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LETTERS TO THE EDITOR

Bisphosphonate-associated orbital inflammation: is it class-specific side effect?

Dear Editor,

Bisphosphonates are synthetic pyrophosphate analogs. They are effective inhibitors of osteoclast-mediated bone resorption and significantly reduce the incidence of skeletal complications in patients with benign skeletal disease such as osteoporosis and Paget's disease and patients with bone metastases from breast, prostate and lung cancer. Orbital inflammation including conjunctivitis, uveitis, scleritis, episcleritis, and keratitis is a rare side-effect of bisphosphonates. Overall, the incidence of orbital inflammation after bisphosphonate exposure ranges from 0.046 to 1%. Bisphosphonate-associated orbital inflammation is thougt to be a relatively nonspecific immune response to local tissue toxicity [1]. The majority of these cases reported in the literature were associated with zoledronate. However, orbital inflammation associated with zoledronate may be due to the higher potency of the drug or more common use of this drug. Case reports related to other bisphosphonates including etidronate, clodronate, pamidronate and oral ibandronate were presented in the literature [2,3]. However, intravenous ibandronate-associated orbital inflammation has not been reported. This might be due to less often use or less potency of this drug. A third probability might be due to class effect of intravenous ibandronate. This proposal needs to be confirmed.

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Association of non-Hodgkin´s lymphoma with advanced endometriosis

Dear Editor,

We reviewed 860 women with endometriosis and 320 without, between 2000-2016. Among them, we reported 4 cases (0.47%) with follicular non-Hodgkin's lymphoma (NHL) in the endometriosis group, which were confirmed by lymph node biopsy, bone marrow biopsy and imaging. The Human Committee of Yale University School of Medicine and the Venizeleio Hospital Ethics Committee for Human Research of Crete approved this study.

Case 1

A 33-year-old Caucasian woman presented with swollen painless generalized lymphadenopathy. Excisional biopsy of a cervical lymph node showed follicular NHL, grade 1 and bone marrow biopsy showed infiltration by lymphoid B cells.

There was a positive family history for endometriosis (sister, aunt). Routine abdominal ultrasound at the age of 17 demonstrated an enlarged adnexal mass after 6-month treatment with combined oral contraceptive pills (cOCPs). The patient underwent laparotomy for removal of an ovarian endometrioma (endometriosis stage III).

Case 2

A 51-year-old, menopausal nulliparous woman presented with swollen and tender abdomen. She reported unexplained weight loss, drenching night sweats and feeling full after a small amount of food intake.
Spleen biopsy showed grade 2 follicular NHL.

At the age of 30, she had undergone laparotomy for removal of the right ovary due to an endometrial cyst (endometriosis stage IV).

Case 3

A 40-year-old white multiparous woman presented with painless, swollen lymph nodes in the groin. Lymph node biopsy confirmed the diagnosis of follicular NHL.

The patient's grandmother and mother were diagnosed with endometriosis, stage IV, in young age. On routine transvaginal scan of the patient, an ovarian cyst increased the suspicion for endometriosis. The patient was operated laparoscopically (endometriosis stage IV).

Case 4

A 46-year-old white primiparous lady presented with a painless lump in the right breast and enlarged axillary lymph nodes.

Excision biopsy of axillary nodes indicated grade 2 follicular NHL.The bone marrow biopsy showed infiltration by B cells.

At the age of 35 she was operated laparoscopically, where endometriosis was confirmed (stage III). Postoperatively the patient was treated with Danazol for 5 months and cOCPs for 5 years.

Women with endometriosis have 40% higher risk for developing hematopoietic malignancies, mainly NHL [1]. Previously, Matalliotakis et al. conducted a retrospective study, where they reported 10 out of 405 (2.5%) women with endometriosis and first-degree relatives with NHL, suggesting a link between a family history of NHL and the development of endometriosis in the first-generation women [2].

Additionally, endometriosis has been linked to generalized polyclonal B-cell autoimmune alteration. This condition lead to the development of B–cell lymphoma via an autoimmune response where lymphocytes are abnormally increased [3].

Data show that increased lymphatic vessel density in the eutopic endometrium may promote the entry and survival of endometrial cells into the lymphatic circulation. Moreover, Danazol seems to have immunosuppressive effects on lymphocyte proliferation and autoantibody production and may also play a role in lymphomas [4]. Other studies support that hormonal contraception may affect the risk for particularly follicular type of NHL [5].

Our cases may support a possible link between endometriosis and NHL and might demonstrate an increased risk of developing neoplasia in patients with a history of advanced stages of endometriosis.

Acknowledgement

We would like to thank Prof. I.Matalliotakis for providing the data used in this study

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A brain ependymoma with psychiatric manifestation

Dear Editor,

A 47-year-old man came after a public prosecutor's order (under Mental Health Act) for involuntary psychiatric examination in our Psychiatric Department. At the very beginning, the patient claimed for a plethora of medical conditions in his personal medical history. An hemangioma on his left half of his face was obvious. He also said that since his adolescence he started to suffer from gastric ulcer and he had to be hospitalized four times up to now due to gastrointestinal bleeding as a result of his ulcer. A cholecystectomy has been also implemented 20 years ago. Finally, 10 years ago, the patient was first diagnosed with ankylosing spondylitis which is being treated by adalimumab inj, one per month up until now. He also reported that 15 years ago he started to mention fatigue, episodes of depressed mood, decreased activity and functionality, social withdrawal, intermittent irritability, symptoms which were treated by the primary care physician of his region with antidepressant treatment - mainly paroxetine - for short periods of time during all these years, with minimal or no effect. Over the course of the last 8 months the patient begun to present more stable behavioral disturbances such as irritability, agitation, feelings of

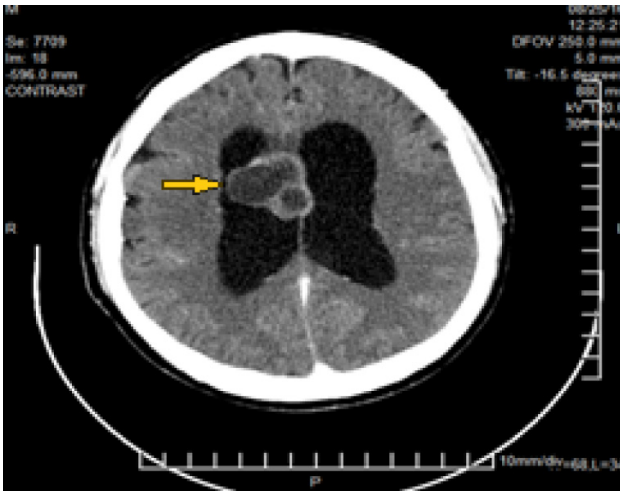

Figure 1. Axial image of brain CT showing ependymoma (arrow).

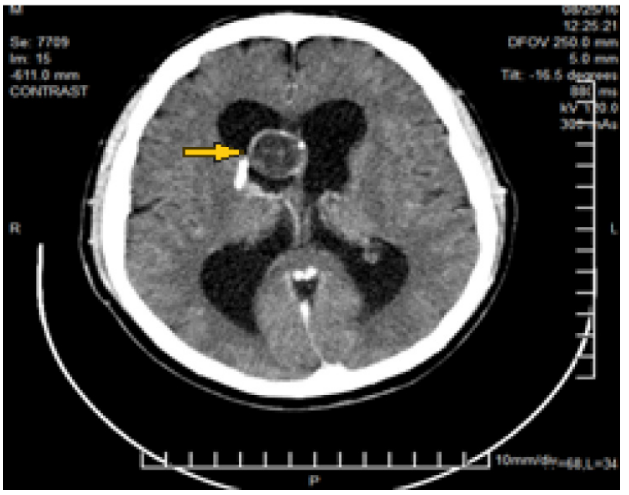

Figure 2. Axial image of brain CT showing ependymoma (arrow).

depersonalization but also delusional ideas of reference which led to frequent quarrels. These symptoms were so continuous and severe, that he was unable to work anymore. In the last few weeks prior to his examination, there was an even more intensification of all the above symptoms, while insomnia and verbal aggression were added to his clinical picture. During his psychiatric evaluation the patient showed emotional apathy. He had no alterations on the form and the process of thought, no perceptual disturbances, he was fully orientated, without cognitive dysfunction or memory loss, with good insight and judgment.

Because of the atypical picture of his psychiatric symptoms and his medical history it was decided to ask for an urgent brain CT scan. CT scan revealed a cyst (density <20HU) with smooth margins and stiff peripheral calcifications within the enlarged ventricular system (Figures 1 and 2).

On brain MRI which followed, a multi-lobed cyst with clear limits, measuring 4.7x3.5x2.8 cm was found at the level of interventricular foramen. Intravenous paramagnetic contrast agent administration demonstrated enhancement to the wall of the lesion. The lesion was in contact with the septum pellucidum and fuzzed it. It also appeared to infiltrate the ependyma at the level of the vertex of the right lateral ventricle, where edema coexisted with the above-mentioned in an extent of approximately 2.2 cm. Neurosurgical assessment followed, ependymoma was diagnosed and surgical treatment was recommended. After a very short time, he was discharged from our psychiatric department and transferred for neurosurgical treatment. Three months after the surgical removal of the ependymoma, the patient was free of psychopathology, without any medication.

The present case is a report of an ependymoma in a patient without neurological symptoms, but with severe psychiatric symptoms (depressed mood, agitation, depersonalisation, irritability, ideas of reference, insomnia, and hostility) which resolved postoperatively. Several previous reports [1,2] have indicated that tumors in this region are associated with psychiatric symptoms. Further reports and discussion will be needed to evaluate possible mechanisms of ependymoma-induced psychiatric symptoms, the relation between the region of the cyst and the type of psychiatric symptoms, and how neurosurgical interventions affect these symptoms.

In our case, the brain tumor might have been also related to gastroduodenal ulcer referred to his medical history and to the bleeding that led the patient to hospitalizations repetitively. Since 1841, it has been suggested that the ulcerative processes of the stomach might involve dysfunction of nervous mechanisms and nowdays we already know [3] that dysfunction of the central nervous system stimulates the hypothalamus, which then stimulates the sympathetic and parasympathetic nervous system and through their action contribute to the development of gastroduodenal ulcers.

In conclusion, psychiatric symptoms may be the only presenting feature of brain tumors. Thorough history and medical examination with a high index of suspicion are important for early diagnosis, especially when are present ulcerative processes. Neuroimaging should be also considered in these patients.

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Medical errors done with good intention, according to the believes of the time in the past: oncology should be evidence-based nowadays

Dear Editor,

With the present letter, we are referring to some characteristic "medical errors" done with good intention, according to the believes of the time, but proved malpractice afterwards. Practicing medicine is a very difficult work. New achievements regarding the prevention and therapy appear every day. Beyond the good intention of the pioneers and the satisfactory results of the time, specific clinical practices are proven "catastrophic" later on. There are innumerable such cases. As an example related to clinical practice in oncology, we will refer to three of the most interesting that appeared in the literature during the last decades:

1. The urologists, between 1958–1980 were prescribing estrogens for prostatic cancer, which was completely justified according to the believes of their time, while afterwards they noticed an increase of breast cancer in men [1].

2. The use of diethylstilboestrol during pregnancy in order to prevent abortion, between 1940–1960 had shown that such use was associated with a 30% increase in the risk of breast cancer in such women. Nowadays the use of diethylstilboestrol during pregnancy is banned [2].

3. The practice of prophylactic mastectomy, according to our view, needs further consideration. It is known since Beatson (1896), that breast cancer is "under the influence of the ovaries-estrogens" [3]. It has been demonstrated that bilateral oophorectomy resulted in remission of breast cancer in a premenopausal woman [4]. However, by prophylactic mastectomy a woman is submitted to a big mutilating operation, removing an organ for which she is very sensitive. But even so, is she secured from the development of a secondary cancer, especially ovarian? If she is very eager to do something because she is afraid of her heredity and predisposition why not remove the ovaries instead? We do not like to be prophets but we are afraid that the incidence of cancer in other organs related to breast, especially ovaries, will increase after prophylactic mastectomy [5].

In conclusion, once upon a time medicine was something between art and science. Nowadays, by focusing mainly in oncology, the evidence-based medicine is included more and more in clinical practice. Studying carefully the published data from randomized controlled trials and considering the beneficial and harmful effects on a patient, of any proposed treatment, is more than necessary. Believes do not matter; evidence-based medicine matters.

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Positional errors in linear accelerator based frameless cranial stereotaxy: A note of caution

Dear Editor,

Frameless stereotaxy (SRS/SRT) for cranial tumours has achieved considerable popularity because of its convenience over the invasive frame [1-5]. BrainLab (BrainLab AG, Feldkirchen, Germany) is a major stereotactic solution provider worldwide which is compatible with both Varian (Varian medical system, Palo Alto, CA) and Elekta (Elekta AB, Stockholm, Sweden) linear accelerators. Frameless stereotactic therapy delivery uses a head and neck extension as a baseplate. This baseplate is an extension to main couch and attached at the cranial end using two clips. With this arrangement, much of the patient's body lies on the main table while the head (with head rest) lies on the extended attachment. Main table and head neck extension are loosely attached to each other and act as a

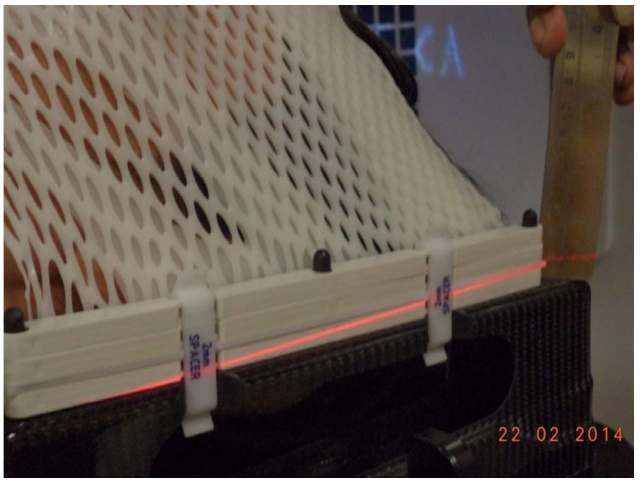

Figure 1. The laser shift due to cranial sagging attributed to the fulcrum effect is shown. The laser shift noted in this particular case was 8 mm.

lever of class 1, hence exhibit a depression in the cranial end (Figure 1). This effect is observable in both Varian and Elekta make couches. When the patient lies on the couch, the cranial end of the couch tends to go down due to gravity. This introduces an unacceptably high rotational error about the X (lateral) axis (pitch) and translational error along Z (vertical) axis depending on the position of the tumour. As shown in Figure 1 cranial end sag due to fulcrum effect is 8 mm.

In our centre regular brain tumour patients are treated with all-in-one (AIO) base plate firmly adhered to the main table. We assessed the cranial end sagging for regular cases and stereotactic cases for 90 patients by calculating the positional shifts in the three translational directions and the rotational shifts about the three axes. We found that the mean± standard deviations (SD) for the vertical shifts (ΔZ) were -0.11±0.18 cm and 0.0±0.48 cm for regular and SRS cases respectively and the mean± SD for the rotational shifts around x-axis (pitch, $\Delta\varphi^0$) were 0.33 ± 0.77^0 and 0.41 ± 1.63^0 for the regular and SRS cases respectively. However, the SDs for the other translational and rotational axes were comparable between regular and SRS cases. For example, roll mean± SD for lateral (ΔX) shift for regular and SRS cases were -0.01±0.19 cm and 0.08±0.1 cm, respectively; mean± SD for craniocaudal (ΔY) shift for regular and SRS cases were 0.16±0.21 cm and 0.05±0.17 cm, respectively; mean±SD of rotational shifts about Y-axis (roll, $\Delta\Theta^0$) for regular and SRS cases were -0.32±1.32° and 0.39±1.05°, whereas that about Z axis (yaw, $\Delta\psi^0$) for regular and SRS cases were -0.16±1.34° and -0.17±1.17°, respectively.

Therefore, we conclude that SRS/SRT patients exhibit a higher positional error in terms of SD in vertical direction and in rotational pitch than that of regular cranial cases due to the use of cranial extension. Higher SD yields a higher setup margin [5]. In the absence of a robotic couch that can account for rotational shifts in addition to the translational shifts, the residual rotational errors can result in unacceptably high error in spatial dose delivery. Hence, it may be prudent not to attempt stereotactic treatment delivery with conventional couches having only translational movements.

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Molecular landscape in laryngeal chondrosarcoma

Dear Editor,

According to the novel molecular categorization criteria, sarcoma superfamily is divided in three main pathological-genetic entities: Ewing sarcoma and also aneurysmal bone cyst are characterized by specific translocations; chondrosarcoma, fibrous dysplasia and chordoma demonstrate specific gene mutations or amplifications and finally sarcomas, such as osteosarcoma with genetic instability (gross chromosome abnormalities-aneuploidy/polysomy) including consequence complex karyotypes [1]. Chondrosarcoma represents a group of malignant cartilage tumors characterized as primary or secondary ones. Histologically, four main variants are recognized including mesenchymal, dedifferentiated, clear cell type and extraskeletal myxoid [2]. Concerning head and neck malignancies, la-

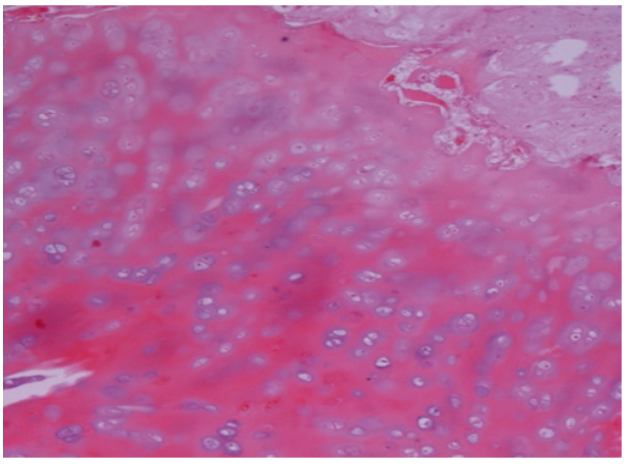

Figure 1. Typical histological pattern of a laryngeal chondrosarcoma case (original magnification 100x).

ryngeal chondrosarcomas (LCs) are rare neoplasms - only 10-12% of total chondrosarcomas - arising from the cartilaginous structures of the larynx, including the cricoid, thyroid cartilage, epiglottis, and arytenoid cartilages. In fact, the most common location is the posterolateral region of the cricoid cartilage (Figure 1). They demonstrate a low tendency to metastatic spread. Based on this biological behavior, prognosis is generally good. The treatment of choice is surgery, which may be endoscopic or "open partial surgery", if the extension of cancer is limited or total laryngectomy. The exact pathogenesis still remains to be elucidated; some aetiopathogenetic hypotheses attribute this pathological condition to local injuries, ossification anomalies, chronic inflammation and metabolic disorders related to old age.

Extensive molecular analyses in morphologically classical LCs based on fluorescence/chromogenic in situ hybridization (FISH/CISH) and/or real time polymerase chain reaction (RT-PCR) techniques have detected point mutations in genes p53 (17p13), COX-2,CD34, isocitratedehydrogenase 1-2 (IDH1-2), CD44v3, BCL-2, deletions in INK4/p16-CDKN2A (9p21), EXT1, EXT2 and also in MMAC1/PTEN on chromosome 10q genes [3]. Additionally, cyclin D1 gene (CCND1) on 11q13 and also 12q13 amplification combined or not with pRB, IHH/PTHLH/Bcl-2, Src, Akt, GADD45b, PDGFR and IGF deregulations compose a broad molecular landscape in conventional mainly LCs. Concerning specific signaling intracellular down-stream signaling transduction pathways, aberrant expression of hypoxia factors such as VEGF/HIF-1a, and CXCR4/SDF1/MMP1/RUNX2 have been reported, leading to increased angiogenesis [4]. Interestingly, the very rare clear cell type LC variant is characterized by a slightly different genetic substrate compared to the conventional LCs. A study group identified allelic loss at 9p22 and 18q21, but neither in the region of the Rb gene on chromosome 13q nor at the p53 locus on chromosome 17p, where allelic loss has already been reported in chondrosarcomas (loss of heterozygosity based on molecular analysis). Furthermore, epigenetic alterations, such as methylation of the cell cycle control gene p16 were also confirmed [5]. Despite the main genetic similarities that LCs share with conventional chondrosarcomas, specific gene numerical and structural abnormalities create a distinct entity, especially regarding the clear cell type histogenetic variant.

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The role of tyrosine kinase inhibitors (TKIs) as adjuvant treatment for renal cancer. Where do we stand today?

Dear Editor,

Primary renal cell cancer (RCC) affects 214,000 people each year with approximately one third eventually dying from metastatic disease although new targeted therapies are available including tyrosine kinase inhibitors (TKIs) for metastatic disease [1]. Prognosis as well as risk of recurrence after nephrecotmy vary widely and depend on

Table 1. Inclusion criteria and results for ASSURE and S-TRAC trials

Trial	*Histology*	*Stage*	*Results*
ASSURE	Clear cell Non-clear cell	T1b, Grade 3-4, N0 T2-T4, Grade any, N0 T any, Grade any, N+	DFS 5.8 vs 6.1 vs 6.6 (p>0.05)
S-TRAC	Clear cell	T2, Grade 3-4, N0 T3-T4, N0 T any, N+	DFS 6.8 vs 5.6 (p<0.05)

tumor stage, histopathological grade and patients' performance status [2]. In order to improve recurrence rates in patients with RCC after primary nephrectomy, a variety of adjuvant treatments were examined including interferon, hormonal therapy, interleukin 2, radiotherapy and chemotherapy. Unfortunately, none of them was successful in reducing disease relapses and improving progression free survival [3]. As a result, up until the present day, no adjuvant treatment is available in high risk patients for recurrence after nephrectomy. The gold standard for such patients is still radiological observation in order to detect as early as possible recurrences or metastasis.

As TKIs proved their role in metastatic disease by improving overall survival, there is a wide interest in their role as adjuvant treatment in RCC patients in order to reduce disease relapses. In a double-blind placebo-controlled randomized phase 3 trial (ASSURE trial), the role of adjuvant sunitinib or sorafenib for high risk non-metastatic RCC was tested. A total of 1943 patients from the National Clinical Trial Network were randomized to receive sunitinib (n=647), sorafenib (n=649) or placebo (n=647). Inclusion criteria were completely resected high risk clear cell or non-clear cell RCC, good performance status and normal liver function. Duration of therapy was 54 weeks and drug dosage was 50mg of sunitinib per day for the first 4 weeks of each week cycle and 400mg of sorafenib twice per day, or placebo. Due to toxicity leading to high rates of treatment discontinuation, the starting dosage was reduced and then titrated up to the original scheduled full dose. With regard to results, neither sunitinib nor sorafenib showed significant differences in disease-free survival (DFS) comparing to placebo. Median DFS was 5.8 years for sunitinib, 6.1 years for sorafenib and 6.6 years for placebo without statistical significant difference between the three groups. The most common serious adverse events in the sunitinib and sorafenib groups were hypertension, hand-foot syndrome, rash and fatigue. Moreover, 5 deaths related to treatment or occurring within 30 days of the end of treatment were recorded, one patient in the sorafenib group and 4 in the sunitinib group. As a result, the authors stated against the adjuvant use of TKIs and suggested that maybe the etiology of disease recurrence was not dependent on angiogenesis [4].

On October 2016, Ravaud et al. published the results of a randomized double-blind phase 3 placebo controlled trial comparing adjuvant use of sunitinib in high risk RCC patients after nephrectomy with placebo (S-TRAC trial). A total of 615 patients were randomized either to receive sunitinib 50 mg per day (n=309) or placebo (n=306) on a 4-week on/2-week off schedule for one year or until disease relapse, drug toxicity or consent withdrawal. In case of drug toxicity, a dose reduction to 37.5 mg was allowed according to protocol. Inclusion criteria were locoregional RCC of clear cell histology, fully resected without metastatic disease. Concerning the results, there was a significant difference in DFS in favor of sunitinib. More specifically, median DFS was 6.8 years in the sunitinib arm compared to 5.6 years in the placebo (p=0.03). Especially in higher-risk patients the sunitinib group presented median DFS of 6.2 years compared to 4.0 years in the placebo arm (p=0.04). Grade 3 and 4 adverse events were encountered more frequently in the sunitinib group but on the other hand no difference was noted concerning grade 5 adverse events among the two groups. In addition, no deaths attributed to drug toxicity were recorded. As a result, the authors stated that patients suffering from locoregional RCC at high risk of recurrence after nephrectomy achieved higher DFS if treated with adjuvant sunitinib compared to placebo, at a cost of higher rates of toxic adverse events due to therapy [5].

In conclusion, we currently have two conflicting trials regarding adjuvant use of TKIs in RCC patients after nephrectomy in order to reduce disease relapses and prolong DFS. A possible explanation for these results is the different criteria for patient selection in these trials. More specifically, in ASSURE trial patients of pT1b stage were included (Fuhrman grade 3-4) while in S-TRAC these patients were not included unless they presented with nodal involvement. Moreover, in the ASSURE trial clear cell histology was not mandatory as in the S-TRAC trial (Table 1). To conclude, there seems to be a role in the future for TKIs as adjuvant treatment in RCC patients in high risk for recurrence but further trials are mandatory in order to strongly support this fact.

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"Pearl oyster": a new ultrasonographic sign of the regressed testicular tumor

Dear Editor,

Regressed tumor of the testis or "burned-out" phenomenon is a rare clinical entity in which the primary testicular tumor spontaneously and completely disappears [1]. It usually presents in metastatic stage [2]. Germ cell testicular tumors are most common in males between 15 and 40 years old in developed countries [1,2]. However, only 5% of germ cell tumors are extragonadal (retroperitoneal, mediastinal, cervical lymph nodes involvement, and occasionally in solid organs such as liver and lungs) [3]. They rarely present without suspicion of a primary testicular tumor [1,3].

A 33-year-old man consulted the emergency ward with sputum mixed with blood for 3 weeks, without fever. There were no other significant symptoms. He gave a past history of left-sided testicular pain and swelling 5 months back which was diagnosed clinically as orchitis, and treated with antibiotics and analgesics. The patient declared no previous surgical history or trauma. On physical examination, we found no signs of peripheral lymphadenopathy, while abdominal examination revealed no palpable masses. The patient did not demonstrate any laboratory signs of inflammation and the rest of the biochemical findings were within normal limits. Chest auscultation was normal. Chest X-ray showed pneumonia in the left lung, while computed tomography (CT) showed multiple nodules diffused in both lung fields. Given the patient's age, gender and imaging findings, an abdomino-pelvic CT and scrotal ultrasonography (US) were performed to evaluate the possibility of a testicular tumor. At the time of referral to our Department of Urology, a scrotal ultrasonography study, using a 10MHz linear probe, revealed a left-sided varicocele showing reflux flow confirmed by scrotal Doppler ultrasonography. Moreover, the testicular US revealed a well-defined highly echogenic lesion with calcified areas in the upper pole of the left testis, measuring 7x8x7 mm, without internal vascularity (Figure 1A). Beta-human chorionic gonadotropin level was markedly elevated to more than 150,000 IU/L, lactic dehydrogenase was 600 U/L and alfa-fetoprotein was normal. To obtain a diagnosis, lung biopsy was performed. Based on these results, diagnosis was germ cell tumor with metastases to lungs. The patient received 4 cycles of neoadjuvant chemotherapy, followed by left testicle-sparing surgery performed by US guidance. Surgical pathology of the left testis reported a regressed testicular germ cell tumor with a fibrohyaline nodule infiltrated by several inflammatory cells and presence of calcifications. The patient remained without evidence of disease more than 1 year after initial treatment.

The most common tumor of the testis is germ cell tumor, and its usual presentation is a palpable nodule in 95% of the patients [3]. Less commonly, the patients have

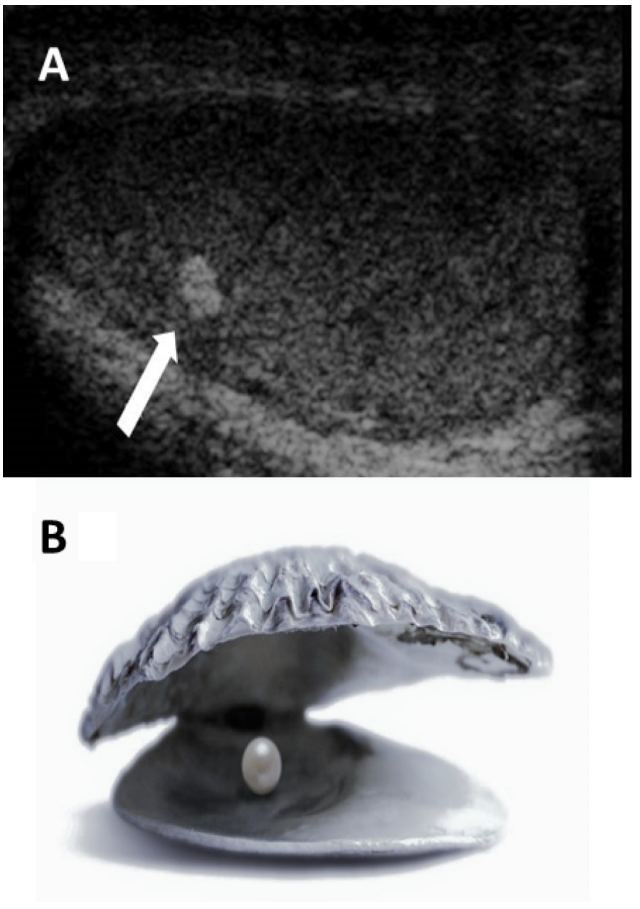

Figure 1. (A) Sagittal sonogram of the left testis showing a small, well-cirumscribed, highly echogenic lesion with microcalcifications (white arrow). **(B)** The small and highly echogenic lesion of the testis mimics a pearl in its oyster. Public domain image: (https://it.pinterest.com/henlestudio/luminous-things/).

symptoms related to metastatic disease such as pulmonary signs like dyspnea and hemoptysis, without a palpable testicular mass. Patients with extratesticular germ cell tumors and a normal testicular examination will have clinical findings in burned-out phenomenon. The mechanism of this phenomenon for testicular tumors remains unclear, though some immunological and ischemic mechanisms have been proposed [5]. Patients with extra-gonadal germ cell tumors with the burned-out phenomenon usually report many vague symptoms, such as scrotal or abdominal pain, and occasionally show elevated testicular tumor markers [2]. The classical US intratesticular appearance of burned-out phenomenon is a detection of small, well-cirumscribed, highly echogenic lesion with microcalcifications or microlithiasis (Figure 1A). The ultrasonic features of these highly echogenic foci resemblance to a pearl (Figure 1B) explain a new US sign of regressed tumor of the testis: the "pearl oyster" sign. The suspicion of an extragonadal germ cell tumor with the "burned-out" phenomenon changes the treatment opinion, which should begin with the orchiectomy, followed by systemic chemotherapy.

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Preliminary testing of anthracycline-induced cardiotoxicity in children

Dear Editor,

Anthracycline cardiotoxicity has been the subject of discussion in a significant number of published articles [1]. These publications have dealt mostly with adult patients who received anthracyclines due to various types of cancer [2]. There are significantly fewer publications dealing with the cardiotoxic effects of anthracyclines in children [3,4]. This can probably be explained by the the fact that children suffer less from malignant diseases compared to adults, hence the number of treated patients is not adequate for sound statistical analysis. The fact that such trials have not been conducted in Serbia and the neighboring countries, has led us to seriously address this problem. On the other hand, children do not have significantly altered myocardial function as seen in adults due to long-standing cardiovascular disease (hypertension, diabetes mellitus, coronary artery disease), hence we will be examining the potential cardiotoxicity of anthracyclines in a relatively healthy heart, with no co-morbidities.

Given the above mentioned reasons, we since 2004 initiated at our clinic prospective cardiac function monitoring in every child with diagnosed malignancy, which required therapeutic administration of anthracyclines (doxorubicin, idarubicin, daunorubicin, epirubicin). Aside from a detailed clinical examination, electrocardiogram and laboratory tests (biomarkers of myocardial lesion), each patient underwent a detailed echocardiographic examination before treatment, after each cycle, at the end of treatment and control echocardiography once a year during the years of follow-up. Our first observation was that, except in a few cases where the diagnosis was dubious, and where patients did not go into remission after treatment, no significant differences in heart morphology and function were noted.

In order to confirm this, we performed a preliminary analysis which included only echocardiographic parameters of the left ventricular systolic function: fractional shortening (FS) and left ventricular ejection fraction (LVEF) in a homogenous group of respondents. We examined 36 children with acute lymphoblastic leukemia who were treated with doxorubicin alone (without daunorubicin) and in which the cumulative anthracycline dose was <300mg/m^2, >250mg/m^2. The children had an average age of 6.76 ± 5.23 years, the youngest was 1.5 years, and the oldest 17 years old at the time of diagnosis, before commencing treatment. Echocardiography parameters, FS and LVEF were determined at the time of diagnosis, one and three years after the start of treatment. Analysis of the obtained results was performed by means of the following statistical tests: Kolmogorov-Smirnov test, the Friedman test, Wilcoxon test, and the inter-dependence between variables was investigated by means of Pearson linear correlation coefficient.

The obtained results were very interesting. No patient presented with cardiac symptoms. Analysis of the absolute values of FS and LVEF in each subject showed that only in 3/36 (8.3%) the values were below the lower limits and this finding seemed to be not statistically significant. However further statistical analysis gave the following results, shown in Tables 1 and 2.

A statistically significant change in the values of FS (x^2=31,953, p<0.001), and LVEF (x^2=48,246, p<0.001) during the study period, was noticed. Table 2 demonstrates the values of the Pearson correlation coefficient of FS and LVEF during the investigated period, where a statistically significant positive correlation was found only in

Table 1. FS and LVEF in the study population over time (mean±SD)

	Before treatment	*1 year after treatment*	*3 years after treatment*	*p**	*Post hoc*
FS (%)	39.83±3.09	36.17±3.63	37.17±7.58	<0.001	A,B
LVEF (%)	75.33±4.27	69.30±4.34	68.42±4.20	<0.001	A,B

FS: fractional shortening, LVEF: left venticular ejection fraction. *Friedman test. A (before treatment vs. 1 year after treatment), B (before treatment vs. 3 years after treatment)

Table 2. Pearson's correlation coefficient of the FS and LVEF

FS		*Before treatment*	*1 year after treatment*	*3 years after treatment*
Before treatment	r	1	0.394	0.067
	p		0.017	0.698
1 year after treatment	r		1	0.251
	p			0.139
3 years after treatment	r			1
	p			
LVEF		*Before treatment*	*1 year after treatment*	*3 years after treatment*
Before treatment	r	1	0.437	0.285
	p		0.008	0.092
1 year after treatment	r		1	0.556
	p			<0.001
3 years after treatment	r			1
	p			

the values of FS measured before treatment and one year following treatment (r=0.394; p=0.017). A statistically significant positive correlation was also found in the LVEF values measured before and one year following treatment (r=0.437; p=0.008), as well as between the first and third year after treatment (r=0.556; p<0.001).

Our pilot study confirms the hypothesis that the cardiotoxic effects of anthracyclines on the LVEF are high and significant in children, regardless of mildly reduced and apparently normal values of echocardiographic parameters registered on routine examination. Cardiotoxicity is mainly manifested after the first year of treatment with anthracyclines, and then seems to progress. This imposes an obligation to detailed long-term monitoring of patients after the remission of malignant disease, as well as consideration of prevention of anthracycline-induced cardiotoxicity [3]. We have presented only a small portion of the total number of examined patients, and plan to present an original paper showing the results of a 14-year extensive and complex research.

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