cumulative nephrotoxicity of administered aminoglycosides, between cisplatin and noncisplatin patients, revealed a significantly greater occurrence of nephrotoxicity ( $p < 0.05$ ) in those who received cisplatin chemotherapy regimen. An analysis of increased nephrotoxicity revealed a statistically significant difference between various aminoglycosides regimens ( $p < 0.05$ ) manifesting as a greater occurrence of nephrotoxicity in the gentamicin compared to the amikacin groups, predominantly in the cisplatin chemotherapeutic regimen.

**Conclusion:** These results have shown that cisplatin chemotherapy regimen followed by once-daily aminoglycosides regimen causes heightened renal toxicity, which is more pronounced in patients treated with gentamicin.

## Predictive factors for chemotherapy induced toxicity in advanced head and neck cancer patients: An univariate analysis

**KEY WORDS:** Chemotherapy, Adjuvant; Drug Toxicity; Head and Neck Neoplasms; Carcinoma, Squamous Cell; Factor Analysis, Statistical

**Background:** The aim of this work was to determine the predictive factors associated with toxicity of neoadjuvant chemotherapy in locoregionally advanced squamocellular head and neck cancer patients, by univariate analysis.

**Patients and methods:** During the period between July 2002 and July 2004 at the Institute of Oncology and Radiology of Serbia, 98 patients with IV B disease stage were treated with neoadjuvant chemotherapy 5-fluorouracil-cisplatin potentiated with cytosinearaboside. Patients median age was 54 years (range: 34-71); mesopharynx-34, hypopharynx-27 and larynx-37; most of them were males (93/98). In order to assess toxicity prediction, we analyzed the following parameters: gender, initial performance status, weight loss, smoking and drinking habits, concomitant diseases, tumor location, TNM status and initial presence of anemia, leucocytosis and thrombocytosis. All assessed toxicities were graded according to National Cancer Institute Common Toxicity Criteria (version 3.0).

**Results:** Patients with the presence of any concomitant disease more frequently developed neutropenia gr. 3/4 ( $p < 0.05$ ). Laryngeal cancer patients had significantly less thrombopenia gr. 3/4 than hypopharyngeal cancer patients ( $p < 0.05$ ) and significantly less neutropenia gr. 3/4 compared to patients with carcinoma mesopharynx i.e. hypopharynx ( $p < 0.01$  in both cases). Also, presence of nausea was significantly less frequent in laryngeal cancer patients than patients with hypopharynx carcinoma ( $p < 0.05$ ). Other toxicities were not significantly related to aforementioned parameters.

**Conclusion:** Concomitant diseases and tumor location were significantly associated with hematological toxicities. Further studies with larger sample size are needed to assess and examine and the predictive factors associated with chemotherapy toxicity in this localization of malignant diseases.



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## Cisplatin or carboplatin-based regimens for small-cell lung cancer – a randomized phase III study

**KEYWORDS:** Lung Neoplasms; Carcinoma, Small Cell; Cisplatin; Carboplatin

**Background:** During the past decade there was a trend to replace cisplatin by carboplatin in the treatment of various malignancies, mainly because carboplatin is easier to manage in everyday practice and because toxicities might be more tolerable. There is a growing evidence that these two analogues are not therapeutically equal; cisplatin represents the superior one in various solid tumors. Results of only a few randomized trials conducted in small-cell lung cancer (SCLC) patients are available and mainly suggest that the two drugs are equal in the activity expressed both as response rate and survival. The aim of the present study was to compare the efficacy of cisplatin and carboplatin in SCLC patients.

**Patients and methods:** From 1995 to 2003, 101 chemotherapy and radiotherapy naive patients with histologic confirmation of SCLC were included in phase III of single-center open prospective randomized study. The group A recruited 52 patients (47 evaluable for response and toxicity) who received etoposide 120 mg/m<sup>2</sup> i.v. (days 1, 3 and 5) and cisplatin 100 mg/m<sup>2</sup> (day 1). The group B recruited 49 patients (46 evaluable) who received etoposide 120 mg/m<sup>2</sup> (days 1, 3 and 5) and carboplatin 400 mg/m<sup>2</sup> (day 1). The cycles have been repeated on 28 days in both groups.

**Results:** Two groups were well balanced according to age, sex, performance status, presence of either limited or extensive disease and median number of applied cycles. There was no statistically significant difference in response rates – 67.3% in group A (95% CI [53.8, 78.5]) versus (vs.) 57.2% in group B (95% CI [43.3, 69.9]). There were two toxic deaths in group A (3.8%) and none in group B. The median survival time in the cisplatin group (arm A) was 12 months (95% CI [10-17]) vs. 10 months (95% CI [9-11]) in the carboplatin group (arm B). This difference was statistically significant in favor of group A, i. e. the cisplatin group ( $p=0.041$ ). There was a trend towards better survival in patients with limited-stage of disease in group A, 16 months (95% CI [11, +∞]) vs. 12 months (95% CI [9,20]) in group B ( $p=0.055$ ). One-year survival was better in group A (17 out of 52 patients) in comparison to group B (8 out of 49 patients) ( $p=0.057$ ). Grade 3 and 4 of hematological toxicities were more experienced in the group B, i.e. the carboplatin group (neutropenia grade 3,  $p<0.05$ ; thrombocytopenia grade 4,  $p<0.01$ ).

**Conclusion:** On the basis of these results, substitution of cisplatin by carboplatin in SCLC patients does not appear to be justified in everyday practice until results of confirmatory randomized studies clearly demonstrate whether the activity of these two platinum compounds is really similar. At the moment cisplatin could be the preferred analogue for majority clinical settings of SCLC.

## Prognostic parameters at the patients with colorectal cancer diagnosed at the loco-regionally stage of disease

**KEY WORDS:** Colorectal Neoplasms; Prognosis

**Background:** Treatment of the loco-regionally stage of colorectal cancer is performed with curative aim. We analyzed the influence of the parameters of the initial status and therapy to the further course and duration of disease.

**Patients and methods:** During the period 1990-2000, 123 patients with loco-regional colorectal cancer were treated at the Dispensary of Oncology in Kruševac. They were observed 60 months after the surgery.

**Results:** Progression of disease was observed at the 71 (57.7%) pts., averagely after 25.5 months. The highest incidence of relapses was observed in left colon cancer (71%) and pts. with poor performance status (83%), and the lowest after the amputation of the distal part of rectum (45%) and adjuvant chemotherapy (36%). Duration of the disease-free interval was the longest at the youngest (30.4 months) and pts operated at the specialized centers in Belgrade and Niš (43.6 months) respectively to 21-23 months at the males, pts. With poor outcome and operated in the regional center overall survival was 61 months. Disease had the longest extension (86 months) at the rectal cancer and pts operated in the specialized centers, followed by pts with good outcome and treated with adjuvant chemotherapy (61 months). Shortest duration (30-39 months) of diseases was observed at the oldest and pts with severe symptoms, after hemicolecotomy or operated in the regional center.

**Conclusion:** Based on these data we consider that, among curatively operated pts., most favorable course of the colorectal cancer should be expected in pts. without symptoms, operated at the specialized centers and treated with postoperative radiotherapy and adjuvant chemotherapy.



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## Carcinoma of the breast – the importance of locoregional treatment of metastatic disease: Case report

**KEYWORDS:** Neoplasm Proteins; Carcinoma; Neoplasm Metastasis; Radiotherapy

Solitary breast cancer metastases in brain, liver, skeleton, and other organs are generally thought to be the sign of disseminated disease, requiring the systemic therapy. However, radical locoregional treatment of solitary metastases sometimes offers not only the possibility to substantially improve the duration and quality of life of our patients, but also to cure them. A 54 year old postmenopausal female patient started oncology treatment in January 2001, when she noticed the right breast mass. Preoperative staging at diagnosis was T3,N2,MO. FNAC of suspect tumor lesion in upper lateral quadrant was done and cytological finding confirmed the malignancy of the breast. Neoadjuvant chemotherapy with CAF regimen was applied from January 2001-May 2001, four cycles in total. After that, radical mastectomy of right breast was performed in May 2001. Pathohistological finding in breast was: Chronic fibrous mastopathy and nonspecific chronic mastitis, while the examination of axillary tissue showed the chronic lymphadenitis, without any sign of malignancy. Four lymph nodes were examined and none of them contained malignant tissue. Both steroid receptor status was positive (ER+, PR+) and breast cancer committee decision was to continue with adjuvant endocrine therapy with tamoxifen (Nolvadex®). In June 2002 the endocranial CT scan was done, showing the solitary metastatic lesion, while the careful examination of all other organs was negative. Then, the complete brain tumor mass was extirpated. Pathohistological examination suggested the adenocarcinoma or planocellular metastatic cancer. In August 2002 patient was submitted to postoperative radiotherapy of whole brain with TD 30 Gy in 10 fractions. Until now, the patient had regular control examinations every second month, during the first year, every fourth month in second, and than every sixth month from the third year. In March 2006, she was still disease-free, without any sign of disease progression and in a very good and stable overall condition. This case report confirms that the adequate loco regional treatment may offer the probability of good local control, not only of primary tumor, but also of metastatic disease.

## The prolonged time of survival of the patient with secondary deposits in liver and possible cancer of pancreas (case report)

**KEY WORDS:** Pancreatic Neoplasms; Neoplasm Metastasis; Liver Neoplasms; Survival Rate

The cancer of pancreas belongs to a group of the most aggressive visceral malignity with five years survival rate of 0.9% for men and 0.5% for women. The average survival time of the patients with inoperable cancer is 5 months. The purpose of this study is to present the review of prolonged time of survival in a patient with secondary deposits in liver and possible cancer of pancreas. A 50 year old patient complained about severe pains in upper medium part of abdomen, with propagation in the back and distention of abdomen, which were persisting in last two months with repetition of several times. Beside clinical examination, electrocardiography was done. The laboratory analysis showed higher values of - LDH 540 U/l, Alkal phosphatase 281 U/l, GAMA GT 188 U/l, Se 37, Le  $16.9 \times 10^9/l$ , Hb 78.1 g/l. The time of bleeding and PV were within physiological values, HbsAg and HCV were negative and tumor markers (CEA 3.82 ng/l, CA19-9 63 IU/ml, AFP 5 IU/ml, CA125 103.5 U/ml). Echosonography showed the following: AP diameter of liver 145 mm, with numerous secondary deposits in both slices, with the greatest clearly visible deposit of about 5 cm. The rest of abdominal organs had regular morphology. Radiology examination of the head, hole spine in both directions, pelvis and the lungs determined the normal morphology of tissue without any secondary deposits. CT of the abdominal region determined secondary deposits in liver from 3 to 11 cm big, and the rest of abdominal organs had normal morphology. CT of the endocranial region determined no signs of extravasation or expansive intracranial processes. Also the laparoscopic biopsy of liver was done (HPDg). The patients was diagnosed clinically as Tu caudae pancreatis cum meta in hepate, and histopathological diagnosis was Carcinoma metastaticum hepatis et carcinoma infiltrativum peritonei. According to the consiliar decision, it is recommended the use of systematic chemotherapy CDDP-inf.5-FU-LV (Degramont). After 12 months and completed XII cycle of the chemotherapy, the patient was without any discomforts based on her primary illness. Clinically and by echosonography there was no sign of the illness progression, and after VI cycle of the chemotherapy, values of tumor markers were normalized. After XII cycle, the value of tumor marker Ca125 was 103.5 IU/ml. The patient is still under observation.



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## Importance of collaboration between departments of surgery and oncology in the treatment of patients with colorectal cancer

**KEY WORDS:** Colorectal Neoplasms; Colorectal Surgery; Medical Oncology; Cooperative Behavior

**Background:** Although surgery is the basic treatment of colorectal carcinoma, in modern approach to this disease, great importance is given to the radio- and chemotherapy, which should start during first 2 months after operation.

**Patients and methods:** We investigated the duration of period after operation and the first patient contact with oncological services with its influence to the further course and overall duration of the disease at the 227 patients with colorectal cancer treated in Dispensary of Oncology Kruševac through period from 1990 to 2000.

**Results:** Median age of all patients was 61 (interval 34-83) years, with almost equal contribution of both genders. Median duration of the period between surgery and first visit to the Dispensary is 10 months, and almost half (mostly curatively operated and patients older than 50) missed the optimal period, so they made the majority (86%-75%) of missed radio- and chemotherapies. In the group of curatively-operated, overall survival of patients who advised Dispensary during first two months was 17 (78:61) months longer than the others, and the occurrence of relapse is 15% (50:65%) less frequent and 6 (21:15) months delayed.

**Conclusion:** Collaboration between surgical and medical oncologists is necessary in the attempting to make the best treatment of the patients with colorectal cancer.

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## Our selection criteria for conservative vs. radical surgical treatment of breast cancer

**KEYWORDS:** Breast Neoplasms; Surgery; Drug Therapy; Mastectomy; Decision Making

**Background:** Our goal is to evaluate the outcome of operations we performed at the Dept. of Breast Cancer Surgery at the Institute of Oncology and Radiology of Serbia in relation to the tumor size and the type of surgical procedure in breast cancer patients.

**Patients and methods:** During the years 2003 and 2004 we performed 1310 modified radical mastectomies (Madden) and 356 quadrantectomies with axillary dissection. We analyzed 137 randomly chosen patients who had quadrantectomy with axillary dissection and 132 randomly chosen patients who had modified radical mastectomy. According to our protocol at the Institute of Oncology and Radiology of Serbia, indications for quadrantectomy with axillary dissection are tumors less than 30 mm in diameter. The average age of our breast cancer patients was 55.9 years (range 40-80).

**Results:** Our analysis shows that 83.2% of the patients who had quadrantectomy with axillary dissection had tumor less than 20 mm and 97.1% had tumor less than 30 mm in diameter. Out of 132 patients who had mastectomy 45.4% had a tumor less than 20 mm and 81.8% had tumor less than 30 mm in diameter, meaning that they were good candidates for quadrantectomy with axillary dissection.

**Conclusion:** The results obtained meet the international standards as far as indications for quadrantectomy with axillary dissection are concerned. We are still not satisfied with a large number of mastectomies performed at our Institute and we think that we should set up higher standards that must be followed more strictly during the process of decision-making in setting up an indication to perform a mastectomy.



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## Conservative breast cancer surgery – relationship between tumors size and axillary lymph node status

**KEYWORDS:** Breast Neoplasms; Surgery; Lymphatic Metastasis; Prognosis

**Background:** The aim of our study was to analyze pathohistological findings in our patients who had conservative surgical procedure and to find a relationship between tumor size and axillary metastases.

**Patients and methods:** During the year 2004 we treated 925 patients with breast cancer at the Dept. of Breast Cancer Surgery at the Institute of Oncology and Radiology of Serbia. Out of 925 patients, 708 had modified radical mastectomy and 217 had quadrantectomy with axillary dissection. We performed quadrantectomy with axillary dissection in patients who were preoperatively staged as T1NoMo. We analyzed pathohistological samples of 72 randomly chosen patients after conservative breast surgery.

**Results:** These were the tumor sizes of our patients: a) tumor size <2 cm – 79.2%, b) tumor size 2-3 cm – 16.6%. c) tumor size >3 cm – 4.2%. We also analyzed postoperative axillary lymph node status: a) negative axillary lymph nodes – 66.7%, b) 1-3 positive lymph nodes – 20.8%, c) > 4 positive lymph nodes – 12.5%. Comparison of tumor size to axillary lymph node status: a) pT1a (1-5 mm) – 0% + Igl, b) pT1b (6-10 mm) – 12.5% + Igl, c) pT1c (11-20 mm) – 37.5% + Igl, d) pT2 (> 20 mm) – 47% + Igl.

**Conclusion:** We can conclude that tumor size is an excellent predictor of axillary lymph node status. On the other hand, presence or absence of axillary metastases is important as a prognostic factor and a factor which determines further treatment.

## Morphological analysis of estrogen receptor negative and HER2 receptor negative (ER-/HER2-) breast carcinomas

**KEY WORDS:** Receptors, Estrogen; Receptor, erbB-2; Breast Neoplasms; Immunohistochemistry

**Background:** Expression profiling studies classified breast carcinomas into ER positive or luminal, normal breast – like, HER2 overexpressing and basal-like groups with the latter two associated with poor outcomes. The aim of this study was to assess the morphological characteristics of ER-/HER2- tumors and thus to understand the biological behavior and unique nature.

**Patients and methods:** One hundred and twenty four breast carcinomas were evaluated using immunohistochemistry (IHC) for ER, PR and HER2 receptor. Hematoxylin-eosin stained sections of all the cases were studied for several morphological parameters. These findings were correlated with tumor characteristics.

**Results:** Results showed that ER was negative in 34.4% of tumors. ER-/HER2 – tumors constituted 8.3% of the our breast cancer series. The majority of tumors were grade 3 (93.3%) and the commonest histological types were ductal (80%) and lobular carcinoma (13.3%). Central acellular zones, spindle, clear and giant cell change, high mitotic activity, lymphoid stroma, pushing margins, comedo type necrosis and negative lymph nodes were the most common morphological features. The presence of a pushing margins and negative lymph nodes showed a significant relation to ER and HER2 receptor negativity.

**Conclusion:** ER-/HER2- breast carcinomas are a distinct group of tumors with several common morphological features. These unique characteristics support the concept that ER-/HER2- tumors are a morphologically distinct entity. Further immunohistochemical research is recommended to explain the observed results.



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## Concomitant chemoradiation in unresectable advanced ovarian cancer patients

**KEYWORDS:** Ovarian Neoplasms; Antineoplastic Combined Chemotherapy Protocols; Radiotherapy

**Background:** Following effects of chemoradiation in advanced ovarian cancer in nonrandomized retrospective analysis. The usual regimens include combination or initial chemotherapy or cisplatin-epirubicin-cyclophosphamide (PEC) and whole abdominal radiation (WAR), at unresectable advanced ovarian cancer.

**Patients and methods:** In period from January 31, 2001 to January 31, 2006, 61 patients were treated with unresectable ovarian tumor in abdomen. 6 (9.84%) are in FIGO stadium IIIb, while 55 (90.16%) patients are in FIGO stadium IIIc.

**Results:** Ordinary age of patients is 55 (from 30 to 67). Karnofsky status from 80 to 100, LVEF >55% were eligible, adequate bone marrow, renal and hepatic function. Treatment started with one to two cycles (median of 2 cycles) chemotherapy by PEC regime (cysplatine 50 mg/m<sup>2</sup> – epirubicine 60 mg/m<sup>2</sup> – cyclophosphamide 500 mg/m<sup>2</sup>). Continuing with WAR 30 Gy in 18 fractions in duration from 5 to 7 weeks (approximately 6 weeks). 2 or 3 cycles of chemotherapy were delivered by the same regime. All patients underwent treatment. Leucopenia grade 3 to 4 appeared in 9 patients (4.5%), anemia grade, in 3 of 11 patients (18.3%), diarrhea in 47 (77%) patients (grade 2). All patients had reduction or normalization of CA 125 (serology partial or complete response), and 37 patients (60.66%) had patients complete and partial response by standard WHO criteria. Median progression-free survival is 10 months (range from 3 to 56 months), 1-, 2- or 3 – years PFS 43%, 21%, and 8%. Median overall survival (OS) is 12 months (range from 7 to 60 months) and one-year and three-year survival is 44.3% and 12.4%. Second line taxane based chemotherapy received 43 (70.01%) with progression of disease.

**Conclusion:** The combination of chemotherapy cum PEC and WAR is an effective and tolerated and unresectable advanced epithelial ovarian cancer. Thus far chemoradiation is promising and it warrants further investigation.

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## Lobular carcinoma *in situ* (LCIS) of breast: Incidence and diagnostic problems

**KEY WORDS:** Breast Neoplasms; Carcinoma, Lobular; Epidemiology; Carcinoma, Ductal, Breast; Carcinoma in Situ; Non MeSH Serbia

**Background:** The aim of this study is to demonstrate the frequency of LCIS on the territory of Central Serbia (1.000.000 inhabitants) and to point out the problems in diagnostic and treatment of this lesion.

**Patients and methods:** The material, used in the retrospective study, has been taken from Surgery Clinic, Oncological Center and Center of Pathology, for a period of five years (2001-2005). Only the patients from the territory of Central Serbia have been monitored.

**Results:** From the total number of all forms of breast cancers (459), there were 179 or 38% inoperable cancers (T4 or N2). There were 4 or 0.68% Carcinoma *in situ*, namely 4 Ductal carcinoma *in situ* (DCIS) and 0 LCIS. 15 atypical lobular hyperplasias have been also diagnosed in this period of time. Since an immunohistochemistry was not accessible, these patients were also classified in a group with an increased risk for getting invasive cancer. To all of them has been proposed to visit the doctor every 6 months. The rest of them (280) had invasive cancers in T2 and T3 stage. Even 121 of patients had already metastases in regional lymph glands.

**Conclusion:** At the moment there is no high-quality and mandatory breast cancer screening on the territory of Serbia. By organizing such of screening, there would be a possibility to diagnose greater number of carcinomas *in situ*. Immunohistochemistry could be rationally used and would be very helpful in high-grade and precise diagnostic of LCIS and in possible preventive using of tamoxifen. All above mentioned would be aimed to prevent appearance of invasive cancer by these patients.