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PRAVI TRENUTEK ZA NOV ZAČETEK

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case report

Treatment of complicated case with subclavia steal syndrome and stenosis of common iliac artery

Bujar Gjikolli[1], Besima Hadžihasanović[2], Suad Jaganjac[3], Edin Herceglija[4], Maida Nikšić[1], Amel Hadzimehmedagić[5], Mirza Dilić[6], Emir Solaković[7], Zulejha Merhemić[1], Šerif Bešlić[8], Lidija Lincender[9], Ramë Miftari[10]

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Background. *The aim of this case report is to describe the realization of complex radiological minimally invasive interventional procedures at the Institute of Radiology in KCU Sarajevo during which we treated a very complicated case with the left subclavia steal syndrome and the stenosis of the left common iliac artery.*

Case report. *The patient was 57 years old with previous history of ischemic lesions in brain, with occlusion of the left arteria carotis communis (ACC) and stenosis of the right arteria carotis interna (ACI), with dizziness and inability to look upward. The patient was treated first with subintimal recanalization and introduction of self-expandable stent into the left subclavia artery to compensate for the very wide remnant of the occluded artery. After four months of follow up with no change, our team attempted to treat stenosis of the right ACI but failed to do so and during this procedure in-stent restenosis in the left subclavia artery was noted. After less than two weeks we performed balloon dilatation of in-stent restenosis of a previously installed stent into the left subclavia artery. The patient underwent CT and CT angiography (CTA), colour Doppler ultrasonography (CDUS), MRI and MR angiography (MRA) before and after the procedures.*

Conclusions. *A follow up and, if needed, a balloon dilation are necessary to prevent the re-occlusion of the previously treated subclavia artery with stenting.*

Key words: subclavia steal syndrome; intentional subintimal recanalisation; restenosis; balloon dilation

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Introduction

Subclavia steal syndrome (SSS) is a group of signs and symptoms resulting from

steno-occlusive disease proximal to the origin of the vertebral artery, in which the arterial flow is reversed.[1-4] It was described in 1960 for the first time, and the association between this phenomenon and neurologic symptoms was recognized in 1961.[5,6,] SSS refers to the retrograde vertebral artery flow associated with transient neurologic symptoms related to cerebral ischemia while subclavia steal phenomena (SSP) refer to the retrograde flow in the vertebral artery only.

Stenosis or occlusion of the proximal subclavia artery causes a reversed vertebral flow with resulting decreased blood pressure in the arm distal to the steno-occlusive disease. A reduced blood pressure causes the ipsilateral vertebral artery blood flow alteration as a compensatory pathway through the arm, and this sign confirms subclavia disease proximal to the origin of the vertebral artery. Other potential collateral pathways include those between the external carotid artery (ECA) and the subclavia artery from occipital branches of ECA and the superior thyroid artery of ECA to the inferior thyroid artery branch of thyrocervical trunk. There are four types of subclavia steal, defined by territory from which blood is "stolen" in SSS: vertebro-vertebral, carotid-basilar, external carotid-vertebral, and carotid-subclavia.[7] Based on vertebral hemodynamic changes, SSS has three defined stages: reduced antegrade vertebral flow (stage I), reversal of flow during reactive hyperemia testing of the arm (stage II), and permanent retrograde vertebral flow indicating subclavia artery occlusion (stage III).[8]

Arm symptoms can be provoked during arm exercise or peripheral reactive hyperaemia, while neurological symptoms occur when compensatory flow to the subclavia artery from the vertebral artery diverts too much flow to the arm and away from brain. Neurologic symptoms result primarily from the insufficient intracranial circulation through circle of Willis mainly through the posterior communicating artery. Absence of a posterior communicating artery, extra cranial carotid artery stenosis and higher flow toward the arm can cause neurologic symptoms. The spontaneous resolution of vertebro-basilar symptoms may be related to the establishment of extra cranial collaterals to the subclavia circulation.

Etiology of SSS is predominantly atherosclerotic in people older than fifty years of age. In Asians Takayasu arteritis as etiology can be seen in up to 36% of the population. Other causes of SSS include giant cell arteritis, tumour encasement, trauma, previous surgical procedure such as aortic stent-graft placement for thoracic dissection or aneurysm, coarctation of aorta with the obliteration of subclavia orifice, extra vascular obstruction, hypoplasia / atresia or isolation of subclavia artery with the anomalous aortic arch, vascular ring, ligation for the correction of tetralogy of Fallot or co-arctation of aorta.[9]

The risk of stroke seems low[10] but patients with SSS can be severely debilitated by arm and intracranial ischemia symptoms. As many as 15% of initially asymptomatic patients can experience vertebro-basilar transient ischemic attacks during two years of follow up.[11]

SSS is more frequent in males than females with incidence 1.5-2:1 while Takayasu arteritis is more common in females. SSS has a left-sided to right-sided ratio of 3-4:1 as a result of turbulence-related atherosclerosis of the acutely angled left subclavia artery.

Symptoms include dizziness, unsteadiness, vertigo, vision changes, arm ischemia causing arm claudication and rest pain, focal sensory or motor loss, dysphasia, and unilateral visual disturbances. Symptoms may develop during the exercise of the upper limbs, when blood is deviated from the vertebro-basilar system to the upper limb.

A reduced blood pressure with change of >20 mm Hg when compared with contra lateral arm, weak or absent radial and ulnar pulse are other signs suggesting SSS.

Colour Doppler US is the preferred examination.[12] CT visualizes calcifications related to atheroma. Contrast enhanced CT angiography (CTA) can visualize the degree of subclavia artery stenosis or occlusion, including other changes in the arteries; mural thrombus, ulceration, and arterial wall calcification can be evaluated.

MRI and contrast enhanced 3-D MR angiography (MRA) after localizing 2-dimensional time-of-flight can also confirm SSP. Phase-contrast MRA measures the vertebral artery flow direction and velocity.[13-15]

SSS can be treated with minimally invasive radiological procedures of percutaneous transluminal angioplasty and stenting if angioplasty fails, using balloon-expandable stents or in some cases self expandable stents.[16-22] Vertebro-basilar stroke during interventional procedures is rare due to the delayed establishment of the ante grade flow in the vertebral artery after the angioplasty/stenting. A distal protection may be useful especially in cases with thrombosis/unstable plaque.

Additionally SSS can be treated with surgical revascularization using either synthetic graft or saphenous vein grafts. Invasive options include carotid-subclavia bypass (CSB), carotid-subclavia transposition (CST), and axillo-axillary bypass.[23-26]

With this presentation we would like to describe the realization of complex radiological interventional therapeutic procedures of treating subclavia steal syndrome and stenosis of the left common iliac artery, at the institute of Radiology KCUS under the supervision of a Bosnian expert Dr. Suad Jaganjac working at the Hamburg Klinik Eilbek in Germany.

Case report

A 57-year-old male patient had complained of multiple symptoms, including weakness, dizziness, inability to look upward, speech difficulties and difficulties in using his left hand, in the five years following cerebral vascular insult. In 2002 he was admitted to the vascular surgery hospital KCUS because of atherosclerotic changes with stenosis of *arteria carotis communis* (ACC) and *arteria carotis*

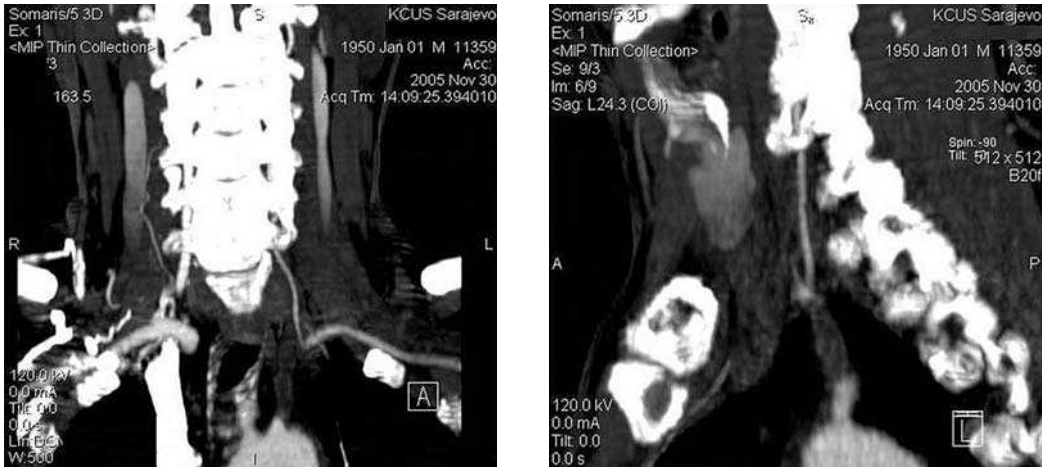


Figure 1 (a, b). CT angiography (CTA) maximum intensity projection (MIP) reformats show the occlusion of the left subclavian artery and the left brachial artery receiving blood from the left vertebral artery- steal syndrome.

interna (ACI) in the left side. In 2003 he was hospitalized in the clinic for cardiovascular diseases in UCC Tuzla where surgeons confirmed stenosis of the right ACI but did not intervene in the artery. The patient also complained for claudicating pain in his legs after 20 meters of walking. He had high blood pressure and increased triglycerides in blood but was not diabetic. He quit smoking in 2002 after more than 40 years of 1-1.5 packages of cigarettes per day.

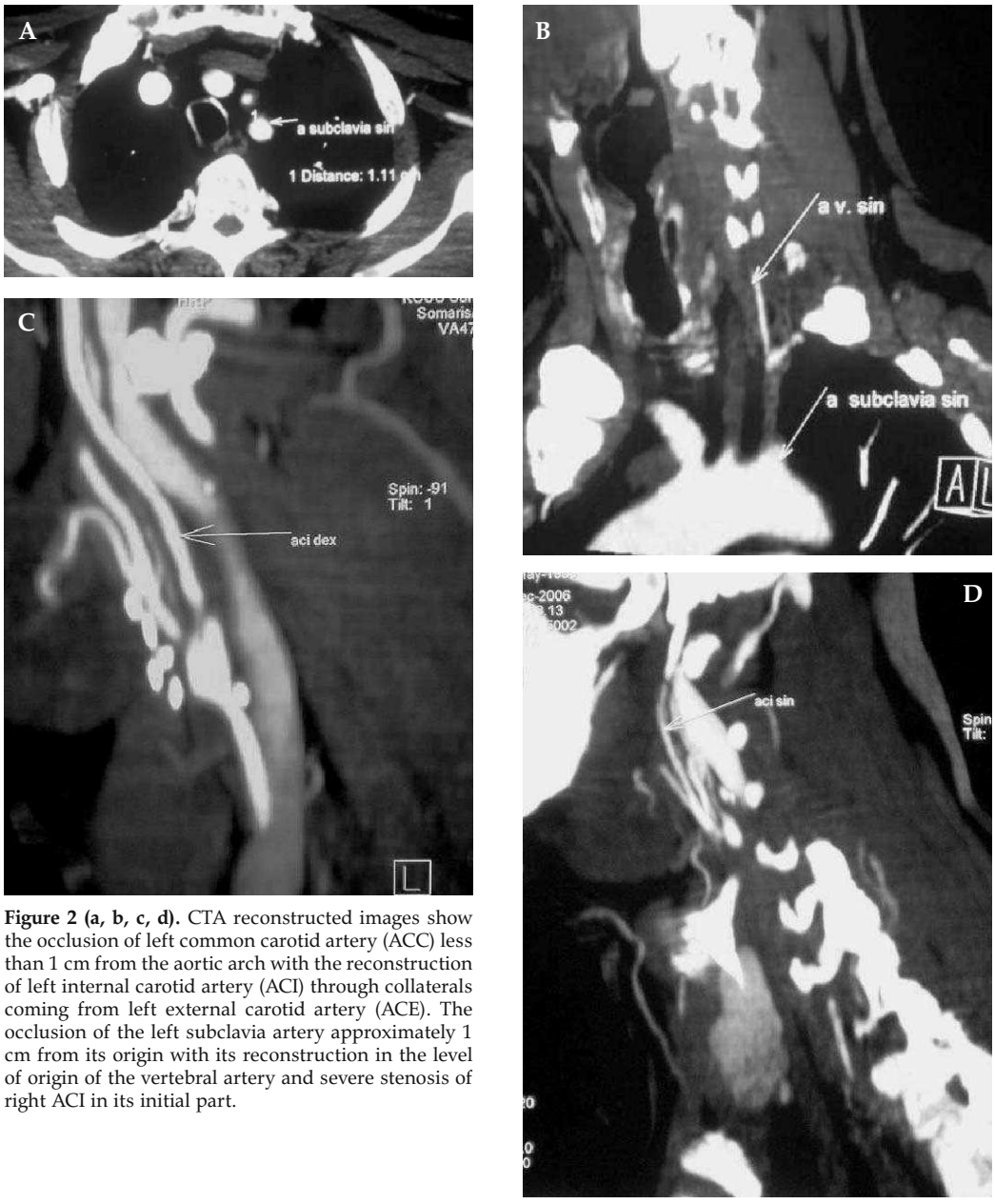


Figure 2 (a, b, c, d). CTA reconstructed images show the occlusion of left common carotid artery (ACC) less than 1 cm from the aortic arch with the reconstruction of left internal carotid artery (ACI) through collaterals coming from left external carotid artery (ACE). The occlusion of the left subclavia artery approximately 1 cm from its origin with its reconstruction in the level of origin of the vertebral artery and severe stenosis of right ACI in its initial part.

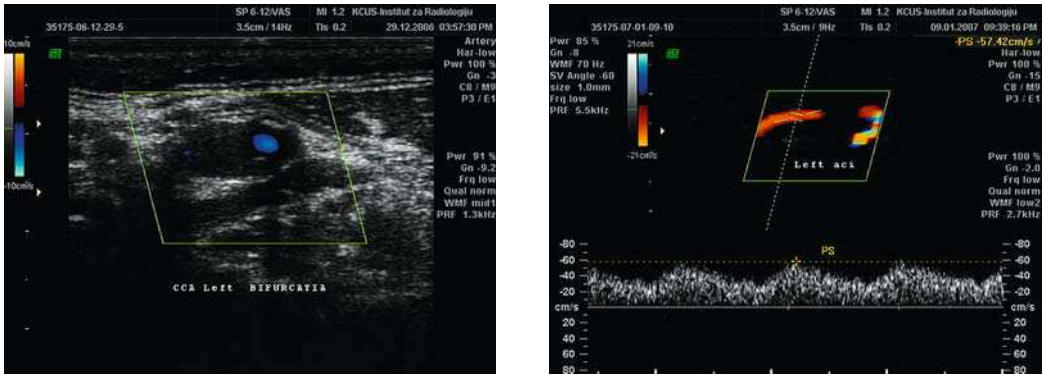


Figure 3 (a, b). Colour Doppler ultrasound (CD US) showing flow in the left internal carotid artery (ACI) and ACE above the occluded left common carotid artery (ACC).

In November 2005, the patient complained of ongoing symptoms and underwent CTA at our institute (Figure 1). The occlusion of left ACC and left subclavia steal syndrome was diagnosed but no interventions were performed.

In December 2006 the patient was referred for CTA again and the occlusion of left ACC and left subclavia artery reconstructed through the left vertebral artery was shown. The remnant subclavia artery below the occlusion was measured at 1.11 cm. High grade stenosis of right ACI has been shown too. Left ACI was reconstructed through collaterals coming mainly through *arteria carotis externa* (ACE) branches (Figure 2). During discussion, the patient mentioned physicians' previous difficulties doctors had accessing his femoral artery for diagnostic digital subtraction angiography (DSA). Additional CTA of abdominal aorta and the upper part of his lower extremities confirmed mild stenosis of the right femoral artery and significant stenosis of the left common iliac artery.

Additionally colour Doppler ultrasound (CD US) confirmed the changes seen in the CTA: the disturbance of the flow and the steal syndrome in the left side (Figures 3, 4). Left ACC showed maximum diameter of 6.5 mm without detectable flow while in ACI and ACE portion there was flow detectable coming from surrounding collaterals. Right ACC had maximum diameter of 7 mm with intima medial thickness of 1.3 mm with laminar flow and Peak Systolic

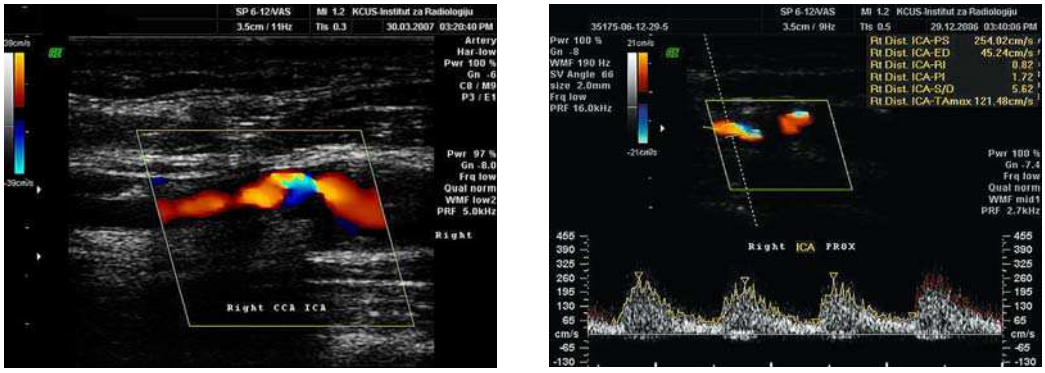


Figure 4 (a, b). Colour Doppler ultrasound (CD US) images showing stenosis of the initial part in the right arteria carotis interna (ACI) and its increased spectral values.

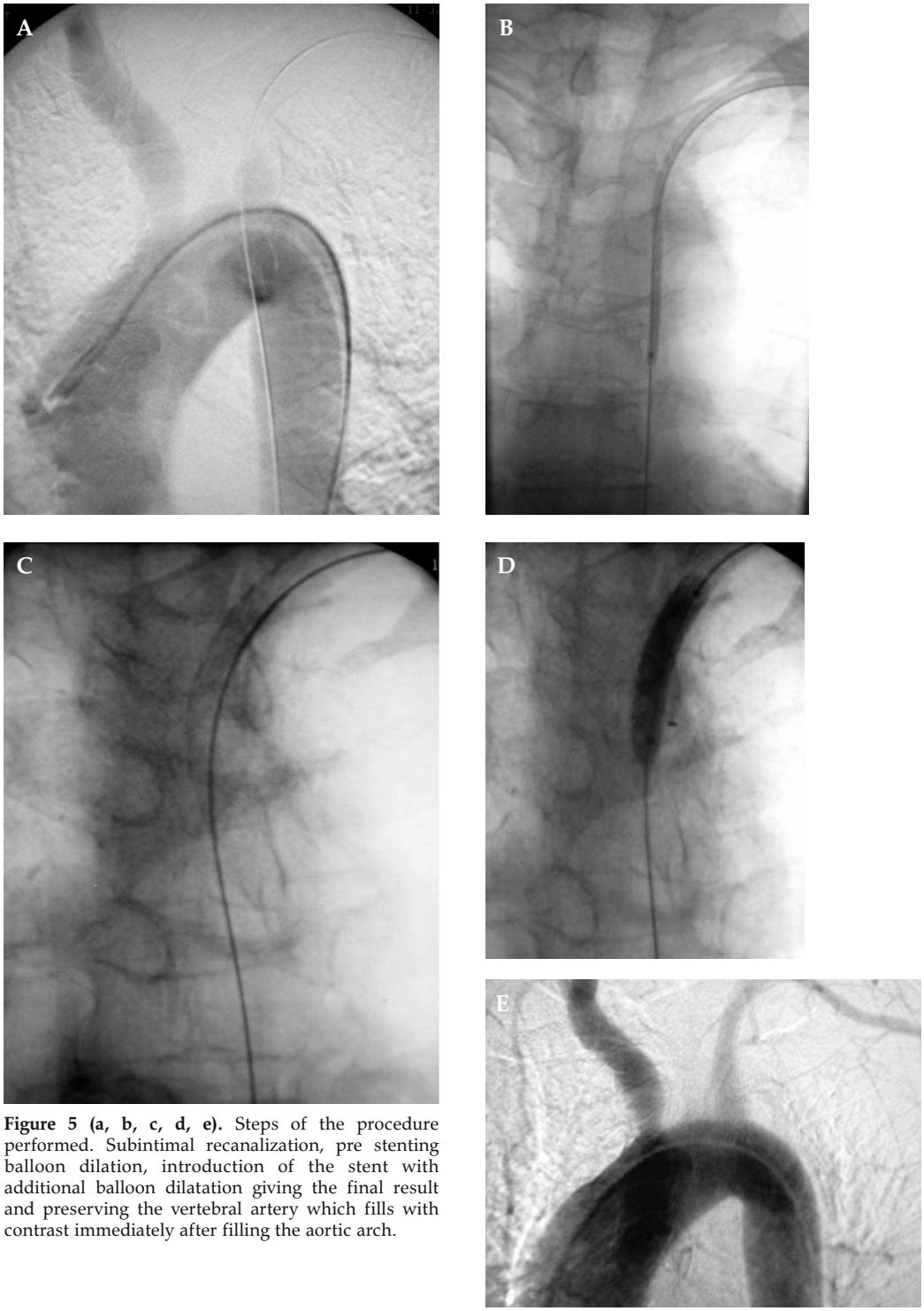


Figure 5 (a, b, c, d, e). Steps of the procedure performed. Subintimal recanalization, pre stenting balloon dilation, introduction of the stent with additional balloon dilatation giving the final result and preserving the vertebral artery which fills with contrast immediately after filling the aortic arch.

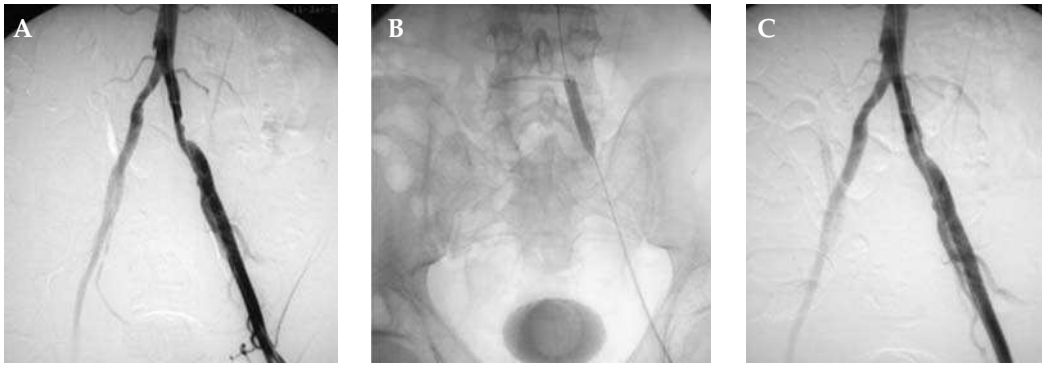


Figure 6 (a, b, c). Stenosis of the left iliac artery before stenting and result gained after stenting.

Velocity (PSV) 91.43 cm/s and End Diastolic Velocity (EDV) 21.33 cm/s in its proximal part and turbulent flow with PSV 79.49 cm/s, EDV 32.56 cm/s in its distal part. The dorsal part of the bifurcation and the initial part of the right ACI showed partly hyper- and partly hypo-echogenic plaque inside the lumen, reducing its width 3.5 mm with increase of PSV to 254.02 cm/s and EDV 45.24 cm/s.

After analyzing all imaging procedures performed, we decided to offer the patient treatment of subclavia syndrome while avoiding treating the stenosis of the right ACI as the only big artery supplying his brain with blood. He agreed and the procedure was performed in January 10, 2007 at the Institute of Radiology – KCU Sarajevo.

We used a left brachial approach and a hydrophilic guiding wire to perform Bolia's intentional subintimal recanalization. After reaching the aorta the guiding wire was pulled out with a goose neck snare from the introducer in the left femoral artery. Meanwhile this introducer was installed to confirm the position of the guide wire in

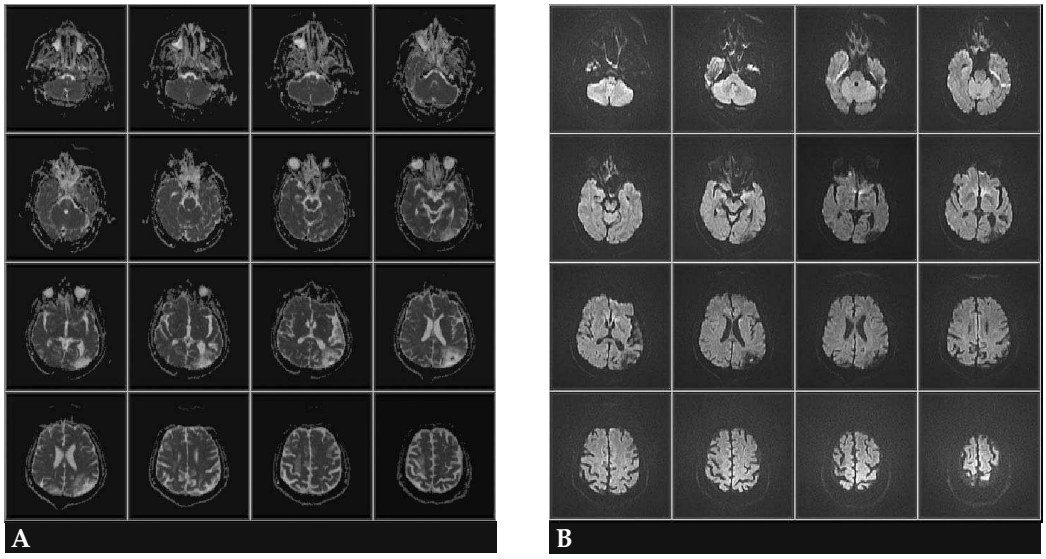
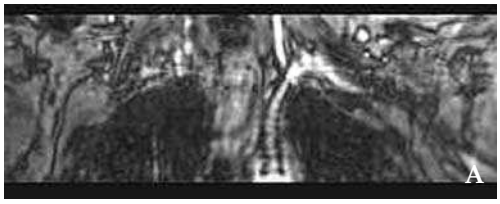


Figure 7 (a, b). Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) images show old ischemic lesions and no new ischemic lesions at all.



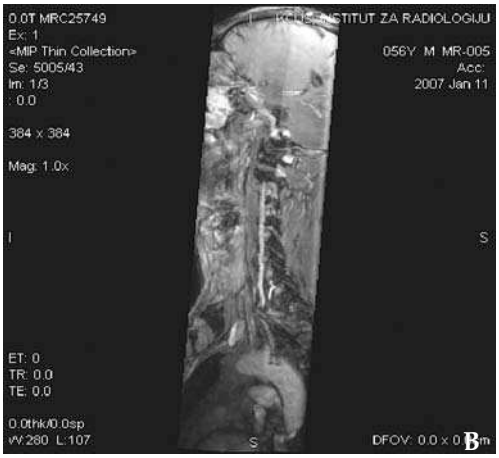
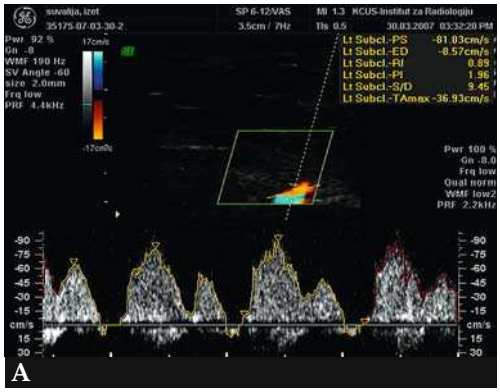
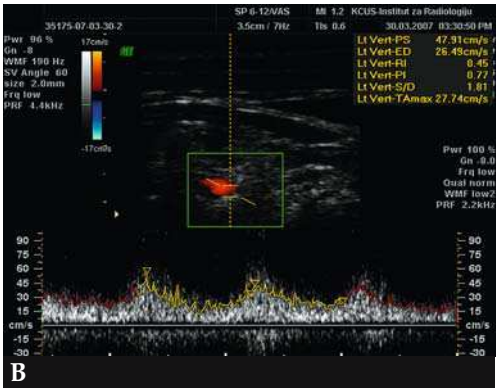
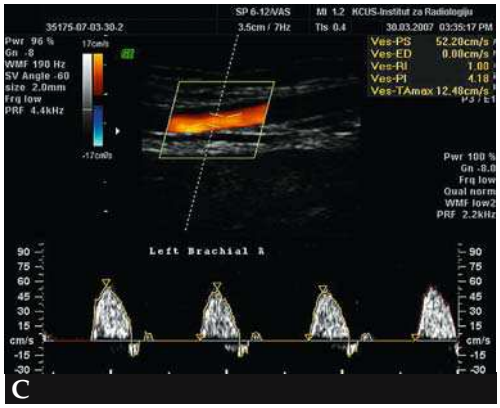


Figure 8 (a, b). Maximum intensity projection (MIP) MR reconstructions after stenting showing position and the patency of the left subclavian and left vertebral arteries.

the right lumen inside aorta. With a 3x120 mm balloon, we dilated the recanalized subclavia artery to create space for passing the stent. We used a self expandable stent to address both the wide proximal portion of the left subclavia artery and its narrow distal part. After introducing a self expandable stent, size 10 x 44 mm, the additional balloon dilation to a width of 6 mm achieved satisfactory lumen diameter of the recanalized left subclavia artery. Tip of the







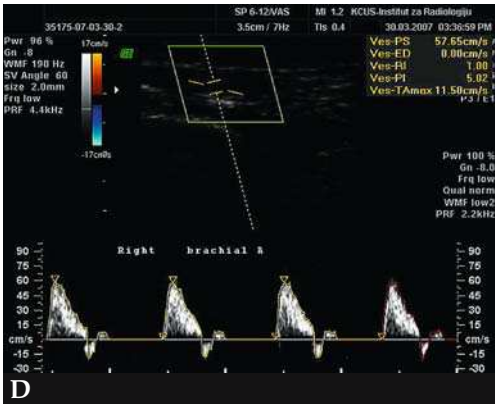


Figure 9 (a, b, c, d). Post procedural follow up with colour Doppler ultrasonography (CDUS) showing good flow in the left subclavian and vertebral arteries, and resulting good flow in the left brachial artery similar to the one in the right side.

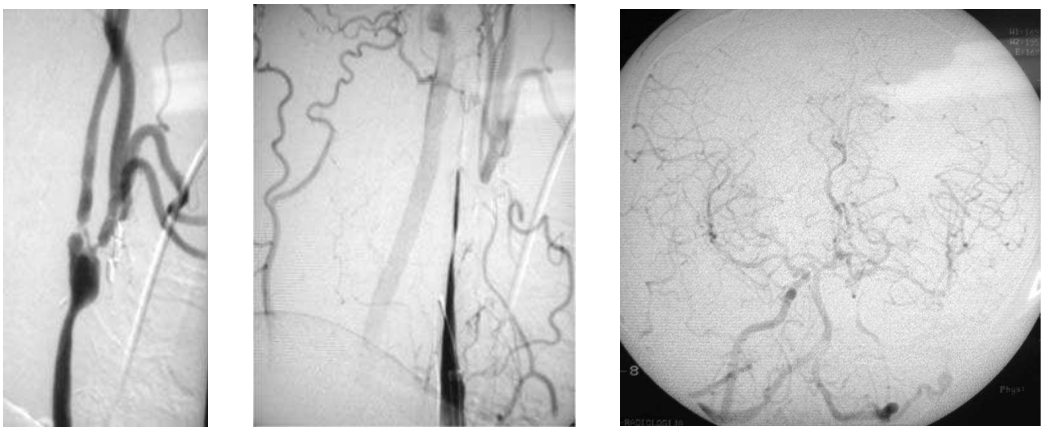


Figure 10 (a, b, c). Working position of the right arteria carotis communis (ACC) before attempt for its stenting and after the dissection made. Brain angio after dissection without new changes.

stent was put several millimetres below the starting point of the left vertebral artery with the proximal part of the stent in the aortic arch lumen (Figure 5).

In the same procedure, the stenosis of the left common iliac artery was treated by introducing a stent 9x38mm on balloon with immediate results (Figure 6).

One hour after the procedure the patient was transferred to the MRI unit to assess consequences to the brain (Figure 7) and to confirm the position and the patency of implanted stent in the left subclavia artery (Figure 8).

Diffusion weighted imaging sequences showed only old and no fresh ischemic lesions. The day of the procedure, the patient was able to look up, walk without dizziness and use his left arm freely.

Patency of the left subclavia and vertebral arteries was followed with Doppler US, confirming a good flow after more than three months. A comparison between right and left brachial arteries confirmed the identical flow (Figure 9).

The patient was very satisfied with the results and insisted on an attempt to stent the right internal carotid artery. Initially, we were reluctant to do so because of high risks for the patient if the procedure failed, but we felt we could not deny him the chance of success, and we offered him a place in a group trial. On May 18, 2007 our team tried to perform stenting of the right internal carotid artery but failed to pass through the stenosis. The attempt resulted in dissection of the right ACC (Figure 10) most probably

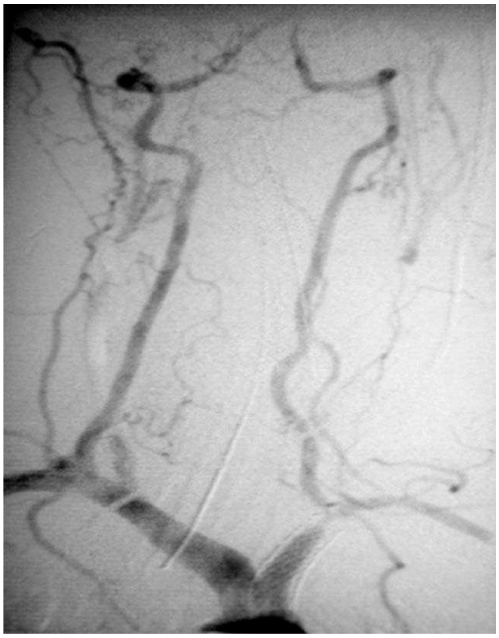


Figure 11. Narrowing of the distal part of the stent in the right subclavian artery. Occlusion of both carotid arteries.

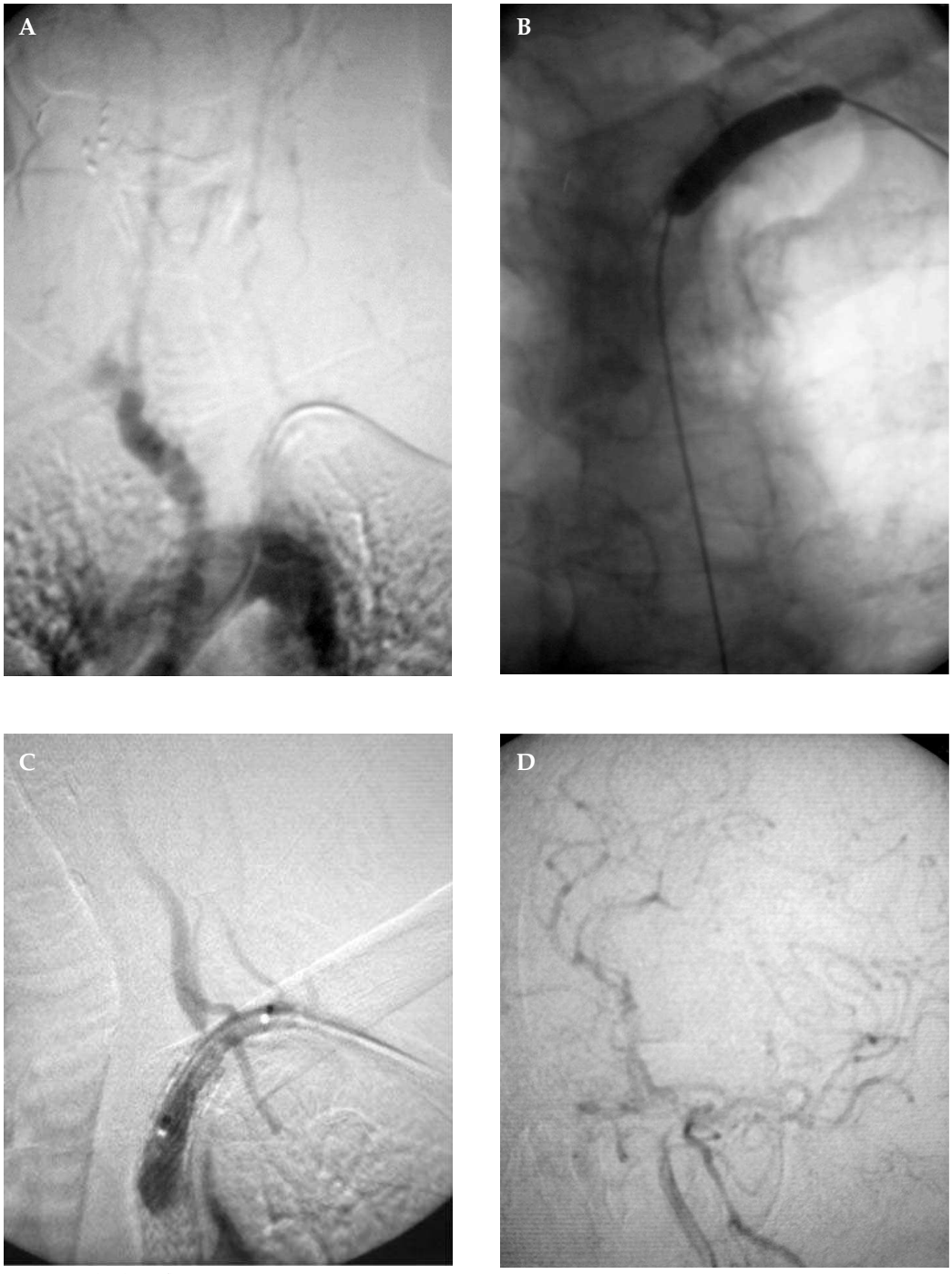


Figure 12 (a, b, c,d). Steps of the procedure of treating the in-stent stenosis in the left subclavian artery and confirming the result without impact in brain blood supply. Stenosis of initial part of the left vertebral artery.

because our college used hydrophilic guide wire for exchanging the long sheath introducer. No other consequences were found.

During this procedure, we noted that the distal part of the stent implanted in the right subclavia artery was narrower than before (Figure 11). The patient has begun complaining of pre-procedural symptoms, including dizziness, not being able to look up and difficulties to use his left arm.

On May 30, 2007 we performed the dilatation of the re-stenosed stent in the left subclavia artery. Through a left brachial approach, we performed dilatation with a balloon 4 x 30 mm; followed by a balloon sized 7 x 50 mm. The satisfactory lumen was achieved. Stenosis of the initial part of the left vertebral artery was identified and remains to be followed and for planning the possible treatment (Figure 12). Following the procedure the patient reported no recurrence of symptoms.

Conclusions

The immediate improvement in the patient's symptoms is a strong motivator for minimally invasive radiological interventional procedures. A follow up is necessary to prevent the re-occlusion of the artery, and the balloon dilation may be necessary to maintain the effect of the intervention. The patient's interest in such procedures is a crucial component for success.

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images in clinical medicine

Planocellular carcinoma of the right cheek

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A 97-year-old female patient was admitted to the outpatient clinic of our Institute for the treatment of an extensive tumour on her right cheek (Figures 1a and 1b). Histological examination of the biopsy sample confirmed planocellular carcinoma.

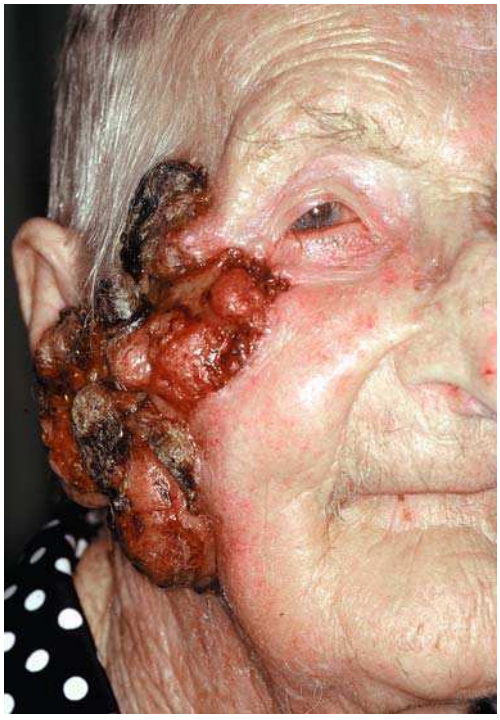

Figure 1a. An extensive tumour on the right cheek.

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Six years ago, she developed a minor skin abscess on the right cheek which was cured by electrodesiccation and curettage. Three years later, a tumour started to grow on the same spot of the right cheek. Until first appointment at the outpatient clinic, the tumour grew up to the size of 13 x 8 cm. The patient was declining any medical help from fear of pain.

She was treated with irradiation by telecobalt unit, with a dose equivalent of 70 Gy. Three months after the beginning of

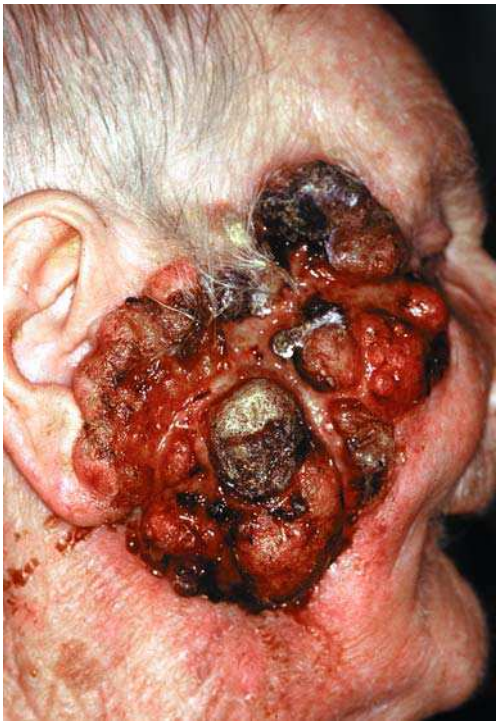

Figure 1b. Confirmed planocellular carcinoma on the right cheek.

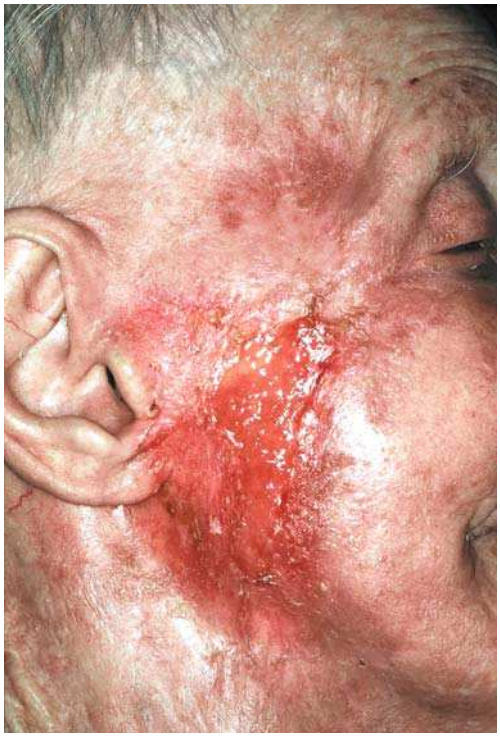

Figure 2a. Wet radiodermatitis, three months after the beginning of irradiation.

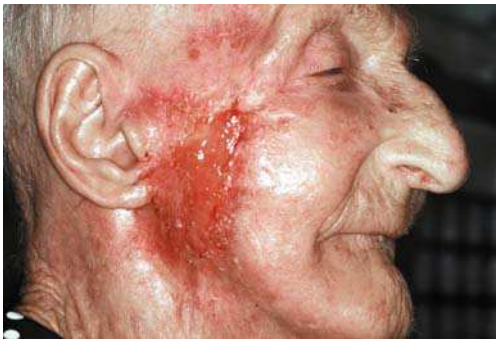

Figure 2b. Coplete response, three months after the beginning of irradiation.

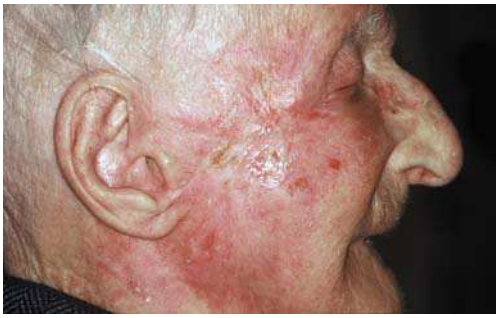

Figure 3. No evidence of disease, six months after the beginning of irradiation.

irradiation, only a wet radiodermatitis was seen on the treatment site (Figures 2a, 2b). In six months, the tumour regressed completely (Figure 3). Thirty months after the completed therapy, teleangiectases still persist on the irradiation site, whereas the tumour regressed completely, with no nodal or cervical involvement (Figure 4).

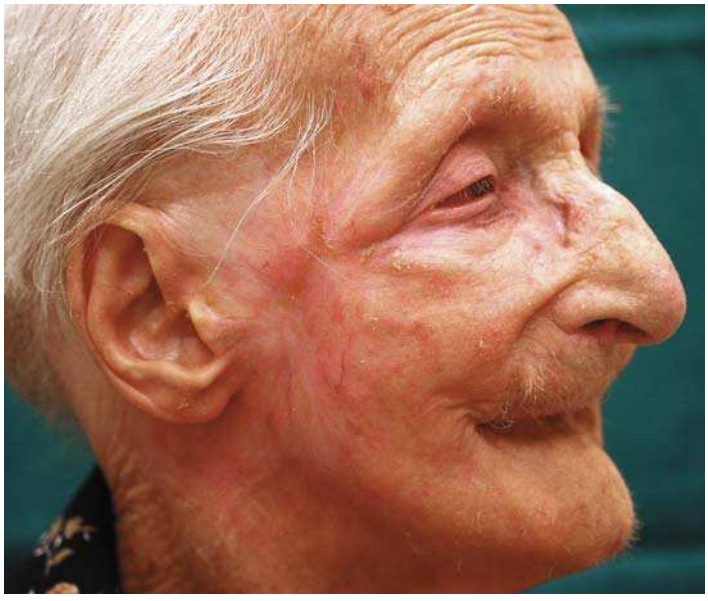

Figure 4. Post-irriadiated teleangiectases without recurrence of disease, with no nodal or cervical involvement, thirty months after the completed therapy.

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review

Radiation effects on skeletal muscle

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Background. *Adult skeletal muscle is considered resistant to ionizing radiation unless higher doses of radiation are applied; a fact that is attributed to the low number of radiosensitive proliferating cells in adulthood. However, developing skeletal muscles are highly sensitive to ionizing radiation, thus radiotherapy in childhood may induce muscular atrophy. Radiation affects muscle satellite cells by impairing their activation, proliferation and differentiation, as well as neuromuscular junction, by influencing the ionic membrane permeability affecting the Na^+/K^+ pump. It also prevents muscle growth during development and after injury.*
Conclusions. *The results of the investigation performed after radiation point to the occurrence of a significant change in muscle satellite cell activity. Inhibitors of some proteins such as cytokines in muscle satellite cells could provide a therapeutic benefit in diseases for which muscle mass is limiting, improve response to cancer therapy, and increase life span in patients with cachexia.*

Key words: radiation effects; neuromuscular junction; muscle satellite cells; aging.

Introduction

The cells of normal tissue are not independent but form a complete integrated structure. Cell death after irradiation occurs mostly as cells attempt to divide. In tissues with a rapid turnover rate, damage quickly becomes evident - in a matter of hours and days after radiation. In tissues in which cells divide rarely, radiation damage to cells may remain latent for a long time and can be expressed very slowly. Radiation damage to cells that are already on the path to differentiation and are not in any case planning to divide many times is of little consequence. Radiation damage to stem cells has serious repercussions because such cells are programmed to divide many times to maintain a large population and if they lose their reproductive integrity, they and their potential descendents are lost from the population. Thus, cells on the path to differentiation appear to be more radioresistant than stem cells.[1]

Radiation effects on tissue are divided into early and late effects, which show quite different patterns of response to fractionations and dose-response relations. Acute damage is rapidly repaired because of rapid proliferation of stem cells and may be completely reversible.[2] Late effects appear after a delay of months or years and occur predominantly in slowly proliferating tissues, such as lung, kidney, heart, liver and central nervous system. Late damage may improve but it is never completely repaired and may result from a combination of vascular damage and loss of parenchymal cells.[2]

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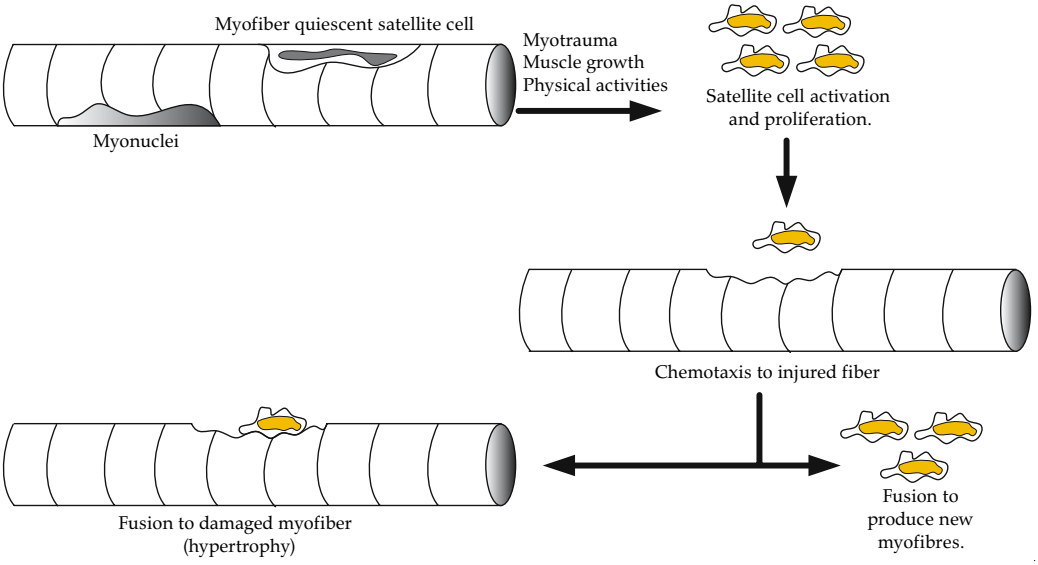

Figure 1. Satellite cell response to skeletal muscle trauma and muscle growth. Skeletal muscle trauma or injury may be minor (resistance exercise) or may be more extensive (muscular dystrophy). In response to both stimuli, satellite cells become activated and proliferate. Satellite cells will migrate to the damaged region and fuse to the extending myofiber or align and fuse to produce a new myofiber.

Casarett and Harris suggest a classification of mammalian cell radiosensitivity based on histopathologic observation.[3] In terms of radiosensitivity, parenchymal cells fall into four categories, from the most sensitive to the most resistant. Adult muscle and nerve cells belong to the last, 4th group, in which radiosensitivity is low and cells are highly differentiated.

It is generally assumed that adult nervous and skeletal muscle tissues are highly radioresistant. This may be true when based on the criterion of morphological damage that is manifested within a few months. The development of damage induces changes in muscle satellite cells, differentiated muscle cells and the neuromuscular junction.

Effect of radiation on muscle satellite cells

Satellite cells, a population of undifferentiated tissue-specific stem cells, were first identified in 1961 by Mauro.[4] They are located at the periphery of the mature, multinucleated myotube and comprise only about 2% of the total nuclei of normal adult skeletal muscle[4,5,6] and are normally non-proliferative.

Satellite cells have only one nucleus and can replicate by dividing. As the satellite cells multiply, some remain as organelles in the muscle fiber, whereas the majority differentiate and fuse to muscle fibers to form new muscle protein stands and/or repair damaged fibers (Figure 1).[6] Muscle cell myofibrils will thus increase in thickness and number. After fusion with the muscle fiber, some satellite cells serve as a source of new nuclei to supplement the growing muscle fiber.

Satellite cells are constantly replenished during a lifetime, although there is a decline in satellite cell numbers and a reduced proliferative capacity in aged individuals.[7,8] In response to stimuli such as myotrauma upon injury or muscle growth[7], or when skel-

etal muscle tissue is heavily used during physical activities[9],satellite cells become activated and they turn into proliferating myoblasts.[7]

Muscle induced myotrauma initiates an immune response, resulting in the influx of macrophages into the damaged region. After acute injury, macrophage infiltration peaks within 48 h.[10] In the absence of a macrophage response, muscle regeneration is absent; in the presence of an enhanced macrophage response, there is an increase in satellite cell proliferation and differentiation.[11]

The purpose of the immune response is to contain, enclose the damage, repair the damage and clean up the injured area of waste products. The immune system causes a sequence of events in response to injury of the skeletal muscle. Macrophages, which are involved in phagocytosis of the damaged cells, move to the injury site and secrete cytokines, growth factors and other substances that regulate the satellite cell pool.[12] Cytokines are responsible for cell-to-cell communication and stimulate the arrival of lymphocytes, neutrophils, monocytes and other healer cells to the injury site to repair the injured tissue.[13] The three important cytokines relevant to myotrauma are Interleukin-1 (IL-1), Interleukin 6- (IL-6) and tumor necrosis factor α (TNF-α). They are responsible for protein breakdown, removal of damaged muscle cells, and increased production of prostaglandins.

Growth factors are highly specific proteins, which include hormones and cytokines that are involved in muscle hypertrophy[14] and in the process of muscle regeneration: These processes result in regulation (activation) of the satellite cell population, which is controlled by growth factors and a sequence of intracellular events following binding of growth factors to their membrane receptors.[15] This biological process often leads to an increase in muscle fiber cross-section area or hypertrophy. Increased muscle mass could restore muscle strength and prevent injuries. This is of particular importance in cachectic patients. Cachexia is a form of wasting that affects 50% of cancer patients.[16] Increased muscle strength in cachectic patients may improve quality of life, improve response to cancer therapy and increase life span.

Radiation inhibits regeneration and muscle hypertrophy by damaging satellite cells. Radiation is thought to prevent satellite cell mitosis by causing breaks in strands of the cell's DNA. If a break occurs only on a single strand, the damage can be repaired by polymerases using the complementary strand as a template. If damage occurs at the same point on both strands, however, the deletion may be irreparable, which can lead to mitotic failure and cell death.[17] Low levels of radiation, which should disable mitotically active satellite cells but not the post-mitotic myonuclei of adult skeletal muscle, prevent compensatory hypertrophy (Figure 2). Following irradiation, a sufficient number of satellite cells were apparently unavailable either to fuse to form new fibers during regeneration or to fuse to

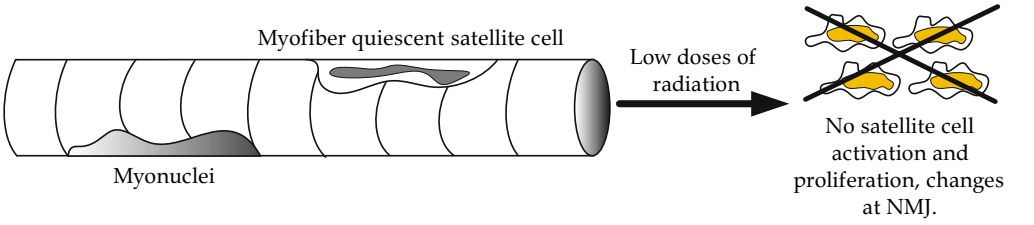

Figure 2. Satellite cells response to low doses of radiation. Low doses of radiation prevent muscle hypertrophy by impairing mitotically active satellite cells and induce changes in polysynaptic systems.

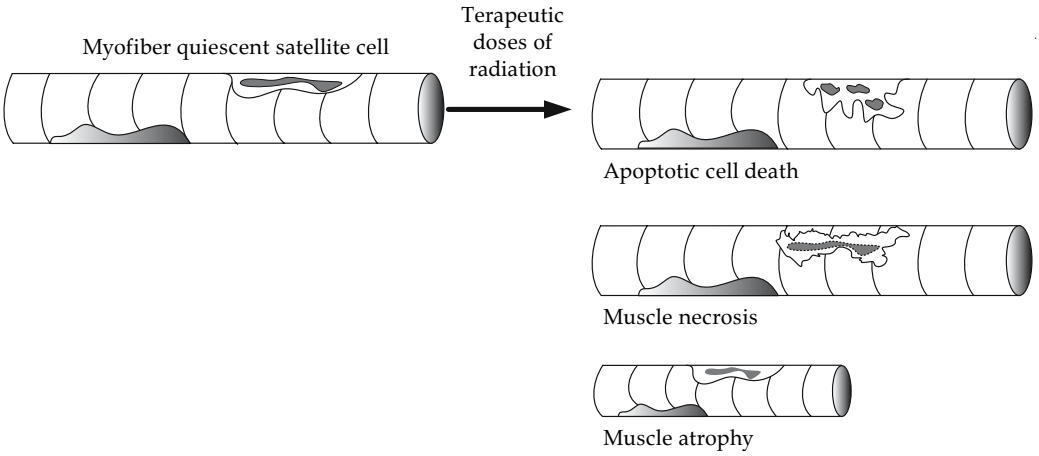

Figure 3. Skeletal muscle fiber response to therapeutic doses of radiation. Higher doses of radiation may induce apoptotic cell death and muscle necrosis, due to damage of blood capillaries and connective tissue. Muscle atrophy, resulting in myofiber degeneration and reduction of satellite cell population, was also observed.

overloaded fibers to allow hypertrophy occurring during overload.[18]

Olivé *et al*. showed that gamma irradiation (2 Gy) affects single skeletal muscle cells (satellite cells or myoblast) during development or cells in small clusters and induces its apoptosis. Since the effects of gamma rays are suppressed when cycloheximide is injected immediately after radiation, it can be suggested that gamma ray induced cell death is an active process associated with protein synthesis (extremely condensed chromatin).[19]

Transforming growth factor – β (TGF-β) is the prototypical family member of cytokines. The function of members of the TGF-β superfamily is to inhibit muscle proliferation and differentiation.[20] Following irradiation, the induction of a strong inflammatory response, fibrosis and vascular changes that associate with late radiation effects are linked to the action of TGF-β. *Myostatin* (GDF-8), a member of the (TGF-β) superfamily is a specific negative regulator of skeletal muscle mass.[21] It has been demonstrated that myostatin inhibitors could provide therapeutic benefit in diseases for which muscle mass is limiting.[22]

Many other factors may be involved in the regulation of satellite cells in skeletal muscle. Hematopoietic cells are responsible for constant maintenance and immune protection of every cell type of the body, including skeletal muscle. Radiation induces IL-1 and IL-6, which act as a radioprotectors of muscle and hematopoietic cells. TGF-β may down-regulate IL-1 and TNF-α and increase damage to hematopoietic tissue. The expression of TNF-α following radiation is believed to be regulated at the transcriptional level and involves the protein kinase C-dependent pathway.

Effects of radiation on differentiated muscle cells

Human striated muscle is highly radio-resistant on the criterion of morphological changes; however, delayed necrosis of muscle is observed after therapeutic doses of radiation (Figure 3).[23] The delayed necrosis of muscle may be primarily due to damage to blood capillaries and connective tissue. A cumulative dose of 4500 rads (45 Gy) produced detectable damage in mus-

cle 3 years post-radiation in patients with otherwise good general health. However, in patients suffering from carcinomatous cachexia or other debilitating diseases, muscle necrosis was constantly observed following exposure to about 2000 rads (20 Gy) after a similar latent period.[24] Lefaix *et al*. demonstrate that muscle fibrosis is a common and irreversible late effect of radiation on skeletal muscle.[25] A thyrotoxicosis condition (hypermetabolic clinical syndrome resulting from serum elevation in thyroid hormone T3 and T4 levels), produces muscle necrosis within 5 months after 2200 rads (22 Gy), whereas the control subjects, irradiated with same dose, did not show any muscle lesion over a period of 2 years. Children who have been treated with radiotherapy for a malignant disease may show muscular atrophy after a long latent period. This is seen in the back muscles of long-term survivors of Wilm's tumor and in the neck muscles of survivors of Hodgkin's disease, after radiation therapy.[23]

Neuromuscular junction

A neuromuscular junction (NMJ) is the synapse or junction of the axon terminal of a motoneuron with the motor end plate, the highly-excitable region of muscle fiber. The plasma membrane responsible for initiation of action potentials across the muscle's surface ultimately causes muscle contraction. In vertebrates, the signal passes through the neuromuscular junction via the neurotransmitter acetylcholine (Ach).

The precise mechanism of the radiation effects on NMJ is unknown. It has been suggested that temporary changes in membrane permeability for potassium and sodium, the liberation of pharmacologically active substances such as serotonin and ACh, and interaction between lipoproteins and free radicals, may contribute to synaptic changes after radiation.[26] Changes in membrane permeability for sodium and potassium influence the activity of electrogenic Na^+/K^+ pump. The pump in the skeletal muscle membrane generates a small electric current by extruding three Na^+ ions, while taking in only two K^+ ions in each cycle, and is responsible for action potential propagation.[27] Modulation of its activity leads to alteration of muscle excitability and contractility.

In general, low doses of radiation result in dose-rate dependent stimulation of synthesis of ACh, which is released by branching motor nerves. This causes Ach receptor-induced postsynaptic potentials and positively regulates the localization and stabilization of developing synaptic contacts and cellular uptake of 5- hydroxytryptamine (serotonin). Neurophysiological studies with intracellular electrodes have shown that irradiation with above 500 rads (5 Gy) reduces metabolic activity,[28] irradiation of 600 rads (6 Gy) produces significant changes in monosynaptic excitory and postsynaptic potentials.[29] Doses of 200 rads (2 Gy) of whole body irradiation cause changes in polysynaptic systems.[30]

Radiation and aging sarcopenia

It is now well established that cancer and aging are connected and that they share the same molecular events. In addition, it has been shown that radiation therapy accelerates the aging process in animals, but this remains controversial in humans.[31,32,33]

In humans, aging is a complex process that determines many physical and metabolic alterations correlated to the accumulation of oxidative damages in different tissues. Sarcopenia is an age-related non-pathological condition that includes a progressive loss of mass and strength in skeletal muscle, associated with a decline in the

fibers' functional capability.[34] A decrease in satellite cell number and/or proliferative capacity has been used to explain this phenomenon. Aging negatively affects the immune response, resulting in a decrease in inflammatory factors and macrophages.[35] $(Ca)^{2+}$ homeostasis also seems to be modified.[36]

The detrimental effects of aging on muscle have been shown to be restrained or even reversed with regular resistance exercise. Resistance exercise also improves the connective tissue harness surrounding muscle, thus being most beneficial for injury prevention and in physical rehabilitation therapy.[37]

The free radical theory of aging suggests a crucial role for free radicals produced by external factors, as well as radiation. The mechanism that is responsible for free radical – mediated damage in an organism is superoxide overproduction by mitochondria, which causes the inhibition of nitric oxide formation and bioavailability, one of the principal characteristics of aging.[38]

Cancer and aging share many common metabolic pathways and mediators during muscle wasting. Both cancer cachexia and aging sarcopenia may represent targets for future promising clinical investigations.[39]

Conclusion

Radiation, which should disable mitotically active satellite cells, prevents compensatory hypertrophy and nearly abolishes small fiber formation in the overloaded mammalian skeletal muscle. Irradiation may prevent hypertrophy by impairing activation, proliferation and/or differentiation of satellite cells. This suggests that satellite cell viability is essential for muscle hypertrophy.[40]

Therapeutic doses of radiation induce muscle atrophy in children and irreversible fibrosis in adult skeletal muscle. Little is known and little work has been done on the precise mechanism of how skeletal muscle adapts after radiation.

The mechanism underlying changes in the neuromuscular junction has not yet been completely clarified, and therefore calls for further investigation, especially of Na^+/K^+ pump expression and its activity.

More research should be devoted to the understanding of muscle wasting mediators, both in cancer and aging. Identification of common mediators in particular may prove to be a good therapeutic strategy for prevention and treatment of wasting in cancer cachexia and during normal aging.

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review

Malignant spinal cord compression

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Background. *Malignant spinal cord compression (MSCC) is a common and debilitating neurological complication of cancer. Because of the rapid progression of the neurological dysfunction, it is considered a medical emergency that demands a prompt diagnosis and treatment. Almost all of the MSCC are caused by an epidural compression from a tumour or a bony fragment from the collapsed vertebra affected by the metastasis. The most common of the tumours that metastasize to the spinal cord are breast and lung cancer, followed by lymphoma, myeloma, prostate cancer and sarcoma.*

Conclusions. *The most common symptom of MSCC is pain, followed by muscular weakness and autonomic dysfunction. MRI provides the best information regarding MSCC, so all patients should have a MRI as soon as possible. If the MRI is contraindicated, patients should have the CT scan done. All patients with newly diagnosed MSCC should receive corticosteroids immediately, even before the definitive diagnosis is made. Other treatment options are surgery with postoperative radiotherapy, radiotherapy only, specific medical therapies according to the tumour type and symptomatic therapy, (mainly opiates). The decision of treatment modalities should be made according to the NOMS (neurological, oncological, mechanical and systemic) principles. In spite of the advances, the treatment is still palliative and many patients with MSCC have a poor prognosis and a short survival.*

Key words: spinal cord; compression; surgery; radiotherapy

Introduction

Malignant spinal cord compression (MSCC) is a serious event that has a major impact on patient's life quality. It occurs in 5-14% of all cancer patients and is the second most common neurological complication of cancer after brain metastasis.[1] The consequences of MSCC can be devastating, leaving the patient with pain, paralysis and incontinence. Most of the affected patients have an advanced cancer with limited survival. Even though it is estimated that up to one third will survive at least a year after MSCC, it is considered a medical emergency that requires immediate diagnostics and treatment.[2]

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Epidemiology

Spine is the most common site of osseous metastases. It is involved in up to 40% of all cancer patients.[3] More or less every type of cancer can cause MSCC, the most common are breast cancer causing 29% of

MSCC and lung cancer with 17%, followed by lymphoma, myeloma, prostate cancer and sarcoma.[1,2,4] This statistics reflects the high incidence of these tumours.[2] Thoracic spine is affected in more than 70% of cases, followed by lumbosacral in 20% and cervical in 10% of cases. The statistics refers to the number (and consequent share) of the vertebrae in the different segments.[1] Around 20% of cancer patients with metastatic disease to the spine will experience MSCC.[4]

Patophysiology

Almost all MSCC (98%) are caused by an epidural compression.[1] It can develop in one of the following ways:[2]

1. Vertebral bone metastasis grows into the epidural space and compresses the spinal cord.
2. Para spinal mass grows through the neural foramina.
3. Metastasis in the vertebral body causes its collapse and bone fragments are displaced in the epidural space.

All mechanisms cause venous plexus compression, which leads to oedema of the spinal cord. Oedema and high vascular permeability cause increased pressure to the small arterioles which results in diminished blood flow causing ischemia of the white matter and, if this continues long enough, cord damage.[2] If the time of the compression is short, the effects are reversible. This is supposed to be the explanation for better treatment results of direct decompressive surgery compared to radiotherapy, which produces results only after several days.[5]

Most commonly the vertebral body is affected, which results in the anterior compression of the spinal cord (85-90%). Para vertebral masses growing trough foramina are less frequent (10-15%) and often caused by lymphoma, neuroblastoma and sarcoma. In these cases, bone is intact and plain radiography is not useful for the diagnostics.[1]

Other mechanisms that include intradural, intramedullary or leptomeningeal metastases are much less frequent, accounting only for about 2% of MSCC.[1]

Symptoms and signs

Most of the patients with MSCC experience one or more of the following symptoms: pain (88-96% of patients), motor weakness (76-78%), autonomic dysfunction (40-64%) and sensory loss 51-80%.[2,4] Some patients (8-37%) with MSCC also have asymptomatic involvement of other vertebral bodies.[1]

Pain

Every cancer patient with new back pain should be investigated for MSCC.[6] The reason for this sweeping approach is that progressive pain is the initial symptom in 96% of patients and it can be present weeks or even months before the development of the true MSCC.[4]

Pain is located at the level of compression and can be present with or without the radicular component. Backache can be elicited or worsened by a movement, vertebral compression, *valsalva* manoeuvre or the percussion of vertebral bodies.[1,6] It can be similar to pain of the degenerative disease of the spine. The difference between these two pains is that pain from MSCC can not be relieved by rest; actually with lying down it worsens. Occasionally Lhermitte's sign is positive (electric shock like sensation elicited in the spinal column and the limbs by neck flexion).[1]

Some authors differentiate between biologic "tumour related" pain and mechanical pain. Biologic pain is worse at night and early

in the morning and resolves during the day. It reflects the diurnal variation of endogen steroid secretion which is smaller at night. Patients experience flairs of pain because of the inflammatory mediators expressed by the tumour. It's an early symptom of the bone involvement without the involvement of the epidural space and is responsive to steroids and radiation. Mechanical instability pain differs from biological pain. It is rare and it worsens with movement. It is not so well respondent to steroids and irradiation. The radicular pain, that is mechanical instability pain in its nature, reflects the involvement of the epidural space and demands immediate diagnostic procedures. Most of the patients complain of biological pain but it may progress to mechanical one.[7]

Neurologic impairment

The second most common symptom is motor weakness. It develops in 80% of patients with MSCC. It usually involves the lower limbs (thoracic spine involvement) and causes difficulties with walking. Weakness can progress to paresis or to paraplegia. Gait disorders can also be seen with sensory ataxia as a symptom of posterior column compression. This sign can be misinterpreted as a polineuropathy due to the drug toxicity or as a part of the paraneoplastic syndrome.[1]

Sensory disturbances are present in half of the patients. They can have an ascending natural history beginning in the toes and progressing to the upper part as stocking-like sensations.[1,6]

Sympathetic involvement with loss of bowel and bladder function (incontinence, impotence and or retence) frequently appears very late in the course of the disease with the exception of *conus medullaris* involvement. It is present in 60% of MSCC patients and it is associated with a very poor prognosis. Bowel and bladder loss is related with perineal numbness. In the absence of numbness one should think of other causes such as narcotics.[1,6,7]

Intramedullary spinal cord metastases (ISCM)

ICSM is a very rare condition and accounts for only 1% of all spinal cord compressions. The most common cause is lung cancer followed by breast cancer. Back pain is less common as in epidural (ESCS) spinal cord compression (only in 38% *vs.* 90%). Other symptoms of ISCM are sensory deficits in 79% of cases, sphincter dysfunction in 60% and weakness in 91% of cases. The difference between ESCS and ISCM is also the incidence of brain metastases, which is very high in ISCM. It is estimated that 41% of ISCM patients have synchronous brain metastases. MRI of the whole spine and brain is the standard diagnostic procedure and therapy consists of corticosteroids in combination with irradiation without the surgical procedure.[2,4]

Diagnostic

Even if plain radiographs, bone scans and CT have some importance in diagnosis of MSCC, the best diagnostic modality is magnetic resonance (MRI). It provides to the clinician the best information on the three dimensional extension of the tumour and is an essential tool for planning the treatment (Figures 1a, 1b). MRI with and without the contrast should be performed in every patient where MSCC is suspected, because patients can have the synchronous MSCC in different spinal segments. Spinal cord compression is graded using T2-weighted MRI images (Table 1).[1-8]

Grades 2 and 3 are considered a high grade epidural spinal cord compression.

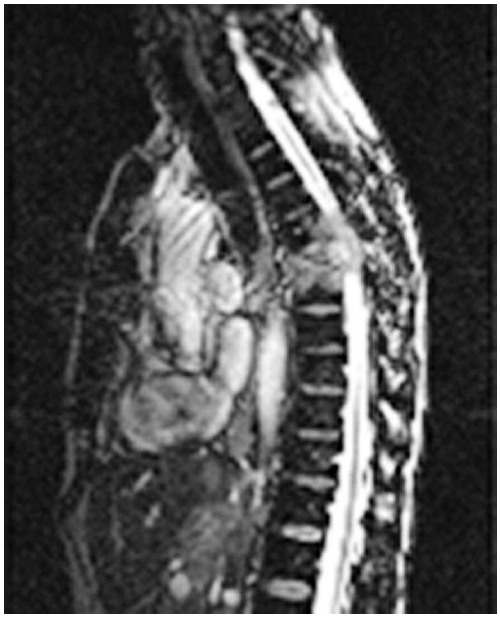

Figure 1a. MRI of patients with multiple vertebral metastases, which caused spinal cord compression.

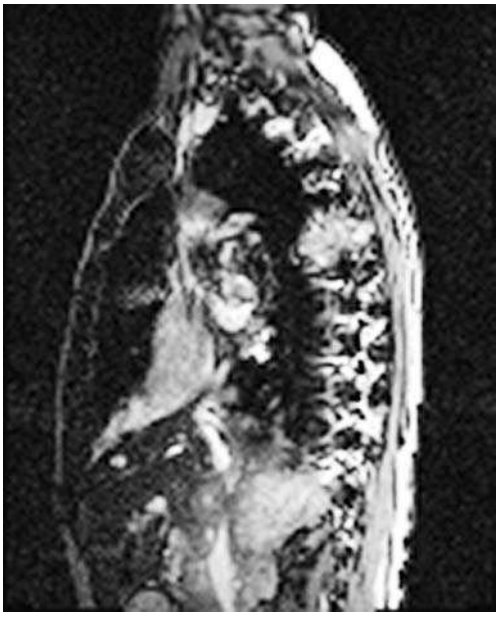

Figure 1b. MRI of patient with multiple vertebral metastases, which caused spinal cord compression.

Patients, who have contraindications for the MR, should be investigated with CT.[1-8]

Treatment

Despite advances in the treatment of cancer patients, the current treatment of MSCC is still palliative.[9] The principal treatment options are corticosteroids, surgery and radiotherapy in different combinations. The goals of such procedures are: improvement or preservation of neurological function and spinal cord stability, local tumour control and pain relief.[7,9] The treatment (irrespective of the type) should be administered immediately after the diagnosis, since it has been proven that the delay in treatment of only a few hours can cause permanent neurological impairment.[6]

Pharmacological approach

Patients with MSCC having neurological symptoms should receive a bolus of dexamethasone 10-20 mg intravenously, followed by 4-8 mg every six to eight hours.[6,8] Dexamethasone should be administered immediately, before any diagnostic or therapeutic procedures are started.[4,6,8]

High dose corticosteroids reduce the oedema by their anti-inflammatory func-

Table 1. Grading score of MSCC

Score number	Description
0	Involvement of the vertebral body without epidural space
1	Subarachnoid space impingement with no spinal cord deformation
2	Obliterated subarachnoid space and spinal cord deformation
3	Spinal cord deformation with no cerebrospinal seen

tion and they serve as an effective bridge to definitive treatment. Although there is a well known effectiveness of steroids, there is only one prospective randomized study that demonstrated it (and several retrospective). Sorensen *et al.* confirmed the superiority of steroids by comparing the results of treatment in patients who received 96 mg of bolus plus 96 mg in the first three days of treatment versus patients who did not receive steroids during the treatment. Three months and six months ambulatory status were better in the steroid group (81% *vs* 63% and 59% *vs* 33%).[10]

The question of the appropriate dosage of corticosteroids has arisen in the last years. Vecht *et al.* reported a study which compared the results of 10 mg versus 100 mg of loading dose plus 16 mg of maintenance dose. There were no differences in ambulatory status, pain reduction or bladder function in the two groups. The conclusion was that the use of a high dose of dexammethasone does not have significant benefits over lower doses, but leads to more serious side effects. That is why at the moment high doses are not recommended.[11]

Patients can be switched to oral steroids after 24-48 hours because corticosteroids have good oral bioavailability.[2] Patients on steroids should be monitored carefully for hyperglycemia, hypertension and electrolyte disorders. All patients should receive H2 blockers for gastric protection. Steroids must be tapered gradually.[4,8]

Surgical approach

First reports of treatment are from a hundred years ago, when Elsberg reported the first therapeutic recommendations regarding MSCC. The only therapeutic goal at that time was pain relief. This was due to the fact that therapeutic procedures for the underlying cancer were modest and because of the lack of appropriate diagnostic and therapeutic procedures. He recommended three interventions: surgical section of the affected nerve root, surgical section of the spinothalamic tracts or immobilization with a plaster.[12]

With the development of myelography and with better understanding of MSCC patophysiology in the 1970s, surgeons developed laminectomy for the decompression of the spinal cord. At that time the standard procedure was urgent laminectomy followed by postoperative RT. In the late 70s some studies were carried, which demonstrated that laminectomy combined with postoperative radiotherapy was not superior to the radiotherapy without surgical procedures. Consequently, surgery was abandoned for a long period.[5]

Today some authors think that laminectomy is not a good surgical option because most spinal metastases are located in the vertebral body anterior to the spinal cord. Laminectomy removes posterior elements of the spine while not removing the tumour. Furthermore, it can cause additional spine instability, because posterior elements, which are not affected by the tumour, are removed.[5]

New imaging modalities (MR, CT) that were developed, provided three-dimensional information about spinal cord compression. It became clear that most of the MSCC are caused by anterior compression of the spine because epidural tumour most often begins in the vertebral body. This information led the surgeons to develop new techniques. They developed the so called "anterior approach" in the 1980. The intention of this procedure is to remove the tumour and accomplish direct decompression of the spine and if needed at the same time to stabilize the spine with immediate spine reconstruction.[5]

In spite of the development of new techniques there were no, until recently, published randomized trials demonstrating

the superiority of surgery alone to another treatment.[5,12]

In the 2005 Patchell *et al* published a randomized trial. They compared radiotherapy and direct decompressive surgery plus postoperative radiotherapy. The study included patients with high grade epidural compression from a radioresistant tumour (confirmed with MRI as a true displacement of the spinal cord) and at least one of the neurological symptoms including pain. Another condition was that the patients should not have had total paraplegia for more than 48 hours before study entry. Compression could only be in one area and tumours of the cauda or spinal roots were excluded. Patients with other neurological impairments (including brain metastases) were also excluded. Other restrictions were: no previous irradiation to the spine and life expectancy of at least three months. Patients were randomized to two treatment groups. One group received surgery (the type of surgery was planned for each patient individually according to the type, extension of the tumour and spinal stability) and postoperative radiotherapy, and the other radiotherapy only. Radiation regimens were the same (10 x 3 Gy) in both groups. The primary study end point was the ability to walk after the treatment. Significantly more patients in the surgery group were able to work than in the radiotherapy group (84% *vs* 57%, p=0.01). Operated patients were able to walk for a longer time (median 122 days, vs. 13 days, p=0.003), and significantly more hospital patients (before treatment) regained the ability to walk (62% vs 19%, p=0.01). The conclusion was that direct decompressive surgery plus postoperative radiotherapy is superior to radiotherapy in the treatment of MSCC.[5]

Bilski reported that the surgical treatment also resulted in the prolonged survival. This is supposed to happen because operated patients remain ambulatory for a longer time and have less infections, thrombosis and other problems causing death in paraplegic patients. Patients treated with surgery also need less corticosteroids and analgesics.[7]

Some authors point out that the study of Patchell did not include patients with radiosensitive tumours, with total paraplegia of more than 48 hour of duration, with multiple areas of spinal cord compression and a large group of patients with only back pain and no neurological impairment who do benefit with radiotherapy. The role of surgery in these patients has not been established yet. A number of patients have radiosensitive tumours with or without spinal cord compression or radioresistant tumours without spinal cord compression. Radiosensitive tumours such as lymphoma, myeloma or breast cancer respond quickly to radiotherapy. They can be safely treated with irradiation because tumour will experience apoptosis soon enough resulting in an early decompression of the cord. The indication for operation in these patients is either progression during radiotherapy (which occurs rarely), prior irradiation of affected segment or spine instability.[7,12]

The goal in the future is to minimize the need for major operations. This can be achieved with the development of medical and radiotherapeutic treatments and with the evolving use of minimally invasive surgical procedures.[12]

Radiotherapeutical approach

Radiotherapy (RT) either with or without surgery is the most common treatment modality. The goals of administrating RT to the patients with MSCC are to reverse neurological impairment or at least to prevent further loss of motor function.[13]

Treatment planning begins with the information gained by MRI. Treatment fields are dependent on the site of the involved cord. Cervical spine is usually treated with

opposite lateral fields to avoid the oral cavity, thoracic spine with posterior field alone, and lumbar spine with the two opposite fields – one anterior and other posterior, and if needed, some alternative field positioning can be used.[4]

The standard radiotherapy regimen is 30 Gy in 10 fractions in two weeks. In spite of the effectiveness of this dose and fractionation, 10-27% of patients have a worse motor function after RT and the question of whether there is a benefit in administering a higher dose of radiation has consequently arisen.[13,14]

Rades *et al* compared the treatment results in patients receiving 30 Gy (10 x 3 Gy) compared to those receiving 37.5-40 Gy (15 x 2.5 Gy or 20 x 2 Gy). The escalation of the dose has not shown any benefit in motor function improvement, local control and survival, but did prolong the overall treatment time and the number of the visits to the RT department, which is a heavy burden for the frail and debilitated patients with MSCC. At the present time the escalation of the dose beyond 10 x 3 Gy is thus not recommended.[13,14]

Another dilemma regarding RT is if the same treatment results can be achieved with a lesser dose or less fractions. The questions arose because patients with MSCC are incapacitated and transport to the radiotherapy department and positioning for treatment causes them a major discomfort.

Different studies compared a standard radiotherapy regimen (10 x 3 Gy) with shorter courses (5 x 4 Gy, 1 x 8 Gy). The functional outcome was similar between different courses, but local control was worse in the "shorter" group. Patients who had a long-term survival needed more re-irradiations. Presently, 1 x 8 Gy is recommended for patients with a very bad prognosis and short survival where there would not be enough time to develop the relapse and other "late" consequences of such treatment.[14] However, some authors disagree with the use of this fractionation and propose 10 x 3 Gy as the best regimen. This is because they are being very cautious about late effects which are not presently known and progression after such treatment. Another argument is that the prediction of duration of life for patients can be quite misleading. Patients usually live longer that the doctors predict they would.[14,15]

Recurrence

Patients that live long enough have a high chance of having a local relapse. Progression leads to a greater need of pain medications, and more devastating events such as paraplegia and loss of the motor function.[2] In some reports as much as 69% of patients relapsed in the first and 94% 4 years after the first diagnosis of MSCC. Pain is the first symptom of recurrence and every new back pain should raise the suspicion. Recurrences are treated with re-operation or radiotherapy whenever possible.[7]

Decision on type of treatment

How to decide which patient should receive which treatment? The decision should be based on the fact that patients with MSCC have a metastatic disease with a poor prognosis, so treatment should be directed toward optimal palliation and minimal side effects.[16,17]

One of the decision making methods is NOMS and it has been developed at the Memorial Sloan-Kettering Cancer Center:[7,17]

1. N - Neurological (the degree of myelophaty, the degree of radiculopathy, the degree of radiologic spinal cord compression)
2. O - Oncological (the known radiosensibility of the tumour)

3. M - Mechanical instability (movement related pain)
4. S - Systemic disease (the extent of the disease, comorbidities and patient status)

Ad 1, 2. Neurological and oncological

The current treatment recommendations, using the NOMS system are:[7,17]

a. Patients with grade 0 or 1 (Table 1) of compression from a radioresistant tumour can be treated with radiotherapy only.
b. Patients with grade 2 or 3 of compression from a radioresistant tumour should be treated with surgery and radiotherapy.
c. Patients with radiosensitive tumours regardless of the degree of compression should be treated with radiotherapy only.

Ad 3. Mechanical instability

Mechanical instability is independently assessed. Instability pain is a movement related pain and differs depending on the level of the spinal cord affected. All patients with mechanical instability should be examined by a surgeon and, if medically suitable, should be operated independently of the N and O.[7,17]

Ad 4. Sistemic disease

If a patient has a high probability of dying from the procedure based on medical issues or would not derive benefit from the operation because related comorbidities would not allow for good rehabilitation, surgery is not offered. The decision to operate should be made on a multidisciplinary basis (surgeon, internist, medical and radiation oncologist).[7,17]

Some authors do not use the NOMS systems, but propose simpler rules instead:

– Surgery is indicated for patients that have a good performance status, expected survival of more than three months and involvement of only one spinal segment.[13-15]
– In the study of Jansson and coworkers the most important surgical indication was neurological impairment due to MSCC and not pain like in other studies.[17]
– The recommendations are that all the patients with MSCC should be evaluated by a surgeon and if the process is operable, patients should undergo surgical decompression, with or without stabilization and postoperative irradiation. Even for radiosensitive tumours surgery can often stabilize the spine. For patients with inoperable tumours definitive radiotherapy still remains the standard of care.[2]
– Because the indication for surgery of MSCC is usually limited to patients with involvement of one spinal segment who have a good performance status and expected survival of more than three months, RT alone is still an important modality in the treatment.[18]

Factors predicting survival

Most patients with MSCC have a bad prognosis, living only a few months after the diagnosis. Different survival rates have been reported in studies. One year survival rates range from 26 to 75%. This reflects the different criteria in selecting patients entering the study.[17]

Patients, who have visceral metastases, have shorter survival compared to those without (one year survival 8% *vs.* 65%; $p=0.01$).[1,18] Ambulatory patients survive longer than non-ambulatory (one year survival of 56% *vs.* 21%; $p<0.01$). A negative prognostic factor is also a short time between tumour diagnosis and development of MSCC. Patients with an interval of less than 15 months have a one year survival rate of 29%, compared to 59% of those with longer intervals ($p<0.01$). This reflects the faster growth of more aggressive tumours

and also explains the rapidity of development of motor dysfunction before the start of the treatment. Faster progression is associated with a worse prognosis (27% *vs.* 64%; p<0.01). Another important prognostic factor is the type of primary tumour. Lung cancer patients have the worst survival with the median survival time of 1 month, compared to breast with 2.5 months and prostate with 4 months.[19,20]

The post-treatment ambulatory status also has an impact on the survival. More mobile patients develop less potentially fatal complications like thrombosis or pneumonia and this is the reason why they survive longer.[17]

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A method on theoretical simulation of chromosome breaks in cells exposed to heavy ions

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Background. *The aim of this study is to assess an easy and quick method on simulating chromosome breaks in cells exposed to heavy charged particles.*
Methods. *The theoretical value of chromosome break was calculated, and the validated comparison with the experimental value by using a premature chromosome condensation technique was done.*
Results. *A good consistence was found to be appeared between the theoretical and experimental value.*
Conclusions. *This suggested that a higher relative biological effectiveness of heavy ions was closely correlated with its physical characteristics and besides, a safe approach on predicting chromosome breaks in cells exposed to heavy ions at off-line environment come to be considered. Furthermore, three key factors influencing the theoretical simulation was investigated and discussed.*

Key words: theoretical simulation; chromosome breaks; cells; heavy ions

Introduction

Radiotherapy is one of the most effective methods for the treatment of malignant tumors. GSI in Germany and HIMAC in Japan have successfully treated hundreds of patients with carcinomas by using accelerated heavy ions, such as carbon and silicon.[1] In comparisons with treatments involving X-rays and γ-rays, the high rate of cure with heavy ions is due to physical characteristics, such as high linear energy transfer (LET) at the Bragg peak region, low side-scattering etc. As reported in previous studies, cells exposed to various radiations resulted in chromosome breaks including chromatid discontinuity, misalignment of the distal, chromatid ring and so on.[2-7] These potential changes possibly cause the death of cells.[1,7] Since Gotoh *et al*. have reported the chemically induced premature condensed chromosome technique in 1995, an easy and quick method on detecting chromosome breakage was widely applied in the radiobiological and oncology works.[8] Murakami *et al*. used atom force microscope (AFM) to assess the accuracy of chemically induced PCC breakages in comparison with the results acquired through the light microscope vision; there

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was no significant difference between two methods, and thus it was validated that the PCC technique was suitable and reliable for radiation induced chromosome damage analysis.[9] Suzuki *et al*.[4-7], Kawata *et al*.[2,3] have employed different heavy ions with various LET and X rays to investigate the radiation induced chromosome breaks both in human normal fibroblast cells and malignant cells. The number of chromatid breaks was found to be linearly correlated with the absorbed dose of radiation. In comparisons with experiments involving X-rays or γ-rays, more isochromatid breaks were produced by the exposure to heavy ions, while chromatid-type breaks were dominantly possessed when cells were exposed to X/gamma rays.

Before the clinical treatment can begin, the therapeutic regimen must be defined and during this stage information on the individual patient radiosensitivity would be of great medical value. Several methods have been developed to measure cell radiosensitivity, for example, the colony assay and the cytoplasm-blocked micronuclei assay.[10-13] Previous data have shown that these two methods are not ideal. Briefly, the colony assay is the classic method for detecting radiosensitivity. The assay is precise but the formation of a clone takes at least 7 days. Conflicting views have been held concerning the detection of cell radiosensitivity with the cytoplasm-blocked micronuclei method.[14,15] Some scientists consider that there is a good relationship between the radiation-induced micronuclei and cell radiosensitivity, but others do not agree. Our previous works further improved the PCC technique in the area of chromosome analysis. Therefore, we have found the radiation induced chromatid /isochromatid breaks were closely correlated with cell surviving when exposed to heavy charged carbon ions.[16,17] The results suggested chemically induced PCC breaks could be possibly regarded as a good signal to predict radiosensitivity when cells exposed to high LET radiations.

Even though, we do not think it is perfectly ideal to predict radiosensitivity by using an experimental PCC technique, heavy ions are of great capability in killing cells, the online detection would bring a vast irradiation risk to operators. Thus, the main idea of this study is to simulate the chromosome breaks and validate the simulation combined with the experimental PCC technique.

Materials and methods

Simulation of chromosome breaks

In radiobiology and therapy the absorbed dose is defined as the energy deposited per mass unit. By definition 1 Gray to 1 Joule per kilogram. If a thin volume-thin compared to changes in the energy loss of a particle- is irradiated by a parallel beam of particles, the dose in Gray in this volume is given as

$$D = 1.602 \times 10^{-9} \times F \times LET \times \frac{1}{\rho} \quad \text{(equ.1)}$$

where D is the absorbed dose of cells, LET the energy loss rate, ρ the density of the stopping material and F the particle fluence i.e. the number of primary ions traversing the unit area. Commonly the density of cells was regarded as 1g/cm^3 in that the main content of cell is H_2O, thus the real-time particle fluence can be described as

$$F = \frac{D \times 1g/cm^3}{1.602 \times 10^{-9} \times LET} \quad \text{(equ. 2)}$$

Supposed that each heavy ion could interact with chromosome effectively and

result in one chromatid break, the number (N) of radiation induced chromosome breaks could be calculated by the following equation

$$N = \frac{F \times \frac{\pi\phi^2}{4}}{Number_{cells}} \qquad \text{(equ. 3)}$$

Cell culture and irradiation

Human normal liver cell line L02 (purchased from the Chinese Center for Type Culture Collection (CCTCC)) was grown in RPMI-1640 medium supplemented with 10% fetal calf serum at 37ºC in 5% CO_2, insulin 0.25 U/ml (Sigma production) was added to the culture medium. In the present study cell numbers need to be accurately counted, 2 ml cell suspension with density of 5×10^6 cells/ml were planted into ϕ 35 mm plastic dish to be irradiated.

L02 cells were irradiated with $^{12}C^{6+}$ ion beams generated by the HIRFL with a dose range from 0 to 8Gy. The initial energy of $^{12}C^{6+}$ ions was 80.55MeV/u, which was decreased by 13.58 mm Lucite (ρ = 1.2g/cm^3) to 20MeV/u before it reached the cells. The LET was 96.05keV/μm when carbon ions interacted with the cells located in the region of the Bragg peak. LET was calculated by the Trim Program 92 which was written by Bierstadt and Zeigler (Figure 1).[18]

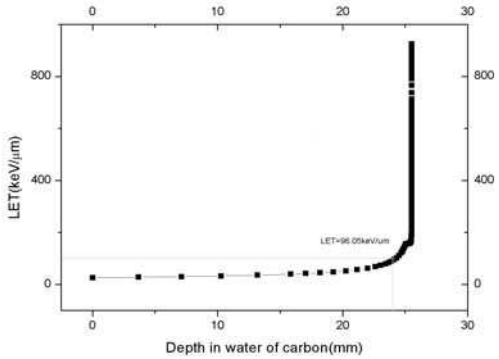

Figure 1. The relationship between the range and LET of carbon ions generated from HIRFL.

Dosimetry was performed with an air ionizing chamber where the uniformity of the carbon ion beams was 85%, as measured by CR39 technique.

Chromosome preparation

Calyculin A (BIOMOL America), used as the PCC inducer, was dissolved in 100% ethanol as a 1 mmol/L stock solution. In order to induce chromatid breaks, 50 nmol/L of calyculin-A was added to cell cultures 5 min before the irradiation. Cells were incubated for a further 30 min at 37ºC in 5% CO_2. The chromosome spread was harvested by swelling cells in 75 mmol/L of KCl for 20min at 37ºC and fixed with Carnoy's fixative. A final wash and fixation were completed before placing the cells on a glass slide and drying at 37ºC and 85% relative humidity.

The cells were stained with 5% Giemsa (5ml original Giemsa solution was diluted with 47.5ml 1/15M Na_2HPO_4 and 47.5ml 1/15M KH_2PO_4) for 20 min. According to the standard criteria, more than 40 G_2-phase cells were scored for each dose level.[19] Briefly, the chromatid discontinuity, misalignment of the region distal to the lesion, or a non-stained region longer than the chromatid width was considered as a chromatid break. An isochromatid break was considered as two breaks that occurred at the same position on each of two sister chromatids, *i.e.* a lesion through the two q arms or p arms of the chromosome was regarded as an isochromatid break. One isochromatid break was therefore scored as two breaks. The total chromatid breaks were calculated by summing the numbers of chromatid and isochromatid breaks. A total of 20 non-irradiated cells were examined; there were very few spontaneous chromatid breaks. The mean number of chromatid breaks in non-irradiated cells was subtracted from the mean number observed in ir-

radiated cells to provide the experimental data given in the result section.

Statistical analysis

All data were analyzed statistically with SPSS 8.0; note the data at each point are Mean ± Standard Error.

Results

Simulation of the chromatid breaks if L02 cells exposed to 12C6+ ions

If each ion interacted with cell resulted in just one chromatid break, the number of chromatid breaks could be simulated according to the equation 3 described above. Figure 2 shows the relationship between the absorbed dose and radiation induced chromatid breaks, fitted curve suggested an increasing linear tendency.

Experimental chromatid type and number in L02 cells exposed to 12C6+ ions

By using the premature chromosome condensation technique, two types of chromatid break were observed under light microscope, *i.e.*, chromatid-type and isochromatid break were induced by the accelerated carbon ion irradiation. With the increasing absorbed dose, both of two types of the chromatid number increased, while the number of isochromatid breaks were significantly higher than that of chromatid-type ones at each dose point (Figure 3).

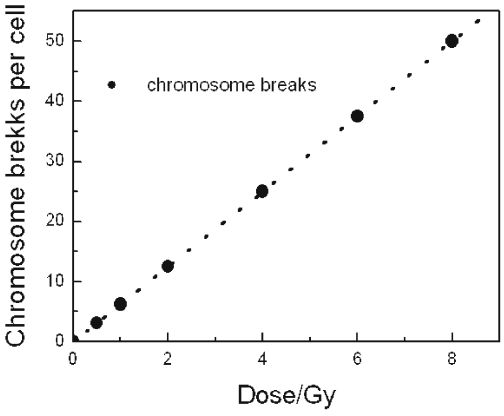

Figure 2. Correlation between chromosome breaks and ion flux of $^{12}C^{6+}$. Assumed that one $^{12}C^{6+}$ ion could produce one chromosome break (n=1)

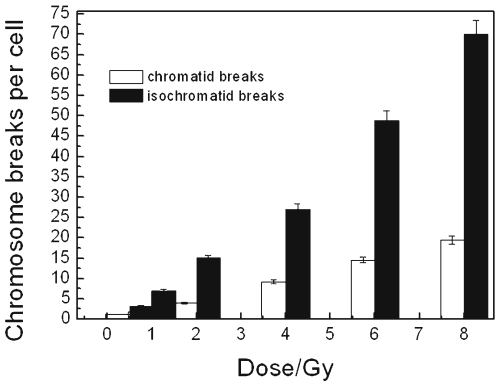

Figure 3. Experimental type and number of chromosome breaks of L02 cell irradiated with $^{12}C^{6+}$ ions chromatid breaks， isochromatid breaks, ($p<0.001$)

Comparison experimental number of chromatid breaks with simulated ones

An isochromatid break was considered as two breaks that occurred at the same position on each of two sister chromatids, *i.e.* a lesion through the two q arms or p arms of the chromosome was regarded as an isochromatid break. One isochromatid break was, therefore, scored as two breaks. The total chromatid breaks were calculated by summing the numbers of chromatid and isochromatid breaks. According to Figure 4, the same increasing linear tendency was apparent both in simulation and experiment regarded the relationship between the absorbed dose and the number of chromatid breaks. Given one ion produced just one break (named n=1), vast discrepancy appeared between simulation and experiment. When simulated curve with n=3, a

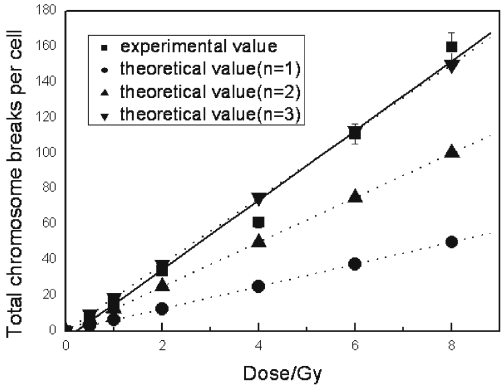

Figure 4. Comparison of simulated number of chromosome break exposed to $^{12}C^{6+}$ ions with experimental one simulation, experiment

good consistency was found.

Discussion

In comparisons with treatments involving X-rays and γ-rays, the high rate of cure with heavy ions is due to biophysical characteristics, such as high LET at the Bragg peak region, high relative biological effectiveness (RBE), low oxygen enhancement ratio (OER), low side-scattering etc.[1] Among these characteristics, high RBE is of most importance in the fact that the equivalent dosimetry of heavy ions would result in much more, even several times, cure ratio than that of low LET rays. Our previous studies confirmed that accelerated carbon ions were much more effective in inducing chromatid breaks than those of gamma rays.[16]

What makes heavy ions hold such priority in inducing chromatid break? Whether it is due to pure physical reaction or combination of the biological and physical reaction? The previous study suggested that bio-system would not be activated immediately by the radiation excitation, and the repair of the injured chromosome occurs in 2-12 h after the exposure.[20] It is obvious that the initial chromatid breaks result from the pure physical interaction. Kawata *et al.*[2,3] regarded a large amount of isochromatid breaks as a sign of cells exposed to high LET radiation, and mechanism of this phenomenon was explicated as a tensely energy deposition at target volume. The result of this study was in agreement with theirs. Recent works by Yang *et al.*[21] supposed that chromatid breaks were linearly negatively related with cell surviving; they suggested chemically induced chomatid breaks measured by PCC technique and can be acted as a quick and precise predictor of radiosensitivity when several normal and tumor cell lines exposed of heavy charged carbon particles.

In this work, carbon ions were used to induce L02 cells to produce chromatid breaks, the experimental result was in good agreement with the theoretical simulation when supposed that each ion leads to three breaks. This suggested some probability of theoretical simulation in place of experiment works to predict radiosensitivity.

Though ion influence (F) and absorbed dose (D) could be accurately detected by professional apparatus, the simulation results approached in this study just to express an ideal status which could be described as:

1. Distribution of carbon beams was uniform, i.e., the uniformity of radiation equate to 1;
2. Cells fully and uniformly covered the culture dish bottle and with single layer, no interspaces exist among cells;
3. Chromosomes occupied all the inner space of a whole cell.

But in fact, no evidence has been applied to support this ideal status. When these three factors neglected, the reliability of radiosensitivity would be discounted when radiotherapy regimen was established. Thus, the better simulation will inevitably be revised by three above factors; we named them approximation of radiation uniformity (K_1), detection of cell coverage rate (K_2)

and approximation of chromosome density (K_3). Based on these revisions, the equation (3) can be rewritten to

$$N' = \frac{F \times \frac{\pi\phi^2}{4}}{Number_{cells} \times K_2} K_1 K_3 \qquad \text{(equ. 4)}$$

As to different rays, their LET was not stable and fluctuates; K_1 can be defined by the equation 5

$$K_1 = \frac{\sum_1^n de/dx}{\frac{n}{de'/dx'}} \qquad \text{(equ. 5)}$$

Where $\sum_1^n de/dx$ is the sum of real-time LET value measured at the different time point, n the measure times, de'/dx' the one real-time LET value.

The equation 6 defined the cell coverage rate at culture dish bottle

$$K_2 = \frac{Number_{cells} \times S_{cell}}{\pi\phi^2/4} \qquad \text{(equ. 6)}$$

Where $Number_{cells}$ is the number of cells grow in culture dish, S_{cell} the area of single cell vertically faced to ion beams, $\pi\phi^2/4$ the inner area of culture dish.

At various phases of cell cycle, the chromosome agglomeration status and the content are different. Though it is not so well impacting the physical density of cells, the cross-section of the interaction between cells and ions closely linked with it. Chromosome in G_2 phase, is of better configuration, which is selected to analyze chromatid breaks, K_3 was denoted as

$$K_3 = \frac{G_2}{G_0 + G_1 + G_2 + S + M} = G_2$$

Where G_0, G_1, G_2, S, M were respectively the content percent of each phase cell number in all cells which were detected. This percent could be measured by flow cytometer (FCM).

In a word, considered these external factors, the simulation of chromatid breaks to predict the radiosensitivity in heavy ion radiotherapy project is of great possibility and feasibility.

Conclusions

Chemically induced PCC technique can be used to analyze chromatid breaks induced by heavy ion, the radiation induced by initial chromatid/isochromatid breaks can be regarded as a possible good sign of intrinsic radiosensitivity of cells exposed to heavy charged ions, the theoretical simulation of radiation induced by chromatid breaks was a simple and convenient and safe approach to measure the radiosensitivity.

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Solid tumors in young children in Moscow Region of Russian Federation

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Background. *The aim of the study was to assess the main epidemiologic characteristics of solid tumours in young children.*

Methods. *The data were retrieved from the Childhood Cancer Registry of Moscow Region, Russian Federation. Children aged 0-4 years with solid tumours diagnosed in 2000-2006 were included in the analysis.*

Results. *The data on total 142 children with solid tumours were analyzed. The average number of annually registered cases was 5.9 ± 1.1 in infants and 14 ± 1.8 in older children with male-to-female ratio 1.1:1 and 0.92:1, respectively. The average incidence rate (IR) of all solid tumours was 10.6 per 100.000 children/year in infants and 7.35 per 100.000 children/year in children 1-4 years old. The prevalent types of solid tumours in infants were hepatic (IR 2.46) and renal (IR 2.26) tumours. In children aged 1-4 years the following IRs for certain malignancies were found: CNS tumours 1.70, renal tumours 1.76, sympathetic nervous system tumours 1.73, retinoblastoma 0.87, soft tissue sarcomas 0.70, germ-cell tumours 0.19, hepatic tumours 0.14, and bone tumours 0.13.*

Conclusions. *The lower IR of CNS tumours can be explained by under-reporting of this cancer type in Moscow region as a result of patient scattering through non-oncological hospitals. As compared to the data from cancer registries of the most European countries and US, lower IR of sympathetic nervous system tumours and retinoblastoma and higher IR of liver tumours and soft tissue sarcomas in infants were revealed in this study.*

Key words: solid tumors; epidemiology; children.

Note: DY Kachanov and KV Dobrenkov contributed equally to this work.

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Introduction

Solid tumours represent about 50% of all malignant neoplasms in children aged less than 15 years.[1,2] The incidence and histological type of solid tumours is age-dependent. They make up more than 80% of all malignancies in infants.[3] The solid tumours to leukemias ratio is 2:1 in children aged 1-14 but 5:1 in infants less than 1 year. The

rate for neuroblastoma is four times higher in infants as compared to children of 1-14 years old.[4] Other embryonal tumors, e.g. Wilms', heptoblastoma and retinoblastoma also show higher rates in infants.

The accurate statistic data on children with solid tumours have been lacking until recently in Russian Federation. The nationwide cancer registration in the USSR was initiated in 1953. New cancer cases were registered by hospitals and were annually reported to Gertsen Oncological Institute in Moscow. The first population-based adulthood cancer registry (CR) was established in Saint-Petersburg in 1993. Despite of the earlier attempts to initiate registry for children with cancer in several regions, the first comprehensive childhood population-based CR was set up in Moscow Region (MR) in 2000. The information for this registry is collected from 10 different hospitals, which carry out an anti-cancer treatment in children residing in MR. This registry is maintained by the devoted cancer registry staff. Local paediatricians actively participate in data reporting, that allows for a more accurate and rapid registration.

The aim of this study was to assess the main epidemiologic characteristics of malignant solid tumours in young children in Moscow Region. MR is located in the central part of Russian Federation and occupies 46 thousand sq. km. Its total population is 6.6 million (2006). MR is divided in 72 municipal districts (*okrug*) which are clustered in 12 medical districts. Moscow city is not an administrative part of the region and its territory is not covered by MR cancer registry.

Patients and methods

The data on patients were collected prospectively starting from 01. 01. 2000 until 31.12.2006 (72 months). Children less than four years old residing in MR with an established diagnosis of malignant solid tumour during the given period of time were included in this study. The stratification was based on the International Classification of Childhood Cancer (ICCC), 2nd edition.[5] The following types of cancer were included in the analysis: III – CNS and miscellaneous intracranial and intraspinal neoplasms, IV – Sympathetic nervous system tumours, V – retinoblastoma, VI – renal tumours, VII – hepatic tumours, VIII – malignant bone tumours, IX – Soft-tissue sarcomas, X – germ-cell, trophoblastic, other gonadal tumours, XII – carcinomas, other malignant epithelial tumours, XIII – Other and unspecified malignant neoplasms.

The data were collected using both an active search and a passive retrieval. All hospitals in the region which carried out the treatment of children with cancer were visited by the CR personnel. The oncologists from the municipal districts of MR were required to send a special notification on every child with malignant neoplasm to the CR. The paediatricians annually informed the CR about all the children followed by them after the end of the anticancer treatment. Data were also routinely collected from pathology laboratories in the region. None of the cases were registered from death certificate only.

For each registered case, the data comprised civil status items (name, surname, gender, date of birth, address at the time of cancer diagnosis), and disease items (incidence date, primary site and histology, diagnostic basis). The localization of the primary tumour and histological type were allocated in accordance with the International Classification of Diseases for Oncology (ICD-O), 2nd edition.[6] The data on multiple primary tumours occurring in the same patient were registered separately.

All malignancies with an ICD-O behaviour code of ''/3'' were included in this study. Benign tumours, tumours of uncertain ma-

lignancy, or in situ carcinomas (ICD-O morphology behaviour code ''/0,'' ''/1,'' or ''/2'') were excluded. The exception was ''Central nervous system and miscellaneous intracranial and intraspinal neoplasms'' (ICCC group III). In line with the international recommendations all types of tumours were registered irrespective of the behaviour code.[5]

Annual population estimates in MR were based on the data of the population census of Russian Federation in 2002 and were received from Moscow Regional Committee of Federal State Statistics Service. The average annual population in the given period was 53,880 ± 2,564 for infants and 196,519 ± 6,105 for children aged 1-4 years. Age-standardized annual incidence rates (IR) were calculated using the direct method for infants and children of 1-4 years old. The IR was expressed as means ± SD per 100,000 children of the corresponding age group. The male to female (F/M) ratio was calculated as a number of solid tumour cases in males divided by that in females. Statistica 6.0 software was used for the statistical analyses.

Results

A total of 142 cases of solid tumours in children aged 0-4 years were registered in Moscow Region over the period 2000-2006. Forty one case (28.9%) was recorded for infants and 101 cases (71.1%) in children aged 1-4 years. The average number of annually registered cases of solid tumours in infants was 5.9 ± 1.1 (range 2-11) with F/M ratio 1.1 : 1 and 14±1.8 (range 10-22) with F/M ratio 0.92 : 1 in older children. Frequencies and annual incidence rates per 100,000 children by age group and tumour type are summarized in Table 1.

The average annual age-standardized IRs in infants was 10.6 ± 1.7. In this age group

Table 1. Frequencies, annual incidence rates (IR) per 100.000 children and F/M ratios by age group over the 2000-2006 registration period

Tumour type	< 1 year old			1-4 years old		
	n	IR	M:F	n	IR	M:F
III. Central nervous system tumours	3	0.79	0.5:1	24	1.70	0.9:1
IV. Sympathetic nervous system tumours	4	0.95	3:1	24	1.73	1.2:1
V. Retinoblastoma	3	0.80	2:1	12	0.87	0.7:1
VI. Renal tumours	9	2.26	0.8:1	24	1.76	0.8:1
VII. Hepatic tumours	10	2.46	2.3:1	2	0.14	1:1
VIII. Malignant bone tumours	0,0	0.0	0.0	2	0.13	1:1
IX. Soft-tissue sarcomas	6	1.69	1:1	9	0.70	1.3:1
X. Germ-cell, trophoblastic, other gonadal tumours	5	1.25	0.7:1	3	0.19	0.0
XI. Carcinomas, other malignant epithelial tumours	1	0.30	-	1	0.07	-
XII. Other and unspecified malignant neoplasms	0	-	-	0	-	-
All tumours	41	10.55	1.1:1	101	7.35	0.9:1

Table 2. Incidence Rates per 100.000 children in Moscow Region (MR) in 2000-2006 as compared to the data from cancer registries of the European Union (ACCISS, 1978–1997) and US (SEER, 1975-2001) for infants and children aged 1-5 years[1,9,11-15]

Tumour type	< 1 year			1-4 years		
	MR	Europe	US	MR	Europe	US
III. Central nervous system tumours	0.79	2.85	2.95	1.70	3.39	3.51
IV. Sympathetic nervous system tumours	0.95	5.26	6.30	1.73	1.81	2.00
V. Retinoblastoma	0.80	2.04	2.70	0.87	0.75	0.82
VI. Renal tumours	2.26	1.89	2.01	1.76	1.81	1.89
VII. Hepatic tumours	2.46	0.72	0.94	0.14	0.22	0.35
IX. Soft-tissue sarcomas	1.69	1.45	1.41	0.70	1.11	0.97

the most common type of cancer were hepatic tumours: 10 cases (24.3%), followed by renal tumours – 9 cases (21.9%) and soft tissue sarcomas – 6 cases (14.6%). The average annual age-standardized IRs in children age 1-4 years was 7.4 ± 0.9. CNS tumours, sympathetic nervous system tumours and renal tumours represented the most common malignancies in this age (24 cases or 23.7% for the each cancer group).

Embryonal solid tumours were prevalent in children younger than 4 years old. Among sympathetic nervous system tumours neuroblastoma was the most common histological type representing 82.2% (23 cases), followed by ganglioneuroblastoma – 17.8% (5 cases). Hepatoblastoma was the only hepatic tumour in this cohort of patients. Wilms tumour was the most common entity among renal tumours representing 84.9% (28 cases) of diagnoses followed by clear cell sarcoma of the kidney (3 cases, 9,1%), renal-cell carcinoma (1 case, 3,0%) and malignant rhabdoid tumour of the kidney (1 case, 3,0%). Rhabdomyosarcoma was the prevalent histological type in children with soft tissue sarcoma comprising of 80% of diagnosis (12 cases).

Discussion

The present study was the first that analyzed incidence rates of solid tumours in children in Moscow Region of Russian Federation. It was also the first study on the comparison of statistical data on solid tumours in young children in the country with international data.

We have shown that the incidence rate of solid tumours in infants was higher than in 1-4 years age group, and was comparable with the data from cancer registries of the industrialized countries.[1-3] The overall incidence rate in the both age groups was lower than in European countries and in the USA (Table 2). It can be attributed, first of all, to under-reporting of patients with CNS and sympathetic nervous system tumours that are the most frequent tumour types for the given age group. CNS tumours represent considerable challenges for registration. As some of the patients with CNS tumours can be treated in neurological departments of non-oncological hospitals and further they do not receive any cancer-specific treatment (i.e. chemotherapy, radiotherapy), the information on them is not transmitted to the childhood cancer registry. The low rate of registration has been also observed in other countries. For example, the incidence rate for childhood CNS tumours in the 1980's in Germany was considerably lower than the median incidence rate for the world's largest registries. This lower incidence has been explained by under-reporting of CNS tumours in Germany. A more complete reg-

istration was achieved in particular by the organization of clinical trials for the given group of patients in the beginning of 90's.[7]

Under-reporting of neuroblastoma in children aged < 1 year was revealed in our study. Since neuroblastoma in infants can have less aggressive course as compared to older children, patients may remain asymptomatic while the tumour mature. Beyond the infancy these children undergo the surgical treatment for the non-malignant tumours (e.g. ganglioneuromas) in non-oncological hospitals and are not registered. The low level of registration of patients with sympathetic nervous system tumours was shown in epidemiologic studies in other regions of Russian Federation. The under-reporting rate was estimated as high as 30%.[8] Spix *et al.*[9] on behalf of Automated Childhood Cancer Information System project (ACCIS) analyzed the incidence of neuroblastoma in Europe over the period 1978–1997. As it was shown, the difference in overall incidence of neuroblastoma across five European regions was mainly the result of variations in incidence in children under 2 years of age, while the incidence at older ages was almost identical. Interestingly, the higher incidence rate (the overdiagnosis phenomenon) was observed in regions with ongoing neuroblastoma screening programs (some countries in Western Europe). The authors suggested that the introduction of screening programs in a number of countries could make an indirect impact on the increased incidence as consequences of the increased awareness of paediatricians on the possibility of development of the given tumour. A wide implication of diagnostic ultrasound during the antenatal and perinatal period in the mid 1980's in Italy has led to the increased incidence of neuroblastoma.[10] Our own experience has shown that a potential improvement of registration quality in young children with solid tumours can be achieved by introducing of educational programs for paediatricians in the regional hospitals. These programs are aimed to increase the level of oncological awareness among paediatricians which can result in earlier diagnostics of tumours in young children, in particular neuroblastoma.

An interesting observation obtained from this study was the high incidence rate of hepatic tumours in infants (2.46 per 100,000 children) (Table 2). The highest incidence rate of hepatoblastoma in infants was noted in East European countries (1.18 per 100,000 children).[11] The further studies are needed to investigate this difference.

As compared to the data from cancer registries of the most European countries and US, lower IR of sympathetic nervous system tumours and retinoblastoma and higher IR of liver tumours and soft tissue sarcomas in infants were revealed in this study. These data reflect difficulties in registration of malignant solid tumours in children in one of the most populated regions of Russian Federation. The scattering of the patients through the different hospitals implies the scrupulous data retrieval by dedicated personnel. Nevertheless, the registry has proved its incremental role in the financial and administrative management in the region by providing accurate information for the evolving methodologies in cancer treatment and has become an integrative component of regional healthcare systems.

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Current system of childhood cancer registration in Belarus

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Background. *The purpose of this article is to describe the current system of childhood cancer registration in Belarus and the main principles of organization of Childhood Cancer Sub-registry of Belarus including the retrospective and prospective (formalized and visualized) data collection.*

Conclusions. *The use of visualized data of the initial diagnostic system not only helps to optimize the prospective recording in the cancer registry, but also contributes to the better verification of individual cases that is sometimes required in the retrospective research and in cases of changes in classification of malignant neoplasm.*

Key words: cancer registry; children

Introduction

A high quality population-based cancer registry approved by the government and a recognized international organization is foundational for any epidemiological study and worldwide acceptance of its results. A review of disputable cases by experts is a necessary step for the data input and for the retrospective and for the prospective cancer registry data base verification. The purpose of this article is to describe the current system of childhood cancer registration in Belarus and the main principles of organization of Childhood Cancer Sub-registry of Belarus including the retrospective and prospective (formalized and visualized) data collection.

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Retrospective data collection

Previously, there were three main data bases for adult and childhood cancer in Belarus: Belarusian State Cancer Registry within the Belarusian Institute for Medical Technologies, Registry for Hemablastoses within the Research Institute for Hematology and Transfusiology, and Cancer-registry within the Research Institute for Oncology and Medical Radiology. These cancer registries had definite limitations in case verification and registration according to the modern classifications and standards used in childhood oncology.

That is why the Childhood Cancer Sub-registry was organized by the Ministry of Health of Belarus in 1999 based at the

department for clinical and epidemiological research of the Belarusian (National) Research Center for Pediatric Oncology and Hematology (BRCPOH) in Minsk. This Center is responsible for diagnosing and treating all types of malignant neoplasm, except thyroid cancer, in children and adolescents of Belarus (all mentioned categories of patients from the entire country must be diagnosed there and most of them are treated at that Center). This fact contributes to the easier collection and verification of cases for the Childhood Cancer Sub-registry.

The childhood Cancer Sub-registry of Belarus has been undertaking the prospective data collection since the August 1999. As a first step of the retrospective accumulation of cases, the data base for all cancer cases in children 0-14 years old had been actively collected with the help of the Belarusian State Cancer Registry back to 1989, and verified by the re-examination of slides, disease histories, death certificates etc. with the participation of oncologists, hematologists and cytomorphologists from BRCPOH and the Research Institute for Oncology and Medical Radiology (Minsk, Belarus). In 2001 the official name 'Childhood Cancer Sub-registry of Belarus', designated and confirmed by certificate, was received (certificate #0170100025 in the state register of information resources of Belarus, in force from 12.12.2001). The leukemia's part of the automatic data base was subsequently extended back to 1986 with the additional collaboration of the Research Institute for Hematology and Blood Transfusion, which has a prospective database of hemablastosis registered according to the ICD-9 since 1979 and had performed leukemia studies previously published.[1-4] Since 2004 the Childhood Cancer Sub-registry of Belarus prospectively collects the cancer cases in adolescents (15-19 years old) and extends the data bases for this age retrospectively.

Principles of prospective data organization

The nationwide Childhood Cancer Sub-registry of Belarus is a computerized system performing previously active data collection that is standardized according to the IARC recommendations[5] with nearly 100% level of microscopically verified cancer cases diagnosed after 1990. Its main goal is to register all malignant neoplasm cases in children and adolescents in Belarus with the creation of the maximally verified data base of nosological/morphological forms and continued follow-up events for clinical and epidemiological studies.

The registry staff is divided into a formalized data input group, a visualized data input group, a follow-up group, and a group for technical service and software assistance.

Since the Childhood Cancer Sub-registry of Belarus is located in the BRCPOH (the only national center responsible for childhood cancer in Belarus), every cancer case is entered into the cancer registry immediately after establishing the diagnosis for more than 95% of cases, and less than 5% are collected actively during the calendar year.

The following parameters are registered: personal data of patients (names, changed names during the life, passport identification number of a patient or his/her parents, date of birth, address at the diagnosis and other addresses changed during the follow-up), information about disease (date of disease, date of diagnosis, basis of diagnosis, stage, reference number, date and conclusion of cytomorphological examination, expert's name, the formalized and visualized data of primary diagnostic examinations); information about the treatment and remission status, date and status at follow-up, sources of information, date and cause of death by death certificate; time- and dis-

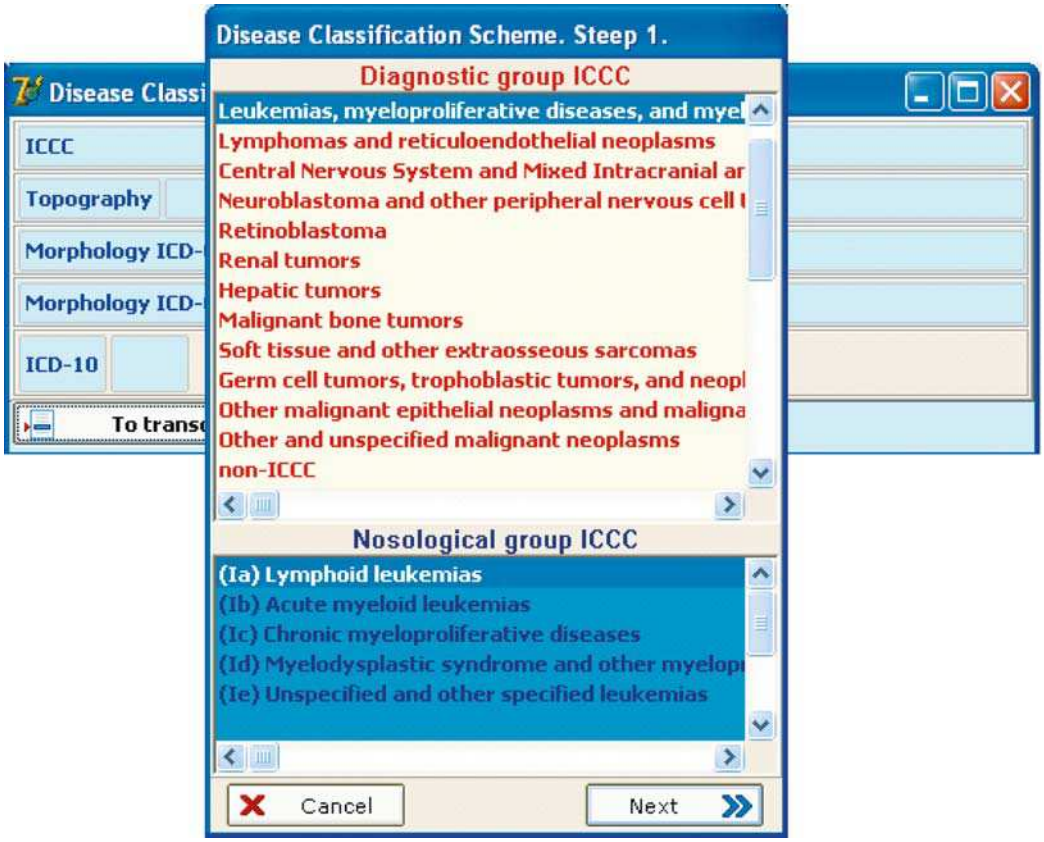

Figure 1. Classification algorithm using in the Childhood Cancer Sub-registry of Belarus.

ease-relation of malignances (*de novo*, secondary, or multiple primaries). All cancer cases are coded according to ICCC-3[6] and ICD-O-3 (morphology and topography), and converted automatically to ICD-O-2 and ICD-10 (Figure 1).

The sources of primary information are the following: hematological departments of regional clinics, hematological consultations, oncological dispensaries, specialized clinics, autopsy units and morphological laboratories. As the filling of the information about the primary established/suspected cancer cases and cancer deaths to Belarusian State Cancer Registry is mandatory for all medical institutions in Belarus, the Childhood Cancer Sub-registry of Belarus fulfils the annual verification of its database with the Belarusian State Cancer Registry using codes ICD-O-2 and ICD-10. Additionally, the Childhood Cancer Sub-registry of Belarus verifies its data base on an ongoing basis with the clinical registries organized in BRCPOH for every nosological group and treatment protocol.

Since 2004, the database of the Childhood Cancer Sub-registry has been also prospectively populated with the visualized data of morphological, immunological, cytogenetic and molecular-biological methods as well as computer tomography (CT) and ultrasound (US) examinations for the prospective and retrospective verification of cancer cases due to the creation of the computer-aided system for the registration and accumulation of the visualized and formalized

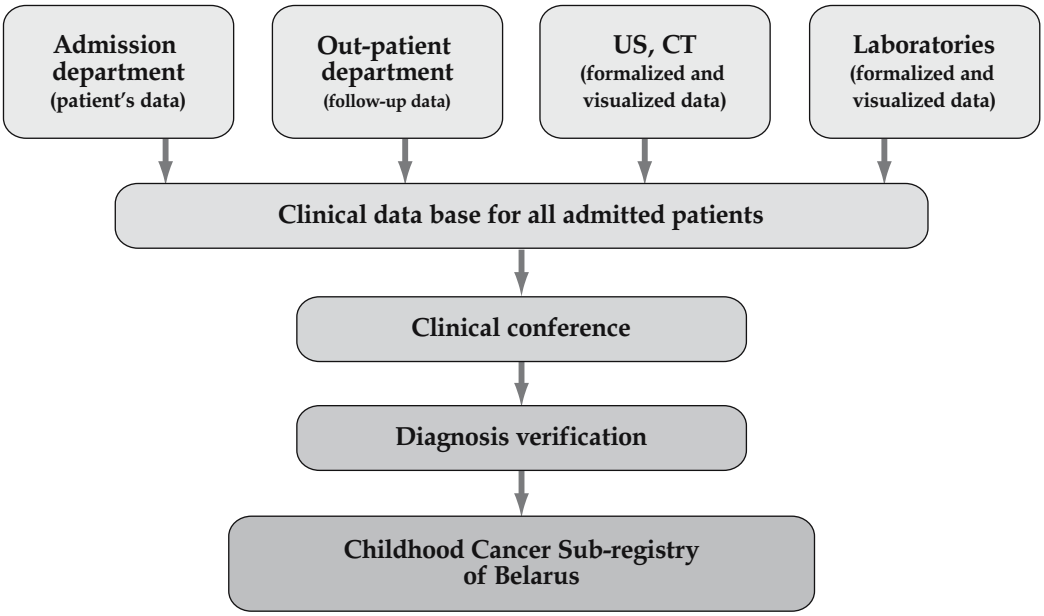

Figure 2. The information flows into the Childhood Cancer Sub-registry realized with help of the computer-aided system for formalized and visualized data of the primary diagnostic complex for patients with cancer inside the Belarusian Research Center for Pediatric Oncology and Hematology.

data of the primary diagnostic complex for patients with cancer.[7,8] This system includes the Clinical Base for Visualized and Formalized Data, where all information is accumulated from the automated (computer-aided) doctor's workplaces located in different laboratories (cytological, morphological, immunological, cytogenetical and molecular genetical) and in the departments for US and X-ray/CT diagnostics. The system of the data visualization also enables us to provide the distant consulting services as well as the weekly clinical conferences where all primary cancer cases are discussed before the input into the data base of the cancer registry (Figure 2).

The short-term (within the first five years after the end of the anti-cancer treatment) and the long-term follow-up is implemented by active (including expeditions) and passive monitoring using the sources of the out-patient department of BRCPOH (information goes automatically into the registry data base), the Belarusian State Cancer Registry, autopsy units and morphological laboratories, medical institutions (clinics and territorial policlinics), registry offices and hospices. The short-term follow-up requires the update of the case's status as minimum as once a year, and long-term – as minimum as once a two years; and the registry's software alarms the necessity of updating and generates a list of cases.

The system enables automatic calculation of incidence (crude, TASR – word and euro standard), overall survival and mortality rates for various nosological groups, ages, regions, and provides TERSON-code maps.

The patient information and consent to registration and continued follow-up are requested to be signed at the time the personalized data are entered into the Childhood Cancer Sub-registry database.

Conclusions

Timely and quality recording of childhood cancer at the national level and accumulation of verified information in the database of the automatic cancer registry not only supports a long-term epidemiologic and clinical research, but also enables experts to quickly obtain data on incidence, survival and death rate for a given span and undertake a prompt analysis of the existing trends, e.g. at request of the Ministry of Health for planning future action. In our opinion, the use of visualized data of the initial diagnostic system not only helps to optimize the prospective recording in the cancer registry, but also contributes to the better verification of individual cases that is sometimes required in the retrospective research and in cases of changes in classification of malignant neoplasm.

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The programs for visualization of primary diagnostic complex and code-converting were created by specialists of United Institute for Informatics Problems of National Academy of Science of Belarus with the support of International Scientific Technical Center, (Project B-736, http://tech-db.istc.ru/ISTC/sc.nsf/html/projects-all-by-number.htm?open&start=B).

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Zdravljenje bolnika s subklavijskim sindromom kraje krvi ter zožitvijo skupne iliakalne arterije

Gjikolli B, Herceglija E, Jaganjac S, Hadžihasanović B, Nikšić M, Hadzimehmedagić A, Dilić M, Solaković E, Merhemić Z, Bešlić Š, Lincender L, Myftary R

Izhodišča. Namen članka je opisati bolnika s subklavijskim sindromom kraje krvi in zožitvijo skupne iliakalne arterije, pri katerem smo na Inštitutu za radiologijo UKC Sarajevo izvedli zapleteno interventno radiološko zdravljenje.

Prikaz primera. Pri 57-letnem bolniku, ki se je predhodno že zdravil zaradi možganske ishemije, smo ugotovili okluzijo leve skupne karotidne arterije in stenozo desne interne karotidne arterije. Bolnik je imel vrtoglvico z moteno sposobnostjo pogleda navzgor. Najprej smo naredili rekanalizacijo in vstavili opornico v levo subklavijsko arterijo. Podobno smo zdravili zožitev desne interne karotidne arterije. Čez 4 mesece pa smo naredili balonsko dilatacijo, saj je prišlo do ponovne stenoze desne interne karotidne arterije.

Pred in po interventnih radioloških posegih smo naredili preiskavo z računalniško tomografijo (CT), CT angiografijo, preiskavo z barvnim Doppler ultrazvokom in magnetno resonanco (MR) ter MR angiografijo.

Zaradi anamnestičnega podatka, da je prišlo do težav pri femoralni digitalni subtrakcijski angiografiji, smo naredili CT angiografijo trebušne aorte in zgornjega dela spodnjih udov ter ugotovili zožitev leve skupne iliakalne arterije.

Zaključki. Po zdravljenju žilne zožitve je potrebno skrbno sledenje bolnika, da bi lahko pravočasno preprečili žilno zaporo.

Radiol Oncol 2008; 42(1): 15-22.

Radiacijake poškodbe skeletne mišice

Jurdana M

Izhodišča. Odrasla skeletna mišica je odporna na ionizirajoče sevanje, razen pri uporabi večjih doz. To dejstvo lahko pripišemo manjšemu številu radiosenzibilnih proliferacijskih celic v odrasli dobi. Razvijajoča se skeletna mišica pa je izjemno senzibilna na ionizirajoče sevanje, poleg tega radioterapija v otroštvu lahko sproži mišično atrofijo. Sevanje preprečuje aktivacijo, proliferacijo in diferencijacijo mišičnih satelitskih celic ter vpliva na živčno-mišični stik, kjer privede do sprememb v propustnosti membrane, povezane z delovanjem Na+/K+ črpalke. Poleg tega sevanje preprečuje mišično rast v razvoju in po poškodbi.
Zaključki. Rezultati raziskav po sevanju kažejo na značilne spremembe v aktivaciji satelitskih celic. Inhibitorji nekaterih beljakovin, podobnih citokinom v skeletni mišici, lahko sprožijo terapevtski učinek pri obolenjih, pri katerih je mišična masa omejena; izboljšajo dovzetnost za tumoralno terapijo ter povečajo življenjsko dobo pri bolnikih s kaheksijo.

Radiol Oncol 2008; 42(1): 23-31.

Metastatska vtesnitev hrbtenjače

Rajer M, Kovač V

Izhodišča. Metastatska vtesnitev hrbtenjače je urgentno stanje, ki zahteva takojšnjo diagnostiko in zdravljenje. Prizadane 5-14% vseh bolnikov z rakom. Vzrok za vtesnitev so bodisi osteolitični kostni zasevki v telesu vretenca, ki povzročijo patološki zlom in premik kostnih delcev v hrbtenični kanal, bodisi tumorske mase, ki rasejo v epiduralni prostor in vtisnjujejo hrbtenjačo. V hrbtenico najpogosteje zasevajo rak dojk in pljuč, sledijo jim limfom, mielom, rak prostate in sarkom.

Zaključki. Najpogostejši simptom vtesnitve je bolečina, ki je lahko podobna bolečini pri degenerativni bolezni hrbtenice. Ostali simptomi so mišična šibkost, vse do pareze ali paralize, ter avtonomne disfunkcije, kot so motnje odvajanja vode in blata, zlasti inkontinenca. Pri vseh bolnikih, pri katerih postavimo sum na maligno vtesnitev, je potrebno narediti MR preiskavo, v primeru kontraindikacij pa CT. Odločitev o načinu zdravljenja je multidisciplinarna in odvisna od nevroloških izpadov, narave tumorja, mehanične nestabilnosti hrbtenice in splošnega bolnikovega stanja. Bolnike lahko zdravimo z operacijo, kateri je dodano pooperativno obsevanje, ali samo z obsevanjem. Vsi bolniki pa potrebujejo dobro podporno zdravljenje, ki vključuje kortikosteroide in protibolečinsko zdravljenje. Kljub napredku diagnostike in terapije bolezni, je zdravljenje še vedno le paliativno. Preživetje je pri teh bolnikih kratkotrajno.

Radiol Oncol 2008; 42(1): 32-8.

Teoretična simulacija prelomov kromosomov v celicah, izpostavljenih težkim ionom

Yang J, Li W, Jing X, Wang Z, Gao Q

Izhodišča. Študija opisuje enostavno in hitro metodo za simulacijo kromosomskih prelomov v celicah po izpostavitvi težkim nabitim delcem.
Metode. Izračunane teoretične vrednosti kromosomskih prelomov smo primerjali z eksperimentalnimi podatki predčasno kondenziranih kromosomov.
Rezultati. Ugotovljena je bila dobra korelacija med teoretičnimi in eksperimentalnimi podatki. Podatki potrjujejo korelacijo med relativno biološko učinkovitostjo težkih nabitih delcev in njihovimi fizikalnimi karakteristikami.
Zaključki. Ta metoda dobro in varno napoveduje kromosomske prelome v celicah, obsevanih z težkimi nabitimi delci.

Radiol Oncol 2008; 42(1): 39-44.

Solidni tumorji pri mlajših otrocih v Moskovski regiji Ruske federacije

Kachanov DY, Dobrenkov KV, Shamanskaya TV, Abdullaev[1] RT, Inushkina EV, Varfolomeeva SR, Rumyantsev AG

Izhodišča. Namen raziskave je bil oceniti glavne epidemiološke značilnosti solidnih tumorjev pri mlajših otrocih.
Metode. Podatke smo dobili iz Otroškega registra raka Moskovske regije Ruske federacije. V analizo smo vključili mlajše otroke, stare od 1-4 leta, ki so jim v letih 2000-2006 odkrili solidni tumor.
Rezultati. Obravnavali smo podatke 101 otrok s solidnim tumorjem. Povprečno število letno ugotovljenih primerov raka je bilo 14,4 ± 1,8. Razmerje med dečki in deklicami je bilo 0,92:1. Povprečna letna incidenčna stopnja vseh solidnih tumorjev je bila 7,35 na 100.000 otrok. Našli smo naslednje letne incidenčne stopnje na 100.000 otrok za posamezne tumorje: tumorji centralnega živčnega sistema 1,70, ledvični tumorji 1,76, tumorji simpatičnega živčevja 1,73, retinoblastomi 0,87, sarkomi mehkih tkiv 0,70, germinalnocelični tumorji 0,19, jetrni tumorji 0,14 in kostni tumorji 0,13.
Zaključki. Nižjo incidenčno stopnjo tumorjev centralnega živčnega sistema lahko razložimo z nezadostnim poročanjem o tej vrsti raka v Moskovski regiji. Takšni bolniki so namreč zdravljeni tudi v neonkoloških bolnicah. Ko smo naše podatke primerjali s podatki registrov raka večine evropskih držav in iz Združenih držav Amerike, smo ugotovili nižjo incidenčno stopnjo tumorjev simpatičnega živčevja in retinoblastomov ter višjo incidenčno stopnjo jetrnih tumorjev in sarkomov mehkih tkiv.

Radiol Oncol 2008; 42(1): 45-9.

Beloruski register raka za otroke

Savva NN, Zborovskaya AA, Aleinikova OV

Izhodišča. Namen članka je opisati Beloruski register raka za otroke ter načela in organizacijo zajemanja podatkov otroškega raka v Belorusiji. Register vključujejo retrospektivno in prospektivno zbiranje podatkov.
Zaključki. Sistem vidne predstavitve podatkov o začetnih diagnozah omogoča optimalno prospektivno beleženje podatkov v registru raka, hkrati pa pripomore k boljšemu preverjanju posamičnih primerov, ki je občasno potrebno pri retrospektivnih raziskavah in pri spremembah klasifikacije rakavih obolenj.

Notices

*Notices submitted for publication should contain a mailing address, phone and/or fax number and/or e-mail of a **Contact** person or department.*

Lung cancer

April 23-26, 2008
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E-mail pia.hirsch@uchsc.edu

Lung cancer

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See http://www.iaslc.org

Lung cancer

June 12-14, 2008
The "11th Central European Lung Cancer Conference" will be offered in Ljubljana, Slovenia.
Contact Conference secretariat, Ms. Ksenia Potocnik, Department of Thoracic Surgery, Medical Centre Ljubljana, Slovenia; or call +386 1 522 2485; or fax +386 1 522 3968; or e-mail ksenia.potocnik @kclj.si; or see http://www.ce-lung2008.org/

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October 9-10, 2008
The ''3rd Latin American Cancer Conference'' will take place in Vina del Mar, Chile.
E mail nisehy@uol.com.br or rodrigo.arriagada@ki.se

Oncology

November 13-15, 2008
The Chicago/IASLC/ASCO/ASTRO symposiums "Malignancies of the Chest and Head and Neck" will be offered in Chicago.
E-mail: evokes@medicine.bsd.uchicago.edu

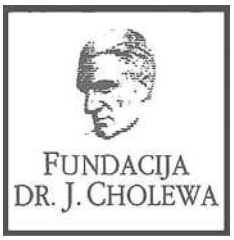
Lung cancer

August 21-24, 2009
The "13th World Conference on Lung Cancer" will be offered in San Francisco, USA.
Contact Conference Secretariat; e-mail WCLC2007@ ncc.re.kr; or see http://www.iaslc.orgIumages/ 12worldconfannounce.pdf

Oncology

September 4-8, 2009
The "34th ESMO Congress" will take place in Vienna, Austria.
Contact ESMO Head Office, Congress Department, Via La Santa 7, CH-6962 Viganello-Lugano, Switzerland; or +41 (0)91 973 19 19; or fax +41 (0)91 973 19 18; or e-mail congress@esmo.org; or see http://www.esmo.org

As a service to our readers, notices of meetings or courses will be inserted free of charge.
Please send information to the Editorial office, Radiology and Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia.



Fundacija "Docent dr. J. Cholewa"
je neprofitno, neinstitucionalno in nestrankarsko
združenje posameznikov, ustanov in organizacij, ki želijo
materialno spodbujati in poglabljati raziskovalno
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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – a report for the first quarter of 2008

The Dr. J. Cholewa Foundation for Cancer Research and Education continues to focus its activities and attention to cancer research and education in Slovenia and continues to deal carefully with the requests and proposals for research grants and scholarships.

The Dr. J. Cholewa Foundation for Cancer Research and Education continues to support the regular publication of "Radiology and Oncology" international medical scientific journal in 2007. This journal is edited, published and printed in Ljubljana, Slovenia. The support for "Radiology and Oncology" emphasizes and addresses the need for the spread of information and knowledge about advances in cancer among professionals and too many interested individuals in lay public and others in Slovenia and elsewhere. "Radiology and Oncology" is an open access journal, available on its own website, thus allowing its users and readers to be freely access, use and re – use it.

There are many professional and lay activities in connection with cancer research, cancer education and information presently taking place in Slovenia. As the public is gearing its attention towards newly established, extended and improved screening programs involving breast, cervical and colon cancers, the Foundation will probably support these activities in its own specific way. As the public and professional awareness of problems associated with these three very common types of cancer in Slovenia need to be improved, especially with regard to screening, there are ample opportunities for the Foundation to take part in promoting these activities.

The Foundation continues to attach a large amount of importance to the support of the publication of the results from cancer research in Slovenia and from Slovenian authors in respectable international scientific journals and other means of communication worldwide.

Borut Štabuc, MD, PhD
Andrej Plesničar, MD
Tomaž Benulič, MD

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Ehret (Nemčija):
Laminar flow tehnika, inkubatorji, sušilniki, suhi sterilizatorji in oprema za laboratorijsko vzrejo živali - kletke

Angelantoni scientifica (Italija):
hladilna tehnika in aparati za laboratorije, transfuzijo, patologijo in sodno medicino

Dako (Danska):
testi za aplikacijo v imunohistokemiji, patologiji, mikrobiologiji, virologiji, mono- in poliklonalna protitelesa

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Biomerica (Amerika):
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Byron (Amerika):
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Dodatne informacije so vam na voljo pri: Merck, d.o.o., Dunajska cesta 119, 1000 Ljubljana, tel.: 01 560 3810, faks: 01 560 3831, el. pošta: info@merck.si

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Epufen 12,5, 25, 50 in 100 mikrogramov/uro transdermalni obliži SESTAVA: 1 transdermalni obliž vsebuje 2,89 mg, 5,78 mg 11,56 mg ali 23,12 mg fentanila. **TERAPEVTSKE INDIKACIJE**: Huda kronična bolečina, ki se lahko ustrezno zdravi le z opioidnimi analgetiki. **ODMERJANJE IN NAČIN UPORABE**: Odmerjanje je treba individualno prilagoditi ter ga po vsaki uporabi redno oceniti. Izbira začetnega odmerka: velikost odmerka fentanila je odvisna od predhod-ne uporabe opioidov, kjer se upošteva možnost pojava tolerance, sočasnega zdravljenja, bolnikovega splošnega zdravstvenega stanja in stopnje resnosti obolenja. Pri bolnikih, ki pred tem niso dobivali močnih opioidov, začetni odmerek ne sme presečі 12,5-25 mikrogramov na uro. Zamenjava opioidnega zdravljenja: pri zamenjavi peroralnih ali parenteralnih opioidov s fentanilom je treba začetni odmerek izračunati na osnovi količine analgetika, ki je bila potrebna v zadnjih 24 urah, jo pretvoriti v odgovarjajoči odmerek morfina s pomočjo razpredelnice in nato preračunati ustrezen odmerek fentanila, spet s pomočjo razpredelnice (glejte SmPC). Prvih 12 ur po prehodu na transdermalni obliž Epufen bolnik še vedno dobiva predhodni analgetik v enakem odmerku kot prej; v naslednjih 12 urah se ta analgetik daje po potrebi. Titracija odmerka in vzdrževalno zdravljenje: obliž je treba zamenjati vsakih 72 ur. Odmerek je treba titrirati individualno, dokler ni dosežen analgetični učinek. Odmerek 12,5 mikrogramov/uro je primeren za titriranje odmerka v manjšem odmernem območju. Če analgezija na koncu začetnega obdobja nošenja obliža ni zadostna, se lahko odmerek po 3 dneh zveča. Možno je, da bodo bolniki potrebovali občasne dodatne odmerke kratko delujočih analgetikov (npr. morfina) za prekinitev bole-čine. Sprememba ali prekinitev zdravljenja: vsaka zamenjava z drugim opioidom mora potekati postopoma, z majhnim začetnim odmerkom in počasnim zvečevanjem. Splošno veljavno pravilo je postopna ustavitev opioidne analgezije, da bi preprečili odtegnitvene simptome, kot so navzeja, bruhanje, diareja, anksioznost in mišični tremor. Uporaba pri starejših bolnikih: starejše in oslabljene bolnike je treba skrbno opazovati zaradi simptomov prevelikega odmerjanja ter odmerek po potrebi zmanjšati. Uporaba pri otrocih: transdermalni obliži Epufen se lahko uporabljajo le pri pediatričnih bolnikih (starih od 2 do 16 let), ki tolerirajo opioide in peroralno že dobivajo opioide v odmerku, enakovrednemu najmanj 30 mg morfina na dan. Bolnik mora prvih 12 ur po prehodu na Epufen še vedno dobivati predhodni analgetik v enakem odmerku kot prej. V naslednjih 12 urah je treba ta analgetik dajati odvisno od kliničnih potreb. Titracija odmerka in vzdrževalno zdravljenje: če je analgetični učinek Epufena prešibak, je treba bolniku dodati morfin ali drugi opioid s kratkim delovanjem. Odvisno od dodatnih potreb po analgeziji in jakosti bolečine pri otroku se lahko uporabi več obližev. Odmerek je treba prilagajati korakoma, po 12,5 mikrogramov/uro. Uporaba pri bolnikih z jetrno ali ledvično okvaro: Zaradi možnosti pojava simptomov prevelikega odmerjanja je treba te bolnike skrbno spremljati in odmerek ustrezno zmanjšati. Uporaba pri bolnikih s povečano telesno temperaturo: Pri teh bolnikih bo morda treba prilagoditi odmerek. **Način uporabe**: transdermalni obliž Epufen je treba takoj po odprtju vrečke nalepiti na nerazdraženo, neobsevano kožo, na ravno površino prsnega koša, zgornjega dela hrbta ali nadlakti. Po odstranitvi zaščitne plasti je treba obliž trdno pritrditi na izbrano mesto in z dlanjo pritiskati približno 30 sekund, da se obliž popolnoma nalepi, še zlasti na robovih. Uporaba pri otrocih: pri mlajših otrocih je obliž priporočljivo nalepiti na zgornji del hrbta, ker je manjša verjetnost, da bi otrok odstranil obliž. Transdermalnega obliža se ne sme deliti, ker podatkov o tem ni na voljo. **KONTRAINDIKACIJE**: Preobčutljivost za zdravilno učinkovino, hidrogenirano kolofonijo, sojo, arašide ali katerokoli pomožno snov. Akutna ali pooperativna bolečina, ko v kratkem časovnem obdobju ni možno titriranje odmerka in obstaja verjetnost za življenjsko ogrožajočo respiratorno depresijo. Huda okvara osrednjega živčnega sistema. Sočasna uporaba MAO ali v obdobju 14 dni po prekinitvi jemanja zaviralcev MAO. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI**: Zaradi razpolovne dobe fentanila je treba bolnika v primeru pojava neželenega učinka opazovati še 24 ur po odstranitvi obliža. Pri nekaterih bolnikih, ki uporabljajo transdermalni obliž Epufen, se lahko pojavi respiratorna depresija. Epufen je treba previdno dajati: bolnikom s kronično pljučno boleznijo, zvišanim intrakranialnim tlakom, možganskim tumorjem, boleznimi srca, jeter in ledvic, tistim z zvišano telesno temperaturo, pri starejših bolnikih in otrocih, bolnikih z miastenijo gravis. Odvisnost od zdravila: kot posledica ponavljajoče se uporabe se lahko razvijeta toleranca na učinkovino ter psihična in/ali fizična odvisnost od nje. Ostali: lahko se pojavijo neepileptične (mio)kloničnе reakcije. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ**: Derivati barbiturne kisline, opioidi, anksiolitiki in pomirjevala, hipnotiki, splošni anestetiki, fenotiazini, mišični relaksanti, sedativni antihistaminiki in alkoholne pijače, zaviralci MAO, itrakonazol, ritonavir, ketokonazol, nekateri makrolidni antibiotiki, pentazocin, buprenorfin. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI**: Zdravilo ima močan vpliv na sposobnost vožnje in upravljanja s stroji. **NEŽELENI UČINKI**: Najbolj resen neželen učinek fentanila je respiratorna depresija. Zelo pogosti (≥ 1/10): dremavost, glavobol, navzeja, bruhanje, zaprtje, znojenje, srbenje, somnolenca. Pogosti (≥ 1/100 do < 1/10): kserostomija, dispepsija, reakcije na koži na mestu aplikacije, sedacija, zmedenost, depresija, tesnoba, živčna napetost, halucinacije, zmanjšan apetit. Občasni (≥ 1/1000 do < 1/100): tahikardija, bradikardija, tremor, parestezija, motnje govora, dispneja, hipoventilacija, diareja, zastajanje urina, izpuščaj, rdečina, hipertenzija, hipotenzija, evforija, amnezija, nespečnost, vznemirljivost. Nekateri od naštetih neželenih učinkov so lahko posledica osnovne bolezni ali drugih zdravljenj. Drugi neželeni učinki: odpornost, fizična in psihična odvisnost se lahko razvijejo med dolgotrajno uporabo fentanila. Pri nekaterih bolnikih se lahko pojavijo odtegnitveni simptomi, ko zamenjajo prejšnje opiodne analgetike s transdermalnim obližem s fentanilom ali po nenadni prekinitvi zdravljenja. **NAČIN IZDAJE**: Samo na zdravniški recept. **OPREMA**: Škatle s 5 transdermalnimi obliži. **IMETNIK DOVOLJENJA ZA PROMET**: Lek farmacevtska družba, d.d., Verovškova 57, Ljubljana, Slovenija **INFORMACIJA PRIPRAVLJENA**: november 2007

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Skrajšan povzetek glavnih značilnosti zdravila Arimidex® 1 mg filmsko obložene tablete

Sestava zdravila: Ena tableta vsebuje 1 mg anastrozola.
Indikacije: Adjuvantno zdravljenje žensk po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji. Adjuvantno zdravljenje zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji pri ženskah po menopavzi, ki so se dve do tri leta adjuvantno zdravile s tamoksifenom. Zdravljenje napredovalega raka dojke pri ženskah po menopavzi. Učinkovitost pri bolnicah z negativnimi estrogenskimi receptorji ni bila dokazana razen pri tistih, ki so imele predhodno pozitiven klinični odgovor na tamoksifen.
Odmerjanje in način uporabe: Odrasle (tudi starejše) bolnice: 1 tableta po 1 mg peroralno, enkrat na dan. Odmerka zdravila ni treba prilagajati pri bolnicah z blago ali zmerno ledvično odpovedjo ali blagim jetrnim odpovedovanjem. Pri zgodnjem raku je priporočljivo trajanje zdravljenja 5 let.
Glavni neželeni učinki: Zelo pogosti (≥ 10 %): navali vročine, običajno blagi do zmerni. Pogosti (≥ 1 % in < 10 %): astenija, bolečine/okorelost v sklepih, suhost vagine, razredčenje las, izpuščaji, slabost, diareja, glavobol (vsi običajno blagi do zmerni)
Posebna opozorila in previdnostni ukrepi: Uporabe Arimidexa ne priporočamo pri otrocih, ker njegova varnost in učinkovitost pri njih še nista raziskani. Menopavzo je potrebno biokemično določiti pri vseh bolnicah, kjer obstaja dvom o hormonskem statusu. Ni podatkov o varni uporabi Arimidexa pri bolnicah z zmerno ali hudo jetrno okvaro ali hujšo ledvično odpovedjo (očistek kreatinina manj kakor 20 ml/min (oziroma 0,33 ml/s)). Pri ženskah z osteoporozo ali pri ženskah s povečanim tveganjem za razvoj osteoporoze je treba določiti njihovo mineralno gostoto kosti z denzitometrijo, na primer s slikanjem DEXA na začetku zdravljenja, pozneje pa v rednih intervalih. Po potrebi je treba začeti z zdravljenjem ali preprečevanjem osteoporoze in to skrbno nadzorovati. Ni podatkov o uporabi anastrozola z analogi LHRH. Arimidex znižuje nivo estrogena v obtoku, zato lahko povzroči zmanjšanje mineralne kostne gostote. Trenutno ni na voljo ustreznih podatkov o učinku bifosfonatov na izgubo mineralne kostne gostote, povzročene z anastrozolom, ali njihovi koristi, če se uporabijo preventivno. Zdravilo vsebuje laktozo.
Kontraindikacije: Arimidex je kontraindiciran pri: ženskah pred menopavzo, nosečnicah in doječih materah, bolnicah s hujšo ledvično odpovedjo (očistek kreatinina manj kot 20 ml/min (oziroma 0,33 ml/s)), bolnicah z zmernim do hudim jetrnim obolenjem, bolnicah, ki imajo znano preobčutljivost za anastrozol ali za katerokoli pomožno snov. Zdravila, ki vsebujejo estrogen, ne smete dajati sočasno z Arimidexom, ker bi se njegovo farmakološko delovanje izničilo. Sočasno zdravljenje s tamoksifenom.
Medsebojno delovanje z drugimi zdravili in druge oblike interakcij: Klinične raziskave o interakcijah z antipirinom in cimetidinom kažejo, da pri sočasni uporabi Arimidexa in drugih zdravil klinično pomembne interakcije, posredovane s citokromom P450, niso verjetne. Pregled baze podatkov o varnosti v kliničnih preskušanjih pri bolnicah, ki so se zdravile z Arimidexom in sočasno jemale druga pogosto predpisana zdravila, ni pokazal klinično pomembnih interakcij.
Imetnik dovoljenja za promet: AstraZeneca UK Limited, 15 Stanhope Gate, London, W1K 1LN, Velika Britanija
Režim predpisovanja zdravila: Rp/Spec
Datum priprave informacije: april 2007

Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.

Dodatne informacije in literatura so na voljo pri:
AstraZeneca UK Limited
Podružnica v Sloveniji
Verovškova ulica 55
1000 Ljubljana

in na spletnih straneh:
www.arimidex.net
www.bco.org
www.breastcancersource.com

AstraZeneca
ONKOLOGIJA

ARI 03/07 P

*adjuvant [ae´džuv*nt]*

1. *adjective* pomagljiv, koristen; *~ treatment with Arimidex:* Adjuvantno zdravljenje žensk po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji.

*advanced [*dva:nst]*

1. *adjective* napreden; zvišan (cene); to be ~ napredovati; ~ in years visoke starosti; *treatment of ~ breast cancer with Arimidex:* Zdravljenje napredovalega raka dojke pri ženskah po menopavzi. Učinkovitost pri bolnicah z negativnimi estrogenskimi receptorji ni bila dokazana razen pri tistih, ki so imele predhodno pozitiven klinični odgovor na tamoksifen.

switch [swič]

1. *transitive verb* udariti, bičati s šibo (z repom); šibati z, hitro mahati z; naglo pograbiti; railway ranžirati, zapeljati (usmeriti) (vlak) na drug tir; electrical vključiti, vklopiti; spremeniti (pogovor), obrniti drugam (tok misli); to ~ back to figuratively (v mislih) vrniti se na;
~ to Arimidex: Adjuvantno zdravljenje zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji pri ženskah po menopavzi, ki so se dve do tri leta adjuvantno zdravile s tamoksifenom.

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- za zdravljenje novo diagnosticiranega glioblastoma multiforme, sočasno z radioterapijo in kasneje kot monoterapija
- malignim gliomom, na primer multiformnim glioblastomom ali anaplastičnim astrocitomom, ki se po standardnem zdravljenju ponovi ali napreduje.

Odmerjanje in način uporabe Temodal smejo predpisati le zdravniki, ki imajo izkušnje z zdravljenjem možganskih tumorjev. **Odrasli bolniki z novo diagnosticiranim glioblastomom multiforme** Temodal se uporablja v kombinaciji z žariščno radioterapijo (faza sočasne terapije), temu pa sledi do 6 ciklov monoterapije z temozolomidom. **Faza sočasne terapije** Zdravilo Temodal naj bolnik jemlje peroralno v odmerku 75 mg/m^2 na dan 42 dni, sočasno z žariščno radioterapijo (60 Gy, danih v 30 delnih odmerkih). Odmerka ne boste zmanjševali, vendar se boste vsak teden odločili o morebitni odložitvi jemanja temozolomida ali njegovi ukinitvi na podlagi kriterijev hematološke in nehematološke toksičnosti. Zdravilo Temodal lahko bolnik jemlje ves čas 42-dnevnega obdobja sočasne terapije do 49 dni, če so izpolnjeni vsi od naslednjih pogojev: absolutno število nevtrofilcev ≥ 1,5 x 109/l, število trombocitov ≥ 100 x 109/l, skupni kriteriji toksičnosti (SKT) za nehematološko toksičnost ≤ 1. stopnje (z izjemo alopecije, slabosti in bruhanja). Med zdravljenjem morate pri bolniku enkrat na teden pregledati celotno krvno sliko. **Faza monoterapije** Štiri tedne po zaključku faze sočasnega zdravljenja z zdravilom Temodal in radioterapijo naj bolnik jemlje zdravilo Temodal do 6 ciklov monoterapije. V 1. ciklu (monoterapija) je odmerek zdravila 150 mg/m^2 enkrat na dan 5 dni, temu pa naj sledi 23 dni brez terapije. Na začetku 2. cikla odmerek povečajte na 200 mg/m^2, če je SKT za nehematološko toksičnost za 1. cikel stopnje ≤ 2 (z izjemo alopecije, slabosti in bruhanja), absolutno število nevtrofilcev (AŠN) ≥ 1,5 x 109/l in število trombocitov ≥ 100 x 109/l. Če odmerka niste povečali v 2. ciklusu, ga v naslednjih ciklusih ne smete povečevati. Ko pa odmerek enkrat povečate, naj ostane na ravni 200 mg/m^2 na dan v prvih 5 dneh vsakega naslednjega ciklusa, razen če nastopi toksičnost. Med zdravljenjem morate pregledati celotno krvno sliko na 22. dan (21 dni po prvem odmerku zdravila Temodal). **Ponavljajoči se ali napredujoči maligni gliom Odrasli bolniki** Posamezen ciklus zdravljenja traja 28 dni. Bolniki, ki še niso bili zdravljeni s kemoterapijo, naj jemljejo Temodal peroralno v odmerku 200 mg/m^2 enkrat na dan prvih 5 dni, temu pa naj sledi 23-dnevni premor (skupaj 28 dni). Pri bolnikih, ki so že bili zdravljeni s kemoterapijo, je začetni odmerek 150 mg/m^2 enkrat na dan, v drugem ciklusu pa se poveča na 200 mg/m^2 enkrat na dan 5 dni, če ni bilo hematoloških toksičnih učinkov (glejte poglavje 4.4). **Pediatrični bolniki** Pri bolnikih starih 3 leta ali starejših, posamezen ciklus zdravljenja traja 28 dni. Temodal naj jemljejo peroralno v odmerku 200 mg/m^2 enkrat na dan prvih 5 dni, potem pa naj sledi 23-dnevni premor (skupaj 28 dni). Otroci, ki so že bili zdravljeni s kemoterapijo, naj prejmejo začetni odmerek 150 mg/m^2 enkrat na dan 5 dni, s povečanjem na 200 mg/m^2 enkrat na dan 5 dni v naslednjem ciklusu, če ni bilo hematoloških toksičnih učinkov (glejte poglavje 4.4). **Bolniki z motnjami v delovanju jeter ali ledvic** Pri bolnikih z blagimi ali zmernimi motnjami v delovanju jeter je farmakokinetika temozolomida podobna kot pri tistih z normalnim delovanjem jeter. Podatki o uporabi zdravila Temodal pri bolnikih s hudimi motnjami v delovanju jeter (razred III po Child-u) ali motnjami v delovanju ledvic niso na voljo. Na podlagi farmakokinetičnih lastnosti temozolomida obstaja majhna verjetnost, da bo pri bolnikih s hudimi motnjami v delovanju jeter ali ledvic potrebno zmanjšanje odmerka zdravila. Kljub temu je potrebna previdnost pri uporabi zdravila Temodal pri teh bolnikih. **Starejši bolniki:** Analiza farmakokinetike je pokazala, da starost ne vpliva na očistek temozolomida. Kljub temu je potrebna posebna previdnost pri uporabi zdravila Temodal pri starejših bolnikih. **Način uporabe** Temodal mora bolnik jemati na tešče. Temodal kapsule mora bolnik pogoltniti cele s kozarcem vode in jih ne sme odpirati ali žvečiti. Predpisani odmerek mora vzeti v obliki najmanjšega možnega števila kapsul. Pred jemanjem zdravila Temodal ali po njem lahko bolnik vzame antiemetik Če po zaužitju odmerka bruha, ne sme še isti dan vzeti drugega odmerka. **Kontraindikacije** Temodal je kontraindiciran pri bolnikih, ki imajo v anamnezi preobčutljivostne reakcije na sestavine zdravila ali na dakarbazin (DTIC). Temodal je kontraindiciran tudi pri bolnikih s hudo mielosupresijo. Temodal je kontraindiciran pri ženskah, ki so noseče ali dojijo. **Posebna opozorila in previdnostni ukrepi** Pilotno preskušanje podaljšane 42-dnevne sheme zdravljenja je pokazalo, da imajo bolniki, ki so sočasno prejemali zdravilo Temodal in radioterapijo, še posebej veliko tveganje za nastanek pljučnice zaradi okužbe s Pneumocystis carinii (PCP). Profilaksa proti tovrstni pljučnici je torej potrebna pri vseh bolnikih, ki sočasno prejemajo zdravilo Temodal in radioterapijo v okviru 42-dnevne sheme zdravljenja (do največ 49 dni), ne glede na število limfocitov. Če nastopi limfopenija, mora bolnik nadaljevati s profilakso, dokler se limfopenija ne povrne na stopnjo ≤ 1. Antiemetična terapija: Z jemanjem zdravila Temodal sta zelo pogosto povezana slabost in bruhanje. **Laboratorijske vrednosti**: Pred jemanjem zdravila morata biti izpolnjena naslednja pogoja za laboratorijske izvide: ANC mora biti ≥ 1,5 x 109/l in število trombocitov ≥ 100 x 109/l. Na 22. dan (21 dni po prvem odmerku) ali v roku 48 ur od navedenega dne, morate pregledati celotno krvno sliko in jo nato spremljati vsak teden, dokler ni ANC nad 1,5 x 109/l in število trombocitov nad 100 x 109/l. Če med katerimkoli ciklusom ANC pade na < 1,0 x 109/l ali število trombocitov na < 50 x 109/l, morate odmerek zdravila v naslednjem ciklusu zmanjšati za eno odmerno stopnjo. Odmerne stopnje so 100 mg/m^2, 150 mg/m^2 in 200 mg/m^2. Najmanjši priporočeni odmerek je 100 mg/m^2. **Moški bolniki** Temozolomid lahko deluje genotoksično, zato morate moškim, ki se zdravijo z temozolomidom svetovati, da naj ne zaplodijo otroka še šest mesecev po zdravljenju. **Interakcije** Sočasna uporaba zdravila Temodal in ranitidina ni povzročila spremembe obsega absorpcije temozolomida ali monometiltriazenoimidazol karboksamida (MTIC). Jemanje zdravila Temodal s hrano je povzročilo 33 % zmanjšanje Cmax in 9 % zmanjšanje površino pod krivuljo (AUC). Ker ne moremo izključiti možnosti, da bi bila sprememba Cmax lahko klinično pomembna, naj bolniki jemljejo zdravilo Temodal brez hrane. Analiza populacijske farmakokinetike v preskušanjih druge faze je pokazala, da sočasna uporaba deksametazona, proklorperazina, fenitoina, karbamazepina, ondansetrona, antagonistov receptorjev H2 ali fenobarbitala ne spremeni očistka temozolomida. Sočasno jemanje z valprojsko kislino je bilo povezano z majhnim, a statistično značilnim zmanjšanjem očistka temozolomida. Uporaba zdravila Temodal v kombinaciji z drugimi mielosupresivnimi učinkovinami la hko poveča verjetnost mielosupresije. **Nosečnost** Študij na nosečih ženskah ni bilo. Predklinične študije na podganah in kuncih z odmerkom 150 mg/m^2 so pokazale teratogenost in/ali toksičnost za plod. Zato naj noseče ženske načeloma ne bi jemale zdravila Temodal. Če pa je uporaba v času nosečnosti nujna, morate bolnico opozoriti na možne nevarnosti zdravila za plod. Ženskam v rodni dobi svetujte, naj med zdravljenjem z zdravilom Temodal preprečijo zanositev. **Dojenje** Ni znano, ali se temozolomid izloča v materino mleko, zato ženske, ki dojijo ne smejo jemati zdravila Temodal. **Neželeni učinki** V kliničnih preskušanjih so bili najpogostnejši neželeni učinki, povezani z zdravljenjem, prebavne motnje, natančneje slabost (43 %) in bruhanje (36 %). Oba učinka sta bila ponavadi 1. ali 2. stopnje (od 0 do 5 epizod bruhanja v 24 urah) in sta prenehala sama, ali pa ju je bilo mogoče hitro obvladati s standardnim antiemetičnim zdravljenjem. Incidenca hude slabosti in bruhanja je bila 4 %. Laboratorijski izvidi: Trombocitopenija in. nevtropenija 3. in. 4. stopnje sta se pojavili pri 19 % in. 17 % bolnikov, zdravljenih zaradi malignega glioma. Zaradi njiju je bila potrebna hospitalizacija in/ali prekinitev zdravljenja z zdravilom Temodal pri 8 % in. 4 % bolnikov. Mielosupresija je bila predvidljiva (ponavadi se je pojavila v prvih nekaj ciklusih in je bila najizrazitejša med 21. in 28. dnem), okrevanje pa je bilo hitro, ponavadi v 1 do 2 tednih. Opazili niso nobenih dokazov kumulativne mielosupresije. Trombocitopenija lahko poveča tveganje za pojav krvavitev, nevtropenija ali levkopenija pa tveganje za okužbe. **Imetnik dovoljenja za promet** SP Europe 73, rue de Stalle B-1180 Bruxelles Belgija. **Način in režim izdaje** Zdravilo se izdaja samo na recept, uporablja pa se pod posebnim nadzorom zdravnika specialista ali od njega pooblaščenega zdravnika. **Datum priprave informacije** oktober 2007.

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Dent RAG, Cole P. *In vitro* maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95.

Chapman S, Nakielny R. *A guide to radiological procedures.* London: Bailliere Tindall; 1986.

Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, editor. *Immunobiology of macrophage.* New York: Academic Press; 1976. p. 45-74.

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Vodilni z GEMZARjem

GEMZAR je indiciran za zdravljenje:

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- karcinoma sečnega mehurja
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Terapevtske indikacije: Lokalno napredovali ali metastatski karcinom sečnega mehurja, v kombinaciji z drugimi citostatičnimi zdravili. Lokalno napredovali ali metastatski nedrobnocelični karcinom pljuč, v kombinaciji z drugimi citostatičnimi zdravili. Lokalno napredovali ali metastatski adenokarcinom trebušne slinavke, pri bolnikih v dobrem splošnem stanju z zadostnimi rezervami kostnega mozga. Lokalno napredovali ali metastatski karcinom dojke v kombinaciji s paklitakselom pri bolnicah, pri katerih je prišlo do relapsa bolezni po predhodnem predoperativnem in/ali dopolnilnim zdravljenju s citostatiki. Predhodno zdravljenje mora vključevati antracikline, razen če so kontraindicirani. Lokalno napredovali ali metastatski epitelijski karcinom ovarijev, v kombinaciji s karboplatinom, pri bolnikih z relapsom bolezni po vsaj 6-mesečnem obdobju brez relapsa po zdravljenju prvega izbora na osnovi platine.
Odmerjanje in način uporabe: *Karcinom sečnega mehurja (v kombinaciji s cisplatinom 70 mg/m²), odrasli in starejši:* Priporočeni odmerek gemcitabina je 1000 mg/m², dan kot infuzija v 30 minutah. Odmerek dajemo 1., 8. in 15. dan vsakega 28-dnevnega ciklusa. Cisplatin dajemo v odmerku 70 mg/m² 2. dan vsakega 28-dnevnega ciklusa. Ta štiritedenski ciklus nato ponavljamo. *Karcinom dojke (uporaba v kombinaciji), odrasli:* Priporočamo uporabo gemcitabina v kombinaciji s paklitakselom, paklitaksel (175 mg/m²) damo 1. dan preko približno 3 ur kot intravensko infuzijo, temu sledi gemcitabin (1250 mg/m²) kot 30-minutna intravenska infuzija 1. in 8. dan vsakega 21-dnevnega ciklusa. Bolniki naj imajo pred uvedbo kombiniranega zdravljenja z gemcitabinom in paklitakselom absolutno koncentracijo granulocitov vsaj 1.500 (x 10⁹/l). *Nedrobnocelični karcinom pljuč (v kombinaciji s cisplatinom), odrasli in starejši:* Pri zdravljenju po tritedenski shemi je priporočeni odmerek gemcitabina 1250 mg/m² površine telesa, dan kot 30-minutna intravenska infuzija 1. in 8. dan ciklusa zdravljenja (21 dni). Odmerek lahko med tekočim ciklusom zdravljenja ali ob naslednjem ciklusu zdravljenja znižamo glede na individualno opazovano toksičnost. Pri zdravljenju po štiritedenski shemi je priporočeni odmerek gemcitabina 1000 mg/m² površine telesa, dan kot 30-minutna intravenska infuzija 1., 8. in 15. dan ciklusa zdravljenja (28 dni). *Karcinom jajčnika (uporaba v kombinaciji), odrasli:* Priporočamo gemcitabin v kombinaciji s karboplatinom, z uporabo 1000 mg/m² gemcitabina 1. in 8. dan vsakega 21-dnevnega ciklusa, v obliki 30-minutne intravenske infuzije. Po gemcitabinu 1. dan damo karboplatin, da dosežemo ciljno AUC 4,0 mg/ml x minuto. *Karcinom trebušne slinavke, odrasli in starejši:* Priporočeni odmerek gemcitabina je 1000 mg/m² površine telesa, ki ga dajemo kot intravensko infuzijo v 30 minutah. To ponavljamo enkrat tedensko v obdobju do 7 tednov, ki mu sledi enotedenska prekinitev. V naslednjih ciklusih Gemzar dajemo enkrat tedensko v obdobju treh tednov, ki mu sledi enotedenska prekinitev. Odmerek lahko med tekočim ciklusom zdravljenja ali ob naslednjem ciklusu zdravljenja znižamo glede na individualno opazovano toksičnost. Odmerek lahko z vsakim ciklusom ali med tekočim ciklusom znižamo glede na toksičnost, izraženo pri bolniku.

Kontraindikacije: Preobčutljivost za gemcitabin ali katero od pomožnih snovi. Bolnikom z zmerno do hudo okvarjenim jetrnim delovanjem ali hudo okvarjenim ledvičnim delovanjem Gemzarja ne smemo dajati.
Posebna opozorila in previdnostni ukrepi: Podaljšanje časa infuzije in skrajšanje priporočenega intervala med odmerki povečujeta toksičnost. Gemcitabin moramo pri bolnikih z blago do zmerno okvarjenim ledvičnim delovanjem in pri bolnikih z blago okvarjenim jetrnim delovanjem uporabljati previdno. Če se pojavijo kakršnikoli znaki mikroangiopatske hemolitične anemije je treba zdravljenje z Gemzarjem prekiniti. Dajanje gemcitabina bolnikom s sočasnimi jetrnimi zasevki ali hepatitisom, alkoholizmom ali jetrno cirozo v preteklosti lahko povzroči poslabšanje osnovnega popuščanja delovanja jeter. Pri bolnikih z okvarjenim delovanjem kostnega mozga je treba zdravljenje začeti previdno. Moškim, zdravljenim z Gemzarjem, odsvetujemo spočetje otroka med zdravljenjem in do 6 mesecev po njem. Pred vsakim odmerkom je treba preveriti koncentracije trombocitov, levkocitov in granulocitov. Tveganje za neželene učinke, povezane z dihali, je višje pri bolnikih s karcinomom pljuč in pljučnimi zasevki, kot pri drugih tipih tumorjev. V primeru intersticijskega pnevmonitisa skupaj s pljučnimi infiltrati ter hudih, redko smrtnih pljučnih neželenih učinkih, denimo pljučnem edemu, intersticijskem pnevmonitisu in sindromu akutne dihalne stiske je treba zdravljenje z Gemzarjem prekiniti. Gemcitabin so pri otrocih preučevali v omejenih preskušanjih faze 1 in 2 pri različnih tipih tumorjev. Te študije niso podale zadosti podatkov za zagotovitev učinkovitosti in varnosti gemcitabina pri otrocih.
Interakcije: Ob sočasni radioterapiji (obsevanja istočasno ali v roku ≤ 7 dni pred kemoterapijo ali po njej) gemcitabin deluje radiosenzitizirajoče, poročali pa so tudi o obsevalnih poškodbah na ciljnih tkivih.
Neželeni učinki: Obsevalna toksičnost in odpoklic obsevanja; *Zelo pogosti:* levkopenija, trombocitopenija, anemija, dispneja, slabost, bruhanje, povišane vrednosti AST, ALT in alkalne fosfataze, alergijski izpuščaj, pogosto s srbenjem, blaga proteinurija in hematurija, edem in periferni edem, gripi podobni simptomi, kašelj, ritnitis, znojenje, motnje spanja, povišana temperatura in astenija; *Pogosti:* febrilna nevtropenija, anoreksija, glavobol, zaspanost, nespečnost, diareja, zaprtje, stomatitis, povišane vrednosti bilirubina, znojenje, srbenje, alopecija, mialgija, bolečine v hrbtu, mrzlica, edem obraza; *Manj pogosti:* pljučni edem, bronhospazem, intersticijski pnevmonitis; *Redki:* miokardni infarkt, popuščanje srca, aritmija, hipotenzija, sindrom dihalne stiske pri odraslem, povišane vrednosti gama-GT, luščenje, tvorba mehurjev in razjed, odpoved ledvic, hemolitično-uremični sindrom; *Zelo redki:* trombocitoza, anafilaktoidna reakcija, klinični znaki periferne vaskulitisa in gangrene, hude kožne reakcije, vključno z luščenjem in bulozni vzbrstmi.
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