УДК 616.728.2-001.52-053.2(048.8)-06:616.8
DOI: https://doi.org/10.17816/PTORS569165

Научный обзор

Нейрогенная гетеротопическая оссификация. Обзор литературы. Часть вторая

В.А. Новиков, А.М. Ходоровская, В.В. Умнов, Е.В. Мельченко, Д.В. Умнов

Национальный медицинский исследовательский центр детской травматологии и ортопедии имени Г.И. Турнера, Санкт-Петербург, Россия

АННОТАЦИЯ

Обоснование. Нейрогенная гетеротопическая оссификация — это образование костной ткани в мягких тканях организма, возникающее в результате тяжелого повреждения головного или спинного мозга различной этиологии. При нейрогенной гетеротопической оссификации чаще всего поражаются тазобедренные суставы.

Цель — проанализировать публикации, посвященные инструментальной диагностике, хирургическим и нехирургическим методам лечения и профилактике нейрогенной гетеротопической оссификации тазобедренных суставов.

Материалы и методы. Во второй части обзора проанализирована литература, посвященная современной диагностике, хирургическим и консервативным методам лечения, профилактике образования и рецидивов нейрогенной гетеротопической оссификации тазобедренных суставов. Поиск данных проводили в базах научной литературы PubMed, Google Scholar, Cochrane Library, Crossref, eLibrary без языковых ограничений.

Результаты. Современные методы диагностики позволяют проводить скрининг нейрогенной гетеротопической оссификации тазобедренных суставов у пациентов с высоким риском их формирования, с последующей верификацией диагноза с помощью компьютерной или магнитно-резонансной томографии. Несмотря на отсутствие в настоящее время единого мнения о сроках удаления нейрогенной гетеротопической оссификации тазобедренных суставов, хирургическое лечение — наиболее эффективный метод, позволяющий ее удалить или уменьшить объем. В большинстве случаев удается купировать болевой синдром и улучшить качество жизни пациентов. При общности этиологического фактора (повреждение центральной нервной системы) эффективность нехирургических методов профилактики и лечения различная у пациентов с нейрогенной гетеротопической оссификацией тазобедренных суставов вследствие травмы спинного мозга, черепно-мозговой травмы и детского церебрального паралича.

Заключение. Рандомизированные контролируемые исследования позволят установить эффективность консервативных методов лечения для профилактики формирования и рецидивов нейрогенной гетеротопической оссификации тазобедренных суставов с учетом причины поражения центральной нервной системы.

Ключевые слова: нейрогенная гетеротопическая оссификация; диагностика нейрогенной гетеротопической оссификации; тазобедренные суставы; лучевая терапия; нестероидные противовоспалительные препараты; бисфосфонаты.

Как цитировать

Новиков В.А., Ходоровская А.М., Умнов В.В., Мельченко Е.В., Умнов Д.В. Нейрогенная гетеротопическая оссификация. Обзор литературы. Часть вторая // Ортопедия, травматология и восстановительная хирургия детского возраста. 2023. Т. 11. № 4. С. 557–570. DOI: https://doi.org/10.17816/PTORS569165

Рукопись получена: 07.09.2023 **Рукопись одобрена:** 10.10.2023 **Опубликована:** 20.12.2023

DOI: https://doi.org/10.17816/PTORS569165

Review

Neurogenic heterotopic ossification: A review. Part 2

Vladimir A. Novikov, Alina M. Khodorovskaya, Valery V. Umnov, Evgenii V. Melchenko, Dmitry V. Umnov

H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: Neurogenic heterotopic ossification is characterized by the formation of bone tissue in the soft tissues of the body caused by severe brain or spinal cord injury of various etiologies. In neurogenic heterotopic ossification, the hip joints are most often affected.

AIM: To analyze publications on the instrumental diagnosis, surgical and nonsurgical methods of treatment, and prevention of neurogenic heterotopic ossification of the hip joints.

MATERIALS AND METHODS: In the second part of our review, we analyzed the literature on modern diagnostics, surgical and conservative methods of treatment, prevention of the formation and recurrence of neurogenic heterotopic ossification of the hip joints. Data were searched in scientific literature databases, namely, PubMed, Google Scholar, Cochrane Library, CrossRef, and eLibrary, without language restrictions.

RESULTS: Modern diagnostic methods allow the screening of hip neurogenic heterotopic ossification in patients at high risk of their formation, with further verification of the diagnosis by computed tomography or magnetic resonance imaging. Despite the lack of consensus on the timing of hip neurogenic heterotopic ossification removal at present, surgical treatment is the most effective method, which allows the removal or reduction of the volume of neurogenic heterotopic ossification. Most cases require controlling the pain syndrome and improving the quality of life of the patients. Despite the common etiologic factor (damage to the central nervous system), nonsurgical methods of the prevention and treatment of patients with neurogenic heterotopic ossification of the hip joints have different effectiveness because of spinal cord injury, cerebral trauma, and cerebral palsy.

CONCLUSIONS: Randomized controlled trials will help to establish the efficacy of conservative treatment methods to prevent the formation and recurrence of hip joint neurogenic heterotopic ossification, taking into account the cause of central nervous system lesions.

Keywords: neurogenic heterotopic ossification; diagnosis of neurogenic heterotopic ossification; hip joints; radiation therapy; nonsteroidal anti-inflammatory drugs; bisphosphonates.

To cite this article

Novikov VA, Khodorovskaya AM, Umnov VV, Melchenko EV, Umnov DV. Neurogenic heterotopic ossification: A review. Part 2. *Pediatric Traumatology, Orthopaedics and Reconstructive Surgery.* 2023;11(4):557–570. DOI: https://doi.org/10.17816/PTORS569165

Received: 07.09.2023 **Accepted:** 10.10.2023 **Published:** 20.12.2023

ECO•VECTOR

DOI: https://doi.org/10.17816/PTORS569165

科学审查

神经源性异位骨化。文献综述。第二部分

Vladimir A. Novikov, Alina M. Khodorovskaya, Valery V. Umnov, Evgenii V. Melchenko, Dmitry V. Umnov

H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery, Saint Petersburg, Russia

简评

论证。神经源性异位骨化是由于各种病因造成的严重脑损伤或脊髓损伤导致的身体软组织骨形成。在神经源性异位骨化中，髋关节最常受到影响。

本研究旨在分析有关髋关节神经源性异位骨化的器械诊断、手术和非手术治疗方法及预防的出版物。

材料和方法。综述的第二部分重点介绍神经源性异位骨化髋关节的现代诊断、手术和保守治疗、预防和复发。数据搜索是在科学文献数据库PubMed、Google Scholar、Cochrane Library、Crossref、eLibrary中进行，无语言限制。

结果。目前的诊断方法可以对髋关节神经源性异位骨化的高危患者进行筛查，随后通过计算机断层扫描或磁共振成像进行确诊。尽管目前对切除髋关节神经源性异位骨化的时机尚未达成共识，但手术治疗是切除或减少其体积的最有效方法。在大多数情况下，疼痛综合征得到控制，患者的生活质量得到改善。由于病因因素（中枢神经系统损伤）的共性，对于脊髓损伤、颅脑外伤和小儿脑瘫导致的髋关节神经源性异位骨化患者，非手术方法的预防和治疗效果也不同。

结论。考虑到中枢神经系统病变的原因，随机对照试验将确定保守治疗方法在预防神经源性异位髋关节骨化形成和复发方面的有效性。

关键词：神经源性异位骨化；神经源性异位骨化的诊断；髋关节；放射治疗；非甾体抗炎药；双磷酸盐。

引用本文

Novikov VA, Khodorovskaya AM, Umnov VV, Melchenko EV, Umnov DV. 神经源性异位骨化。文献综述。第二部分. *Pediatric Traumatology, Orthopaedics and Reconstructive Surgery.* 2023;11(4):557–570. DOI: https://doi.org/10.17816/PTORS569165

收到：07.09.2023 **接受：**10.10.2023 **发布日期：**20.12.2023

论证

异位骨化是一种在骨骼外形成分化骨组织的病理过程，与最初确定的骨骼形成间质没有连续性的组织[1]。导致异位骨化形成的原因有很多。其中包括进行性骨化性纤维发育不良等遗传性疾病的临床表现，以及创伤和烧伤导致的后天性疾病[2]。

另一种异位骨化是神经源性的，它是由各种原因造成的严重脑损伤或脊髓损伤引起[3]。神经源性异位骨化最常影响髋关节[4，5]。我们的文献综述[6]的第一部分专门分析了神经源性异位骨化的流行病学、形成的危险因素、发病机制、临床表现和实验室诊断。

本研究旨在分析有关髋关节神经源性异位骨化的器械诊断、手术和非手术治疗方法及预防的出版物。

材料和方法

数据搜索是在科学文献数据库PubMed、Google Scholar、Cochrane Library、Crossref、eLibrary中进行，无语言限制。搜索深度为50年。在撰写文章的过程中，我们采用了分析和综合信息的方法。考虑到神经源性异位骨化的特异性，大部分资料都是关于髋关节周围的病理过程。

结果与讨论

神经源性异位骨化诊断

诊断神经源性异位骨化的主要方法是放射法，包括以下类型[7，8]。

*髋关节和骨盆骨的X射线检查*是诊断异位骨化的最便捷和最广泛使用的方法。通常情况下，形成中的异位骨化在临床上表现明显，然后才能在X光片上看到它[4]。一般认为，异位骨化通常在病理过程出现最初临床症状后3-6周才能通过放射学诊断出来[2，3]。

*髋关节多螺旋计算机断层扫描（CT）*与X线摄影一样，特异性不高，异位骨化显像时间相似，即此方法不能应用于过程的早期诊断[7]。与传统的X线摄影相比，这种技术由于可以在骨三维模式下观察异位骨化，因此不仅可以诊断病理，还可以进行详细的术前规划[8]。

大动脉与静脉不同，静脉会因异位骨化的发展而受到挤压，而大动脉即使完全被骨化物包围也能保持直径不变[9]；因此，进行CT血管造影与其说是为了观察向髋关节和周围肌肉供血的动脉血管，不如说是为了评估动脉血管与异位骨化的具体位置[10]，这有助于选择最佳手术途径来切除神经源性异位骨化。

*传统上，使用氚-99进行的三相骨闪烁扫*描被认为是早期检测异位骨化的最灵敏的方法，最早可在临床症状出现2周后验证诊断[11]。异位骨化形成的前两个阶段是早期检测异位骨化最敏感的阶段（2-3周）。放射性药物在异位骨化形成的第三阶段（受伤后4-6周）积累，其数量在2个月内达到峰值，然后逐渐减少。大约12个月后，放射性药物积累会减少，但即使在异位骨化的慢性成熟期也可能持续存在[12]。闪烁照相法的缺点是必须服用放射性药物，而且特异性较低，这导致在鉴别诊断异位骨化与其他炎症性、创伤性或退行性骨过程时遇到困难，因为在这些过程中也会观察到成骨细胞活性增加以及相应的促骨放射性核素摄取增加的情况[13]。目前，大多数学者认为闪烁扫描不能作为诊断异位骨化的首选方法，因为已经开发出了更有效、更安全的方法[2，14]。

在异位骨化形成的急性期，*磁共振成像（MRI）*显示血管和组织密度增加。在磁共振成像上，异位骨化的特征T1加权图像上相对于肌肉的等密度或高密度信号，以及T2加权图像上的高密度信号。外围的低信号区与骨化的起始点相对应[15]。H. Wang等人描述了异位骨化形成初期（甚至在骨化之前）的MR模式特征。在急性期异位骨化的T2-和T1后对比图像上，受影响的肌肉呈不均匀的高信号强度，其间夹杂着与完整肌纤维相对应的若干低密度线状结构，在与这些肌纤维平行的平面上呈现“条纹状图案”。在弥漫性高信号强度的病灶内，可发现与完整肌纤维束相对应的具有几何图形的相对低密度区，在与肌纤维垂直的平面上可看到”“棋盘状图案”[16]。在异位骨化的早期阶段，识别这些MR模式可能很有用，因为这种病症经常被误认为是骨髓炎甚至肉瘤[15，16]。

事实证明，*超声波检查（超声波造影术）*是观察软组织损伤和钙化的灵敏方法。该方

法的优点是无需转运病人即可使用，这与卧床不起的病人息息相关[17]。Q. Wang等人建议使用超声波来监测异位骨化的形成，因为与射线摄影不同，超声波可以在不同平面上观察异位骨化，而不需要额外的辐射负荷，还可以根据“灰度”值来量化异位骨化在不同发展阶段的结构变化[18]。T. Rosteius等人分析了217名超声波患者的超声波结果，发现该方法在脊髓或脑损伤后平均间隔62.4天内检测病理过程的灵敏度为88.9%[19]。

髋关节异位骨化的分类

D.E. Garland[20]根据骨化的位置和病因提出了神经元异位骨化分类法。

1. 大腿背肌区域的神经元异位骨化。脊髓损伤（SCI）和脑中风患者以及全髋关节置换术后患者的特征。
2. 前外侧神经元异位骨化，多见于脑外伤（TBI）后遗症患者。
3. 前内侧神经元异位骨化，多见于脊髓损伤后遗症患者。
4. 股骨颈周围的神经元异位骨化，多见于全髋关节置换术后的患者。
5. 股骨后表面和髋关节的神经元异位骨化，在脑外伤和脊髓损伤患者以及各种髋关节手术后患者的X光片上均可看到。
6. 主要在脑外伤后形成的髋关节内侧下方的神经元异位骨化。

A.F. Mavrogenis等人认为，根据前胸X光片对髋关节神经元异位骨化进行分类无法评估强直程度和确定神经元异位骨化的确切位置。作者提出了一种基于髋关节CT扫描数据和强直程度临床评估的神经元异位骨化分类方法。确定了髋关节神经元异位骨化的前方、后方、前内侧、前内侧和环形。作者认为，这种分类的目的是优化神经元异位骨化切除术的手术入路[21]。然而，根据M. Arduini等人认为，A.F. Mavrogenis等人没有考虑到神经元异位骨化形成过程中肌肉参与的特殊性。M. Arduini等人分析了55名患者（73个髋关节）的检查和手术治疗结果，确定了髋关节神经元异位骨化的7种模式，并认为每组神经元异位骨化均应采用最佳手术入路[8]。像M. Arduini一样，A.F. Mavrogenis等人也区分了神经元异位骨化的前、后、前内侧和环形模式，以及内侧、外侧和后外侧模式。例如，在内侧模式（A.F. Mavrogenis等人的分类中没有这种模式）中，只有大腿骨嵴、短收肌和大收肌参与了神经元异位骨化过程；在这种情况下，作者建议使用髂腰肌入路；如果只有骨嵴的神经元异位骨化，则建议使用Ludloff入路[8]。

在过去的50年中，人们提出了许多不同的髋关节异位骨化分类[8，21，22]。不过，A.F. Brooker等人[23]于1973年提出的分类法仍是文献中最流行的分类法。

第1类--股骨近端周围软组织中的骨岛。

第2类--骨刺源自骨盆或股骨近端，相对骨面之间的距离至少有1厘米。

第3类--骨刺源自骨盆或股骨近端骨骼，相对骨面之间的距离缩小到1厘米以下。

第4类级--髋关节强直。

神经元异位骨化的预防和治疗

治疗神经元异位骨化通常采用综合方法。神经元异位骨化切除是最有效的治疗方法[2，3，9]。与肿瘤不同的是，在切除异位骨化时并不需要完全切除病理组织[9，14]。目前认为，最好进行“功能性”切除，这样既能增加髋关节的活动幅度，又能尽量减少对周围组织的创伤。在大多数情况下，神经元异位骨化患者的髋关节僵硬是由关节外原因引起的。在极少数情况下，髋关节关节面的退行性病变和/或关节强直也是导致髋关节活动范围受限的原因[4，9，24]。

手术治疗的指征是髋关节活动幅度逐渐减小、疼痛综合征明显、血管和神经结构受到压迫以及生活质量普遍下降[9，14，25]。

M.J. Taunton认为，表达性疼痛综合征不能作为手术治疗的唯一指征，因为它不仅是由异位骨化引起的[26]。T.K. Cobb也持类似观点，并列举了在切除异位骨化髋关节后疼痛综合征仍未完全缓解的临床案例[27]。

根据P. Denormandie等人认为，生活质量下降是切除异位骨化的重要指征。对于因脊髓损伤而患有神经元异位骨化的患者，切除位于股骨前表面和髋关节的骨赘可让患者坐起来，必要时还可进行膀胱自导尿。通过切除脑损伤后遗症患者特有的位于股骨前内侧表面的异位骨化，可以消

除髋关节的屈曲-内收-内旋挛缩，并在大多数情况下对患者的步态产生积极影响[14]。

手术切除神经元异位骨化的一个重要条件是保留认知功能，这对于术后接受全方位的康复措施非常必要[2]。T.J. Moore指出，在认知功能严重受损的患者中，可以观察到运动幅度减小和神经元异位骨化复发的不良功能预后[28]。

目前，矫形外科医生尚未就移除神经元异位骨化的时间达成共识。根据一些学者的观点，应推迟12-18个月，直到生长结束和异位骨化形成，因为这有助于将复发率降至最低[4，26]。F. Genêt等人认为，根据闪烁扫描显示的神经元异位骨化不成熟迹象并不是手术的禁忌症，尤其是在髋关节活动幅度逐渐减小的情况下[25]。此外，等待时间过长会导致严重的骨质疏松和髋关节病[9，29]。早期干预扩大了康复措施的范围[20，25]。Chalidis等人发现，重度脑外伤患者的异位骨化复发风险与创伤后手术干预的时间无明显相关性。手术干预前13、21和30个月的预测复发概率分别为9%、14% 和19%[30]。虽然无法从这项研究中得出明确的结论，但所获得的数据并不支持早期切除异位骨化会带来高复发风险的说法。

关于髋关节神经元异位骨化手术切除的临床和放射学结果，文献中只有少数系列和单个病例，但所有文献都指出，手术切除神经元异位骨化可以消除或减少神经元异位骨化的体积，增加髋关节的活动幅度，从而提高生活质量。G.A. Macheras等人指出，切除神经元异位骨化后，26名患者（3名患者采用Brooker III级评分标准，23名患者采用Brooker IV级评分标准）的活动范围和Harris量表评分均有显著增加[31]。这与其他出版物[28、32、33]的数据相吻合。然而，一些学者报告称，在髋关节强直的病例中，术后的运动幅度明显低于在关节强直形成之前进行手术干预的病例[5，25]。这一事实可能是支持早期手术治疗神经元异位骨化的另一个论据。

切除神经元异位骨化极易引发并发症，如大量失血、大动脉和静脉干及神经损伤、感染、股骨和髋臼骨折等；因此，对小体积的异位骨化（无明显临床症状）不予切除，并对此类患者进行动态观察[9，14，25]。

神经元异位骨化的特点是血管丰富[34]，这导致在切除过程中大量失血[4，10]。由于位于异位骨化厚度内的血管破裂，异位骨化移除过程中的术中失血量可能会增加[4，35]。J.H. Kim等人描述了一例因脊髓损伤导致的异位骨化背景下的双侧髋关节强直。在未进行术前栓塞的情况下切除异位骨化时，失血量约为1500毫升，而在另一侧髋关节进行术前栓塞后切除异位骨化时，失血量少于500毫升[35]。N. Papalexis等人公布了一项关于髋关节神经元异位骨化术前栓塞疗效的单中心比较研究结果。在接受髋关节神经元异位骨化手术切除的16名患者中，8名患者在术前对涉及异位骨化供血的动脉进行了栓塞，而对照组的8名患者没有进行栓塞。术前栓塞组患者的术中平均失血量为875±320毫升，与对照组（1350±120毫升）相比，明显减少（p=0.035）。失血量较少的患者的住院时间也有明显缩短（p=0.014）。术前接受栓塞治疗的患者住院时间为（6.4±1.6）天，未接受栓塞治疗的患者住院时间为（11.5±1.4）天。因此，在异位骨化切除术前进行栓塞可以大大减少术中失血量和住院时间[36]。然而，我们在文献中没有发现任何关于髋关节异位骨化术前栓塞的适应症和禁忌症的数据。

据报道，神经元异位骨化中坐骨神经受损的病例占3.8%-5.6%，因为神经可能完全被异位组织包围[31]。根据P. Koulouvaris等人认为，术中刺激坐骨神经可避免或减少坐骨神经受损的风险[37]。

髋关节异位骨化患者术中发生股骨颈骨折的风险很高，尤其是在髋关节强直的情况下。据F. Gene等人的报告，在髋关节异位骨化切除术中，术中股骨颈骨折的发生率为13.7%[24]。在股骨颈骨折的不同手术阶段，都可能需要一期关节内假体[14]。目前，除关节内假体外，还有其他解决这一问题的方案：股骨近端切除术或使用髓内棒的股骨骨合成术[14，31]。

根据不同作者的研究，术后感染性并发症的发生率为9-38%[9，38]。根据L. Gatin等人认为，与严重脑外伤患者相比，有脊髓损伤后遗症的患者在异位骨化切除术后出现感染性并发症的风险更高[38]，这与其他作者的数据一致[4，39]。L. Gatin列出了异位骨化切除术后发生感染性

并发症的其他风险因素：年龄在30岁以下；根据ASA（American Society of Anesthesiologists评分表，等级为III级或以上，表明患者躯体状况严重[38]。l'Escalopier等人认为，有压疮和尿路炎症的患者术后并发症的风险会增加。作者认为，在移除异位骨化之前，尤其是有脊髓损伤后遗症的患者[9]。

根据文献，神经元异位骨化的复发率变化很大，从0%到92%不等。之所以存在如此大的差异，可能是因为作者在发表文章时并不总是明确说明复发的性质：无症状复发，患者需要反复进行手术治疗；或在随访检查时偶然在X光片上发现[9]。

大多数学者认为，复发率与病因、年龄、神经功能缺损的严重程度、神经元异位骨化 的多发性和体积无关[25，29]，也与异位骨化的切除体积无关[9，38]。然而，S.L. Stovner认为，与脑外伤后遗症患者相比，脊髓损伤后遗症患者复发异位骨化的风险更高[39]。N. de l'Escalopier等人认为，术后血肿和局部炎性改变是神经元异位骨化复发的风险因素[9]。

目前，有多种药物和非药物疗法可用于预防异位骨化复发，以及预防推测复发风险较高的患者形成异位骨化[2，3]。

早期康复。关于不同病因的异位骨化患者早期进行体育锻炼的必要性，文献中存在相互矛盾的观点。

Y. Xu指出，在异位骨化的早期阶段，任何机械刺激都能激活软组织中间充质干细胞的多能分化。例如，mTORC1可激活静止干细胞，促进软骨和成骨，从而启动异位骨化的形成[40]。A.K. Huber等人在实验小鼠模型中发现，关节固定通过减少机械传导信号几乎完全抑制了异位骨化的形成，因此间充质干细胞的进一步软骨分化未被激活[41]。此外，一些学者认为，积极参加体育运动的人容易形成异位骨化[42]，因为他们一方面受伤的概率较高，另一方面软组织过度拉伸，会刺激其中干细胞的活化和随后的分化[40]。C.M. Crawford在分析烧伤后患者早期康复治疗的结果时发现，进行主动和被动运动锻炼的患者，其关节运动幅度超过无痛极限时，形成异位骨化的概率较高。后来，他们的活动范围逐渐减小，直至因异位骨化形成而导致关节强直。患者的康复计划包括旨在将肌肉拉伸到轻微不适程度的锻炼，其活动范围的恢复令人满意[43]。

O. Daud等人的研究表明，脊髓损伤后遗症患者瘫痪肢体被动运动开始时间的延迟与神经元异位骨化发生率的增加相关；因此，预防关节挛缩的早期运动疗法是预防神经元异位骨化的首要且非常重要的方法[44]，这一观点在医学出版物中也很普遍[3，29]。

*放射治疗。*使用放射疗法预防异位骨化主要基于以下假设：在异位骨形成初期，软组织中的造骨干细胞具有很高的有丝分裂活性，因此对放射疗法很敏感[45]。体外实验证明，放射治疗对间充质干细胞的成骨分化有抑制作用，伴随而来的是RUNX2的表达减少[46]，骨形态发生蛋白（BMP-2）的活性受到抑制，成骨细胞的增殖和分化减少，并促进其凋亡[47]。神经元异位骨化的放射治疗既可用于预防异位骨化的发生，也可作为一种独立的治疗方法[7，48]。

E. Davis和合著者分析了小儿脑瘫患者（平均年龄为15.5±6.1岁，22名患者的GMFCS分级为5级，1名患者为4级）在股骨近端骨骺切除术前接受剂量为7.5Gy的预防性放疗的疗效、4级的患者有1名）发现，在0.2年至17.1年的随访期间，接受放射治疗的17例患者中有6例（35%）发生了神经元异位骨化，而未接受放射治疗的18例手术患者中有15例（83%）发生了神经元异位骨化[49]。

A.C. Museler等人介绍了对244名髋关节神经元异位骨化患者进行放疗的结果，这些患者都是在异位骨化形成初期接受脊髓损伤治疗后（根据髋关节超声波检查，随后通过核磁共振成像验证诊断）。只有13例（5.3%）患者在接受了一次（7Gy）放疗后，异位骨化增生有所进展，随后又接受了一次（7Gy）放疗，而这13例患者中只有1例后来因髋关节强直而需要手术治疗[50]。不过，由于随访时间范围很广（14-505天），我们无法判断随访时间短的患者是否没有复发[51]。

根据C.H. Lee等人的研究，总剂量为20Gy的放射治疗可使髋关节神经元异位骨化患者的疼痛综合征消退，并使碱性磷酸酶活性恢复正常。不过，作者仅提供了3名因各种脑部病变导致的

神经元异位骨化患者的治疗数据，且随访时间仅为6个月[52]。

为预防非神经源性异位骨赘复发，联合治疗（手术和放疗）的效果明显优于单纯切除异位骨化[53，54]。

T. Ebinger等人在比较神经源性、非神经源性和混合病因的髋关节异位骨化综合治疗结果时发现，在5年的门诊随访中，各组的复发率相似[55]。

目前，还没有令人信服的数据表明放疗作为一种预防复发的方法，在不同病因的异位骨化患者术前或术后使用效果更佳[48，56]。此外，T. Honore等人根据对95例脊髓损伤和脑外伤术后神经元异位骨化患者数据的回顾性分析得出结论，髋关节区域神经元异位骨化手术切除前的预防性放疗与术后脓毒症的高风险相关，并不能降低复发性神经元异位骨化 的发生率[57]，这与C. Cipriano等人的数据不谋而合[58]。

人们对神经元异位骨化放疗的长期影响知之甚少，但大型随机试验的结果表明，放疗没有肿瘤风险[48，56]。不过，Mourad等人描述了因外伤引起的复发性髋关节异位骨化接受放疗16个月后出现股骨未分化肉瘤的情况[59]。M.K. Farris等人也报告了因髋关节外伤性异位骨化而接受放疗11年后诊断出骨盆骨肉瘤的病例[60]。

非甾体抗炎药（NSAIDs）。异位骨化形成的机制之一是前列腺素分泌过多，前列腺素参与调节间充质细胞向成骨细胞的分化，并间接影响骨形态形成蛋白的表达。非甾体抗炎药通过抑制环氧化酶，减少前列腺素、前列环素和血栓素的合成，从而可能抑制骨化[61]。

2001年，K. Banovac等人公布了一项随机前瞻性双盲安慰剂对照研究的结果，该研究对33名患者进行了调查，研究了吲哚美辛（75毫克）在脊髓损伤后每天使用3周预防神经元异位骨化的疗效。结果发现，与安慰剂相比，吲哚美辛组的神经元异位骨化发生率明显降低（$p<0.001$）[62]。2004年，K. Banovac发表了另一项前瞻性双盲安慰剂对照研究的结果，该研究对76名患者进行了研究，其中研究了环氧化酶-2选择性抑制剂罗非昔布的效果。研究结果表明，与安慰剂相比，罗非昔布组神经元异位骨化形成的发生率在统计学上明显降低[63]。由S.Y.N. Schincariol等人指出，在脊髓损伤术后早期使用非甾体抗炎药可以有效预防异位骨化的形成[51]。这与E.C. Zakrasek等人的数据相关，他们的数据显示，与未接受此类治疗的患者相比，在脊髓损伤后的头60天内接受非甾体抗炎药治疗15天或更长时间的脊髓损伤后遗症患者发生异位骨化的概率要低得多[64]。Y.U. Yolcu等人的系统综述和荟萃分析结果增加了人们对非甾体抗炎药预防神经元异位骨化疗效的总体积极印象。虽然作者没有找到足够的证据证明已知的预防性药物在预防神经元异位骨化方面与安慰剂相比具有统计学上的显著优势，但在分析非甾体抗炎药的使用数据时发现，与安慰剂相比，非甾体抗炎药的神经元异位骨化发生率著降低[65]。

J. Dartnell等人认为，非甾体抗炎药不能有效预防高危患者--股骨近端切除术后患脑瘫的青少年--的神经元异位骨化形成。在一组21名患者中，吲哚美辛的剂量为0.5毫克/千克，术后10天服用，随访4.5年，发现5名患者出现症状性异位骨化。在-21例未服用吲哚美辛的患者中，随访4.3年，发现5例患者出现症状性 异位骨化。根据这些数据，作者认为吲哚美辛不适合用于预防这类患者的神经元异位骨化[66]。

此外，非甾体抗炎药还会产生严重的胃肠道副作用，并增加患者骨折不愈合和发生“行进性骨折”的风险。非甾体抗炎药超过2周，骨折不愈合的风险就会增加，这就限制了它们在多发性创伤患者中的使用[67]。

双膦酸盐。双膦酸盐是一种抗还原剂，可诱导破骨细胞凋亡并抑制钙化。一些学者认为，双膦酸盐可被视为预防神经元异位骨化的一种手段[68，69]。在一项前瞻性双盲研究中，S.L. Stove等人的前瞻性双盲研究中发现，依替膦酸（I代双膦酸盐）可通过抑制骨矿化而对神经元异位骨化的发展产生抑制作用。根据对所得结果的分析，作者认为在创伤性脊髓损伤后60天内开始的依替膦酸治疗比损伤后60天开始的治疗更有效[68]。这与G. Spielman及合著者的数据相吻合，这些数据表明依替膦酸对严重脑外伤后患者预防异位骨化具有疗效[70]。然而，K. Banovac认为，当通过闪烁照相发现异位骨化时，即使没有影像学征兆，依替膦酸也不会产生预期

效果[71]。根据一些学者的观点，依替膦酸并不能阻止神经元异位骨化的发展，而只能减缓基质矿化，在双膦酸盐用药结束后，骨基质矿化，即神经元异位骨化的生长仍在继续[72，73]。

除第一代外，后续几代双膦酸盐只影响破骨细胞，对异位骨化的抑制能力较弱[40]。

根据A. Ploumis等人的研究，在脊髓损伤后遗症患者早期预防性使用阿仑膦酸（第二代双膦酸盐）并不能降低异位骨化形成的风险。根据作者的研究，与安慰剂组相比，使用阿仑膦酸后的患者意外地倾向于形成挛缩[74]。

P. Schuetz等人认为，帕米膦酸（第二代双膦酸盐）可以有效预防异位骨化在切除后复发。不过，这一观点是基于对5名脊柱创伤后遗症患者的治疗结果以及治疗后5–54个月的随访结果[75]。

Y.U. Yolcu等人根据药物预防的综合分析数据发现，服用双膦酸盐时，异位骨化的检出率无统计学差异（p=0.58）[65]。总体而言，推荐将双膦酸盐作为预防神经元异位骨化的治疗药物的证据尚不明确[51]。

结论

现代诊断方法可根据超声波检查结果对髋关节神经元异位骨化的高危患者进行筛查，并通过CT或磁共振成像进一步核实诊断。

虽然目前对髋关节神经元异位骨化清除的时机还没有达成共识，但手术治疗似乎是清除或减少神经元异位骨化数量、控制大多数病例疼痛以及改善患者生活质量的最有效方法，目前患者面临术后并发症和复发的风险。在目前的科学文献中，还没有发现关于对脑外伤患者的神经元异位骨化形成和复发进行有效药物预防的令人信服的数据，而在脊髓损伤患者中，使用非甾体抗炎药可减少神经元异位骨化复发。关于放疗治疗神经元异位骨化的有效性和安全性，已发表的数据相互矛盾。文献中没有对放疗治疗髋关节神经元异位骨化的长期效果进行分析，因此无法确定这种方法对神经元异位骨化患者的适应症和禁忌症。尽管病因相同（中枢神经系统受损），但对于因脊髓损伤、脑外伤和脑瘫导致的患者，非手术预防和治疗方法的效果却各不相同。考虑到中枢神经系统病变的性质，开展随机对照试验将有助于确定这些治疗方法在预防神经元异位骨化形成和复发方面的有效性。药物预防和治疗神经元异位骨化的一个有前景的方向可能是对中枢神经系统受损患者神经元异位骨化发病机制的各个环节产生选择性作用。

其他信息

资金来源。作者声明在撰写文章时没有资金来源。

利益冲突。作者声明，本文的发表不存在明显和潜在的利益冲突。

作者贡献。*V.A. Novikov*，研究设计、最终编辑和文章撰写；*A.M. Chodorovskaya*，文章撰写、搜索和分析文献资料；*V.V. Umnov*，阶段编辑；*D.V. Umnov*、*E.V. Melchenko*，搜索和分析文献资料。*D.V. Umnov*，*E.V. Melchenko*，搜索和分析文献资料。

所有作者都对研究和文章做出了重要贡献，并在发表前阅读和批准了最终版本。

СПИСОК ЛИТЕРАТУРЫ

1. Деев Р.В., Берсенев А.В. Роль стволовых стромальных (мезенхимальных) клеток в формировании гетеротопических оссификатов // Клеточная трансплантология и тканевая инженерия. 2005. № 1. С. 46–48.

2. Meyers C., Lisiecki J., Miller S., et al. Heterotopic ossification: a comprehensive review // JBMR Plus. 2019. Vol. 3. No. 4. DOI: 10.1002/jbm4.10172

3. Brady R.D., Shultz S.R., McDonald S.J., et al. Neurological heterotopic ossification: current understanding and future directions // Bone. 2018. Vol. 109. P. 35–42. DOI: 10.1016/j.bone.2017.05.015

4. Garland D.E., Orwin J.F. Resection of heterotopic ossification in patients with spinal cord injuries // Clin. Orthop. Relat. Res. 1989. No. 242. P. 169–176. DOI: 10.1097/00003086-198905000-00016

5. Ippolito E., Formisano R., Caterini R., et al. Operative treatment of heterotopic hip ossification in patients with coma after brain injury // Clin. Orthop. Relat. Res. 1999. No. 365. P. 130–138. DOI: 10.1097/00003086-199908000-00018

6. Wong K.R, Mychasiuk R., O'Brien T.J., et al. Neurological heterotopic ossification: novel mechanisms, prognostic biomarkers and prophylactic therapies // Bone Res. 2020. Vol. 8. No. 1. P. 42. DOI: 10.1038/s41413-020-00119-9

7. Arduini M., Mancini F., Farsetti P., et al. A new classification of periarticular heterotopic ossification of the hip associated with neurological injury: 3D CT scan assessment and intra-operative findings // Bone Joint J. 2015. Vol. 97-B. No. 7. P. 899–904. DOI: 10.1302/0301-620X.97B7.35031

8. de l'Escalopier N., Denormandie P., Gatin L., et al. Resection of neurogenic heterotopic ossification (NHO) of the hip, lessons learned after 377 procedures // Annals of Physical and Rehabilitation Medicine. 2018. Vol. 61. DOI: 10.1016/j.rehab.2018.05.385

9. Zielinski E., Chiang B.J.L., Satpathy J. The role of preoperative vascular imaging and embolisation for the surgical resection of bilateral hip heterotopic ossification // BMJ Case Rep. 2019. Vol. 12. No. 8. DOI: 10.1136/bcr-2019-230964
10. Cholok D., Chung M.T., Ranganathan K., et al. Heterotopic ossification and the elucidation of pathologic differentiation // Bone. 2018. Vol. 109. P. 12–21. DOI: 10.1016/j.bone.2017.09.019
11. Svircev J.N., Wallbom A.S. False-negative triple-phase bone scans in spinal cord injury to detect clinically suspect heterotopic ossification: a case series // J. Spinal Cord Med. 2008. Vol. 31. P. 194–196. DOI: 10.1080/10790268.2008.11760711
12. Van Kuijk A.A., Geurts A.C.H., van Kuppevelt H.J.M. Neurogenic heterotopic ossification in spinal cord injury // Spinal Cord. 2002. Vol. 40. P. 313–326. DOI: 10.1038/sj.sc.3101309
13. Denormandie P., de l'Escalopier N., Gatin L., et al. Resection of neurogenic heterotopic ossification (NHO) of the hip // Orthop. Traumatol. Surg. 2018. Vol. 104. No. 1S. P. S121–S127. DOI: 10.1016/j.otsr.2017.04.015
14. Mujtaba B., Taher A., Fiala M.J., et al. Heterotopic ossification: radiological and pathological review // Radiol. Oncol. 2019. Vol. 53. No. 3. P. 275–284. DOI: 10.2478/raon-2019-0039
15. Wang H., Nie P., Li Y., et al. MRI findings of early myositis ossificans without calcification or ossification // Biomed Res. Int. 2018. Vol. 2018. DOI: 10.1155/2018/4186324
16. Stefanidis K., Brindley P., Ramnarine R., et al. Bedside ultrasound to facilitate early diagnosis and ease of follow-up in neurogenic heterotopic ossification: a pilot study from the intensive care unit // J. Head Trauma Rehabil. 2017. Vol. 32. No. 6. P. E54–E58. DOI: 10.1097/HTR.0000000000000293
17. Wang Q., Zhang P., Li P., et al. Ultrasonography monitoring of trauma-induced heterotopic ossification: guidance for rehabilitation procedures // Front. Neurol. 2018. Vol. 9. P. 771. DOI: 10.3389/fneur.2018.00771
18. Rosteius T., Suero E.M., Grasmucke D., et al. The sensitivity of ultrasound screening examination in detecting heterotopic ossification following spinal cord injury // Spinal Cord. 2017. Vol. 55. No. 1. P. 71–73. DOI: 10.1038/sc.2016.93
19. Garland D.E. A clinical perspective on common forms of acquired heterotopic ossification // Clin. Orthop. Relat. Res. 1991. No. 263. P. 13–29. DOI: 10.1097/00003086-199102000-00003
20. Mavrogenis A.F., Guerra G., Staals E.L., et al. A classification method for neurogenic heterotopic ossification of the hip // J. Orthop. Traumatol. 2012. Vol. 13. No. 2. P. 69–78. DOI: 10.1007/s10195-012-0193-z
21. Della Valle A.G., Ruzo P.S., Pavone V., et al. Heterotopic ossification after total hip arthroplasty: a critical analysis of the Brooker classification and proposal of a simplified rating system // J. Arthroplasty. 2002. Vol. 17. No. 7. P. 870–875. DOI: 10.1054/arth.2002.34819
22. Brooker A.F., Bowerman J.W., Robinson R.A., et al. Ectopic ossification following total hip replacement. Incidence and a method of classification // J. Bone Joint Surg. Am. 1973. Vol. 55. No. 8. P. 1629–1632.
23. Genet F., Marmorat J.L., Lautridou C., et al. Impact of late surgical intervention on heterotopic ossification of the hip after traumatic neurological injury // J. Bone Joint Surg. Br. 2009. Vol. 91. No. 11. P. 1493–1498. DOI: 10.1302/0301-620X.91B11.22305
24. Genêt F., Jourdan C., Schnitzler A., et al. Troublesome heterotopic ossification after central nervous system damage: a survey of 570 surgeries // PLoS One. 2011. Vol. 6. No. 1. DOI: 10.1371/journal.pone.0016632
25. Taunton M.J. Heterotopic ossification // Complications after primary total hip arthroplasty: a comprehensive clinical guide. Ed. by M.P. Abdel, C.J. Della Valle. Springer Cham, 2017. P. 213–224.
26. Cobb T.K., Berry D.J., Wallrichs S.L., et al. Functional outcome of excision of heterotopic ossification after total hip arthroplasty // Clin. Orthop. Relat. Res. 1999. No. 361. P. 131–139. DOI: 10.1097/00003086-199904000-00018
27. Moore T.J. Functional outcome following surgical excision of heterotopic ossification in patients with traumatic brain injury // J. Orthop. Trauma. 1993. Vol. 7. No. 1. P. 11–14. DOI: 10.1097/00005131-199302000-00003
28. Almangour W., Schnitzler A., Salga M., et al. Recurrence of heterotopic ossification after removal in patients with traumatic brain injury: a systematic review // Ann. Phys. Rehabil. Med. 2016. Vol. 59. No. 4. P. 263–269. DOI: 10.1016/j.rehab.2016.03.009
29. Chalidis B., Stengel D., Giannoudis P.V. Early excision and late excision of heterotopic ossification after traumatic brain injury are equivalent: a systematic review of the literature // J. Neurotrauma. 2007. Vol. 24. No. 11. P. 1675–1686. DOI: 10.1089/neu.2007.0342
30. Macheras G.A., Lepetsos P., Leonidou A., et al. Results from the surgical resection of severe heterotopic ossification of the hip: a case series of 26 patients // Eur. J. Orthop. Surg. Traumatol. 2017. Vol. 27. No. 8. P. 1097–1102. DOI: 10.1007/s00590-017-1980-2
31. Behery O.A., Dai A.Z., McLaurin T.M. Posttraumatic heterotopic ossification of the hip // J. Orthop. Trauma 2018. Vol. 32. No. 1. P. S18–S19. DOI: 10.1097/BOT.0000000000001197
32. Meiners T., Abel R., Bohm V., et al. Resection of heterotopic ossification of the hip in spinal cord injured patients // Spinal Cord. 1997. Vol. 35. No. 7. P. 443–445. DOI: 10.1038/sj.sc.3100415
33. Dilling C.F, Wada A.M., Lazard Z.W., et al. Vessel formation is induced prior to the appearance of cartilage in BMP-2-mediated heterotopic ossification // J. Bone Miner. Res. 2010. Vol. 25. No. 5. P. 1147–1156. DOI: 10.1359/jbmr.091031
34. Kim J.H., Park C., Son S.M., et al. Preoperative arterial embolization of heterotopic ossification around the hip joint // Yeungnam Univ. J. Med. 2018. Vol. 35. No. 1. P. 130–134. DOI: 10.12701/yujm.2018.35.1.130
35. Papalexis N., Peta G., Errani C., et al. Preoperative arterial embolization for heterotopic ossification of the hip // J. Vasc. Interv. Radiol. 2023. Vol. 34. No. 4. P. 608–612. DOI: 10.1016/j.jvir.2022.11.030
36. Koulouvaris P., Tsailas P., Tsiavos K., et al. Clinical observations on surgical details of resection of heterotopic ossification at the hip in traumatic brain-injured adult // J. Surg. Orthop. Adv. 2010. Vol. 19. No. 3. P. 177–180.
37. Gatin L., Genêt F., Dinh A., et al. Postoperative infections after excision of neurogenic heterotopic ossifications at the hip: risk factors and causative organisms // Orthop. Traumatol. Surg. Res. 2017. Vol. 103. No. 3. P. 357–361. DOI: 10.1016/j.otsr.2017.02.001
38. Stover S.L., Niemann K.M., Tulloss J.R. Experience with surgical resection of heterotopic bone in spinal cord injury patients // Clin. Orthop. Relat. Res. 1991. No. 263. P. 71–77.
39. Xu Y., Huang M., He W. Heterotopic ossification: clinical features, basic researches, and mechanical stimulations // Front. Cell Dev. Biol. 2022. Vol. 10. DOI: 10.3389/fcell.2022.770931
40. Huber A.K., Patel N., Pagani C.A., et al. Immobilization after injury alters extracellular matrix and stem cell fate // J. Clin. Invest. 2020. Vol. 130. No. 10. P. 5444–5460. DOI: 10.1172/JCI136142

41. Jones N.A., Bentley B.C., Wahl L. Nonsurgical management of heterotopic ossification in a runner // J. Orthop. Sports Phys. Ther. 2019. Vol. 49. No. 9. P. 676. DOI: 10.2519/jospt.2019.8491
42. Crawford C.M., Varghese G., Mani M.M., et al. Heterotopic ossification: are range of motion exercises contraindicated? // J. Burn Care Rehabil. 1986. Vol. 7. No. 4. P. 323–327. DOI: 10.1097/00004630-198607000-00005
43. Daud O., Sett P., Burr R.G., et al. The relationship of heterotopic ossification to passive movements in paraplegic patients // Disabil. Rehabil. 1993. Vol. 15. No. 3. P. 114–118. DOI: 10.3109/09638289309166001
44. Craven P.L., Urist M.R. Osteogenesis by radioisotope labelled cell populations in implants of bone matrix under the influence of ionizing radiation // Clin. Orthop. Relat. Res. 1971. Vol. 76. P. 231–243. DOI: 10.1097/00003086-197105000-00030
45. Wang Y., Zhu G., Wang J., et al. Irradiation alters the differentiation potential of bone marrow mesenchymal stem cells // Mol. Med. Rep. 2016. Vol. 13. No. 1. P. 213–223. DOI: 10.3892/mmr.2015.4539
46. Pohl F., Hassel S., Nohe A., et al. Radiation-induced suppression of the Bmp2 signal transduction pathway in the pluripotent mesenchymal cell line C2C12: an *in vitro* model for prevention of heterotopic ossification by radiotherapy // Radiat Res. 2003. Vol. 159. No. 3. P. 345–350. DOI: 10.1667/0033-7587(2003)159[0345:risotb]2.0.co;2
47. Georhakopoulos I., Kouloulias V., Kougiountzopoulou A., et al. Radiation therapy for the prevention of heterotopic ossification: efficacy and toxicity of single fraction radiotherapy // Orthop. Rev. 2020. Vol. 12. No. 2. P. 8577. DOI: 10.4081/or.2020.8577
48. Davis E., Williams K., Matheney T.H., et al. Radiation prophylaxis for hip salvage surgery in cerebral palsy: can we reduce the incidence of heterotopic ossification? // J. Pediatr. Orthop. 2019. Vol. 39. No. 5. P. e386–e391. DOI: 10.1097/BPO.0000000000001314
49. Museler A.C., Grasmucke D., Jansen O., et al. Inhospital outcomes following single-dose radiation therapy in the treatment of heterotopic ossification of the hip following spinal cord injury-an analysis of 444 cases // Spinal Cord. 2016. Vol. 55. No. 3. P. 244–246. DOI: 10.1038/sc.2016.112
50. Schincariol C.Y.N., Echauri E.M.I., Silvestre O.F., et al. Heterotopic ossification after spinal cord injury: prevention and treatment – a sistematic review // Acta Ortop. Bras. 2023. Vol. 31. No. 3. P. 1–5. DOI: 10.1590/1413-785220233103e267451
51. Lee C.H., Shim S.J., Kim H.J., et al. Effects of radiation therapy on established neurogenic heterotopic ossification // Ann. Rehabil. Med. 2016. Vol. 40. P. 1135–1139. DOI: 10.5535/arm.2016.40.6.1135
52. Hu Z.H., Chen W., Sun J.N., et al. Radiotherapy for the prophylaxis of heterotopic ossification after total hip arthroplasty: a systematic review and meta-analysis of randomized controlled trails // Med. Dosim. 2021. Vol. 46. No. 1. P. 65–73. DOI: 10.1016/j.meddos.2020.07.010
53. Milakovic M., Popovic M., Raman S., et al. Radiotherapy for the prophylaxis of heterotopic ossification: a systematic review and meta-analysis of randomized controlled trials // Radiother. Oncol. 2015. Vol. 116. No. 1. P. 4–9. DOI: 10.1016/j.radonc.2015.05.022
54. Ebinger T., Roesch M., Kiefer H., et al. Influence of etiology in heterotopic bone formation of the hip // J. Trauma. 2000. Vol. 48. No. 6. P. 1058–1062. DOI: 10.1097/00005373-200006000-00010
55. Padgett D.E, Holley K.G., Cummings M. The efficacy of 500 centigray radiation in the prevention of heterotopic ossification after total hip arthroplasty: a prospective, randomized, pilot study // J. Arthroplasty. 2003. Vol. 18. No. 6. P. 677–686. DOI: 10.1016/s0883-5403(03)00265-1
56. Honore T., Salga M., Grelier A., et al. Effectiveness of radiotherapy to prevent recurrence of heterotopic ossification in patients with spinal cord injury and traumatic head injury: a retrospective case-controlled study // J. Rehabil. Med. 2020. Vol. 52. No. 5. P. 1–6. DOI: 10.2340/16501977-2692
57. Cipriano C., Pill S.G., Rosenstock J., et al. Radiation therapy for preventing recurrence of neurogenic heterotopic ossification // Orthopedics. 2009. Vol. 32. No. 9. DOI: 10.3928/01477447-20090728-33
58. Mourad W.F., Packianathan S., Shourbaji R.A., et al. Radiation-induced sarcoma following radiation prophylaxis of heterotopic ossification // Pract. Radiat. Oncol. 2012. Vol. 2. No. 2. P. 151–154. DOI: 10.1016/j.prro.2011.06.005
59. Farris M.K., Chowdhry V.K., Lemke S., et al. Osteosarcoma following single fraction radiation prophylaxis for heterotopic ossification // Radiat. Oncol. 2012. Vol. 7. No. 1. P. 1–6. DOI: 10.1186/1748-717X-7-140
60. Liu H., Zhao J.G., Li Y., et al. Non-steroidal anti-inflammatory drugs for preventing heterotopic bone formation after hip arthroplasty // Cochrane Database Syst. Rev. 2019. Vol. 2019. No. 7. DOI: 10.1002/14651858.CD012861.pub2
61. Banovac K., Williams J.M., Patrick L.D., et al. Prevention of heterotopic ossification after spinal cord injury with indomethacin // Spinal Cord. 2001. Vol. 39. No. 7. P. 370–374. DOI: 10.1038/sj.sc.3101166
62. Banovac K., Williams J.M., Patrick L.D., et al. Prevention of heterotopic ossification after spinal cord injury with COX-2 selective inhibitor (rofecoxib) // Spinal Cord. 2004. Vol. 42. No. 12. P. 707–710. DOI: 10.1038/sj.sc.3101628
63. Zakrasek E.C., Yurkiewicz S.M., Dirlikov B., et al. Use of nonsteroidal antiinflammatory drugs to prevent heterotopic ossification after spinal cord injury: a retrospective chart review // Spinal Cord. 2019. Vol. 57. No. 3. P. 214–220. DOI: 10.1038/s41393-018-0199-3
64. Yolcu Y.U., Wahood W., Goyal A., et al. Pharmacologic prophylaxis for heterotopic ossification following spinal cord injury: a systematic review and meta-analysis // Clin. Neurol. Neurosurg. 2020. Vol. 193. DOI: 10.1016/j.clineuro.2020.105737
65. Dartnell J.H., Paterson J.M., Magill N., et al. Proximal femoral resection for the painful dislocated hip in cerebral palsy // J. Pediatric Orthop. 2014. Vol. 34. No. 3. P. 295–299. DOI: 10.1097/BPO.0000000000000146
66. Borgeat A., Ofner C., Saporito A., et al. The effect of nonsteroidal anti-inflammatory drugs on bone healing in humans: a qualitative, systematic review // J. Clin. Anesth. 2018. Vol. 49. P. 92–100. DOI: 10.1016/j.jclinane.2018.06.020
67. Stover S.L., Hahn H.R., Miller J.M. Disodium etidronate in the prevention of heterotopic ossification following spinal cord injury (preliminary report) // Spinal Cord. 1976. Vol. 14. No. 2. P. 146–156. DOI: 10.1038/sc.1976.25
68. Teasell R.W., Mehta S., Aubut J.L., et al. A systematic review of the therapeutic interventions for heterotopic ossification after spinal cord injury // Spinal Cord. 2010. Vol. 48. P. 512–521. DOI: 10.1038/sc.2009.175
69. Spielman G., Gennarelli T.A., Rogers C.R. Disodium etidronate: its role in preventing heterotopic ossification in severe head injury // Arch. Phys. Med. Rehabil. 1983. Vol. 64. No. 11. P. 539–542.
70. Banovac K. The effect of etidronate on late development of heterotopic ossification after spinal cord injury // J. Spinal Cord Med. 2000. Vol. 23. No. 1. P. 40–44. DOI: 10.1080/10790268.2000.11753507

71. Shafer D.M., Bay C. Caruso D.M., et al. The use of eidronate disodium in the prevention of heterotopic ossification in burn patients // Burns. 2008. Vol. 34. No. 3. P. 355–360. DOI: 10.1016/j.burns.2007.04.006
72. Thomas B.J., Amstutz H.C. Results of the administration of diphosphonate for the prevention of heterotopic ossification after total hip arthroplasty // J. Bone Jt. Surg. Am. 1985. Vol. 67. No. 3. P. 400–403. DOI: 10.2106/00004623-198567030-00008
73. Ploumis A., Donovan J.M., Olurinde M.O., et al. Association between alendronate, serum alkaline phosphatase level, and heterotopic ossification in individuals with spinal cord injury // J. Spinal Cord Med. 2014. Vol. 38. No. 2. P. 193–198. DOI: 10.1179/2045772314Y.0000000213
74. Schuetz P., Mueller B., Christ-Crain M., et al. Amino-biphosphonates in heterotopic ossification: first experience in five consecutive cases // Spinal Cord. 2005. Vol. 43. No. 10. P. 604–610. DOI: 10.1038/sj.sc.3101761

REFERENCES

1. Deev RV, Bersenev AV. Rol' stvolovykh stromal'nykh (mezenkhimal'nykh) kletok v formirovanii geterotopicheskikh ossifikatov. *Kletochnaya transplantologiya i tkanevaya inzheneriya.* 2005;(1):46–48. (In Russ.)
2. Meyers C, Lisiecki J, Miller S, et al. Heterotopic ossification: a comprehensive review. *JBMR Plus.* 2019;3(4). DOI: 10.1002/jbm4.10172
3. Brady RD, Shultz SR, McDonald SJ, et al. Neurological heterotopic ossification: Current understanding and future directions. *Bone.* 2018;109:35–42. DOI: 10.1016/j.bone.2017.05.015
4. Garland DE, Orwin JF. Resection of heterotopic ossification in patients with spinal cord injuries. *Clin Orthop Relat Res.* 1989;(242):169–176. DOI: 10.1097/00003086-198905000-00016
5. Ippolito E, Formisano R, Caterini R, et al. Operative treatment of heterotopic hip ossification in patients with coma after brain injury. *Clin Orthop Relat Res.* 1999;(365):130–138. DOI: 10.1097/00003086-199908000-00018
6. Wong KR, Mychasiuk R, O'Brien TJ, et al. Neurological heterotopic ossification: novel mechanisms, prognostic biomarkers and prophylactic therapies. *Bone Res.* 2020;8(1):42. DOI: 10.1038/s41413-020-00119-9
7. Arduini M, Mancini F, Farsetti P, Piperno A, Ippolito E. A new classification of peri-articular heterotopic ossification of the hip associated with neurological injury: 3D CT scan assessment and intra-operative findings. *Bone Joint J.* 2015;97-B(7):899–904. DOI: 10.1302/0301-620X.97B7.35031
8. de l'Escalopier N, Denormandie P, Gatin L, et al. Resection of neurogenic heterotopic ossification (NHO) of the hip, lessons learned after 377 procedures. *Annals of Physical and Rehabilitation Medicine.* 2018;61. DOI: 10.1016/j.rehab.2018.05.385
9. Zielinski E, Chiang BJL, Satpathy J. The role of preoperative vascular imaging and embolisation for the surgical resection of bilateral hip heterotopic ossification. *BMJ Case Rep.* 2019;12(8). DOI: 10.1136/bcr-2019-230964.
10. Cholok D, Chung MT, Ranganathan K, et al. Heterotopic ossification and the elucidation of pathologic differentiation. *Bone.* 2018;109:12–21. DOI: 10.1016/j.bone.2017.09.019
11. Svircev JN, Wallbom AS. False-negative triple-phase bone scans in spinal cord injury to detect clinically suspect heterotopic ossification: a case series. *J Spinal Cord Med.* 2008;31(2):194–196. DOI: 10.1080/10790268.2008.11760711
12. van Kuijk AA, Geurts AC, van Kuppevelt HJ. Neurogenic heterotopic ossification in spinal cord injury. *Spinal Cord.* 2002;40(7):313–326. DOI: 10.1038/sj.sc.3101309
13. Denormandie P, de l'Escalopier N, Gatin L, et al. Resection of neurogenic heterotopic ossification (NHO) of the hip. *Orthop Traumatol Surg Res.* 2018;104(1S):S121–S127. DOI: 10.1016/j.otsr.2017.04.015
14. Mujtaba B, Taher A, Fiala MJ, et al. Heterotopic ossification: radiological and pathological review. *Radiol Oncol.* 2019;53(3):275–284. DOI: 10.2478/raon-2019-0039
15. Wang H, Nie P, Li Y, et al. MRI findings of early myositis ossificans without calcification or ossification. *Biomed Res Int.* 2018;2018. DOI: 10.1155/2018/4186324
16. Stefanidis K, Brindley P, Ramnarine R, et al. Bedside ultrasound to facilitate early diagnosis and ease of follow-up in neurogenic heterotopic ossification: a pilot study from the intensive care unit. *J Head Trauma Rehabil.* 2017;32(6):E54–E58. DOI: 10.1097/HTR.0000000000000293
17. Wang Q, Zhang P, Li P, et al. Ultrasonography monitoring of trauma-induced heterotopic ossification: guidance for rehabilitation procedures. *Front Neurol.* 2018;9:771. DOI: 10.3389/fneur.2018.00771
18. Rosteius T, Suero EM, Grasmücke D, et al. The sensitivity of ultrasound screening examination in detecting heterotopic ossification following spinal cord injury. *Spinal Cord.* 2017;55(1):71–73. DOI: 10.1038/sc.2016.93.
19. Garland DE. A clinical perspective on common forms of acquired heterotopic ossification. *Clin Orthop Relat Res.* 1991;(263):13–29. DOI: 10.1097/00003086-199102000-00003
20. Mavrogenis AF, Guerra G, Staals EL, et al. A classification method for neurogenic heterotopic ossification of the hip. *J Orthop Traumatol.* 2012;13(2):69–78. DOI: 10.1007/s10195-012-0193-z
21. Della Valle AG, Ruzo PS, Pavone V, et al. Heterotopic ossification after total hip arthroplasty: a critical analysis of the Brooker classification and proposal of a simplified rating system. *J Arthroplasty.* 2002;17(7):870–875. DOI: 10.1054/arth.2002.34819
22. Brooker AF, Bowerman JW, Robinson RA, et al. Ectopic ossification following total hip replacement. Incidence and a method of classification. *J Bone Joint Surg Am.* 1973;55(8):1629–1632.
23. Genet F, Marmorat JL, Lautridou C, et al. Impact of late surgical intervention on heterotopic ossification of the hip after traumatic neurological injury. *J Bone Joint Surg Br.* 2009;91(11):1493–1498. DOI: 10.1302/0301-620X.91B11.22305
24. Genêt F, Jourdan C, Schnitzler A, et al. Troublesome heterotopic ossification after central nervous system damage: a survey of 570 surgeries. *PLoS One.* 2011;6(1). DOI: 10.1371/journal.pone.0016632
25. Taunton MJ. Heterotopic Ossification. In: Complications after primary total hip arthroplasty: a comprehensive clinical guide. Ed. by M.P. Abdel, C.J. Della Valle. Springer Cham; 2017. P. 213–224.
26. Cobb TK, Berry DJ, Wallrichs SL, et al. Functional outcome of excision of heterotopic ossification after total hip arthroplasty. *Clin Orthop Relat Res.* 1999;(361):131–139. DOI: 10.1097/00003086-199904000-00018
27. Moore TJ. Functional outcome following surgical excision of heterotopic ossification in patients with traumatic brain injury. *J Orthop Trauma.* 1993;7(1):11–14. DOI: 10.1097/00005131-199302000-00003

28. Almangour W, Schnitzler A, Salga M, et al. Recurrence of heterotopic ossification after removal in patients with traumatic brain injury: a systematic review. *Ann Phys Rehabil Med.* 2016;59(4):263–269. DOI: 10.1016/j.rehab.2016.03.009
29. Chalidis B, Stengel D, Giannoudis PV. Early excision and late excision of heterotopic ossification after traumatic brain injury are equivalent: a systematic review of the literature. *J Neurotrauma.* 2007;24(11):1675–1686. DOI: 10.1089/neu.2007.0342
30. Macheras GA, Lepetsos P, Leonidou A, et al. Results from the surgical resection of severe heterotopic ossification of the hip: a case series of 26 patients. *Eur J Orthop Surg Traumatol.* 2017;27(8):1097–1102. DOI: 10.1007/s00590-017-1980-2
31. Behery OA, Dai AZ, McLaurin TM. Posttraumatic heterotopic ossification of the hip. *J Orthop Trauma.* 2018;32(1):S18–S19. DOI: 10.1097/BOT.0000000000001197
32. Meiners T, Abel R, Böhm V, et al. Resection of heterotopic ossification of the hip in spinal cord injured patients. *Spinal Cord.* 1997;35(7):443–445. DOI: 10.1038/sj.sc.3100415
33. Dilling CF, Wada AM, Lazard ZW, et al. Vessel formation is induced prior to the appearance of cartilage in BMP-2-mediated heterotopic ossification. *J Bone Miner Res.* 2010;25(5):1147–1156. DOI: 10.1359/jbmr.091031
34. Kim JH, Park C, Son SM, et al. Preoperative arterial embolization of heterotopic ossification around the hip joint. *Yeungnam Univ J Med.* 2018;35(1):130–134. DOI: 10.12701/yujm.2018.35.1.130
35. Papalexis N, Peta G, Errani C, et al. Preoperative arterial embolization for heterotopic ossification of the hip. *J Vasc Interv Radiol.* 2023;34(4):608–612. DOI: 10.1016/j.jvir.2022.11.030
36. Koulouvaris P, Tsailas P, Tsiavos K, et al. Clinical observations on surgical details of resection of heterotopic ossification at the hip in traumatic brain-injured adult. *J Surg Orthop Adv.* 2010;19(3):177–180.
37. Gatin L, Genêt F, Dinh A, et al. Postoperative infections after excision of neurogenic heterotopic ossifications at the hip: Risk factors and causative organisms. *Orthop Traumatol Surg Res.* 2017;103(3):357–361. DOI: 10.1016/j.otsr.2017.02.001
38. Stover SL, Niemann KM, Tulloss JR. Experience with surgical resection of heterotopic bone in spinal cord injury patients. *Clin Orthop Relat Res.* 1991;(263):71–77.
39. Xu Y, Huang M, He W, et al. Heterotopic ossification: clinical features, basic researches, and mechanical stimulations. *Front Cell Dev Biol.* 2022;10. DOI: 10.3389/fcell.2022.770931
40. Huber AK, Patel N, Pagani CA, et al. Immobilization after injury alters extracellular matrix and stem cell fate. *J Clin Invest.* 2020;130(10):5444–5460. DOI: 10.1172/JCI136142
41. Jones NA, Bentley BC, Wahl L. Nonsurgical management of heterotopic ossification in a runner. *J Orthop Sports Phys Ther.* 2019;49(9):676. DOI: 10.2519/jospt.2019.8491
42. Crawford CM, Varghese G, Mani MM, et al. Heterotopic ossification: are range of motion exercises contraindicated? *J Burn Care Rehabil.* 1986;7(4):323–327. DOI: 10.1097/00004630-198607000-00005
43. Daud O, Sett P, Burr RG, et al. The relationship of heterotopic ossification to passive movements in paraplegic patients. *Disabil Rehabil.* 1993;15(3):114–118. DOI: 10.3109/09638289309166001
44. Craven PL, Urist MR. Osteogenesis by radioisotope labelled cell populations in implants of bone matrix under the influence of ionizing radiation. *Clin Orthop Relat Res.* 1971;76:231–243. DOI: 10.1097/00003086-197105000-00030
45. Wang Y, Zhu G, Wang J, et al. Irradiation alters the differentiation potential of bone marrow mesenchymal stem cells. *Mol Med Rep.* 2016;13(1):213–223. DOI: 10.3892/mmr.2015.4539
46. Pohl F, Hassel S, Nohe A, et al. Radiation-induced suppression of the Bmp2 signal transduction pathway in the pluripotent mesenchymal cell line C2C12: an *in vitro* model for prevention of heterotopic ossification by radiotherapy. *Radiat Res.* 2003;159(3):345–350. DOI: 10.1667/0033-7587(2003)159[0345:risotb]2.0.co;2
47. Georhakopoulos I, Kouloulias V, Kougiountzopoulou A, et al. Radiation therapy for the prevention of heterotopic ossification: efficacy and toxicity of single fraction radiotherapy. *Orthop Rev (Pavia).* 2020;12(2). DOI: 10.4081/or.2020.8577
48. Davis E, Williams K, Matheney TH, et al. Radiation prophylaxis for hip salvage surgery in cerebral palsy: can we reduce the incidence of heterotopic ossification? *J Pediatr Orthop.* 2019;39(5):e386–e391. DOI: 10.1097/BPO.0000000000001314
49. Müseler AC, Grasmücke D, Jansen O, et al. In-hospital outcomes following single-dose radiation therapy in the treatment of heterotopic ossification of the hip following spinal cord injury-an analysis of 444 cases. *Spinal Cord.* 2017;55(3):244–246. DOI: 10.1038/sc.2016.112
50. Schincariol CYN, Echauri EMI, Silvestre OF, et al. Heterotopic ossification after spinal cord injury: prevention and treatment – a sistematic review. *Acta Ortop Bras.* 2023;31(3). DOI: 10.1590/1413-785220233103e267451
51. Lee CH, Shim SJ, Kim HJ, et al. Effects of radiation therapy on established neurogenic heterotopic ossification. *Ann Rehabil Med.* 2016;40(6):1135–1139. DOI: 10.5535/arm.2016.40.6.1135
52. Hu ZH, Chen W, Sun JN, et al. Radiotherapy for the prophylaxis of heterotopic ossification after total hip arthroplasty: a systematic review and meta-analysis of randomized controlled trails. *Med Dosim.* 2021;46(1):65–73. DOI: 10.1016/j.meddos.2020.07.010
53. Milakovic M, Popovic M, Raman S, et al. Radiotherapy for the prophylaxis of heterotopic ossification: A systematic review and meta-analysis of randomized controlled trials. *Radiother Oncol.* 2015;116(1):4–9. DOI: 10.1016/j.radonc.2015.05.022
54. Ebinger T, Roesch M, Kiefer H, et al. Influence of etiology in heterotopic bone formation of the hip. *J Trauma.* 2000;48(6):1058–1062. DOI: 10.1097/00005373-200006000-00010.
55. Padgett DE, Holley KG, Cummings M, et al. The efficacy of 500 CentiGray radiation in the prevention of heterotopic ossification after total hip arthroplasty: a prospective, randomized, pilot study. *J Arthroplasty.* 2003;18(6):677–686. DOI: 10.1016/s0883-5403(03)00265-1
56. Honore T, Bonan I, Salga M, et al. Effectiveness of radiotherapy to prevent recurrence of heterotopic ossification in patients with spinal cord injury and traumatic head injury: a retrospective case-controlled study. *J Rehabil Med.* 2020;52(5). DOI: 10.2340/16501977-2692
57. Cipriano C, Pill SG, Rosenstock J, et al. Radiation therapy for preventing recurrence of neurogenic heterotopic ossification. *Orthopedics.* 2009;32(9). DOI: 10.3928/01477447-20090728-33
58. Mourad WF, Packianathan S, Shourbaji RA, et al. Radiation-induced sarcoma following radiation prophylaxis of heterotopic ossification. *Pract Radiat Oncol.* 2012;2(2):151–154. DOI: 10.1016/j.prro.2011.06.005
59. Farris MK, Chowdhry VK, Lemke S, et al. Osteosarcoma following single fraction radiation prophylaxis for heterotopic ossification. *Radiat Oncol.* 2012;7:140. DOI: 10.1186/1748-717X-7-140

60. Liu H, Zhao JG, Li Y, et al. Non-steroidal anti-inflammatory drugs for preventing heterotopic bone formation after hip arthroplasty. *Cochrane Database Syst Rev.* 2019;2019(7). DOI: 10.1002/14651858.CD012861.pub2
61. Banovac K, Williams JM, Patrick LD, et al. Prevention of heterotopic ossification after spinal cord injury with indomethacin. *Spinal Cord.* 2001;39(7):370–374. DOI: 10.1038/sj.sc.3101166
62. Banovac K, Williams JM, Patrick LD, et al. Prevention of heterotopic ossification after spinal cord injury with COX-2 selective inhibitor (rofecoxib). *Spinal Cord.* 2004;42(12):707–710. DOI: 10.1038/sj.sc.3101628
63. Zakrasek EC, Yurkiewicz SM, Dirlikov B, et al. Use of nonsteroidal anti-inflammatory drugs to prevent heterotopic ossification after spinal cord injury: a retrospective chart review. *Spinal Cord.* 2019;57(3):214–220. DOI: 10.1038/s41393-018-0199-3
64. Yolcu YU, Wahood W, Goyal A, et al. Pharmacologic prophylaxis for heterotopic ossification following spinal cord injury: a systematic review and meta-analysis. *Clin Neurol Neurosurg.* 2020;193. DOI: 10.1016/j.clineuro.2020.105737
65. Dartnell J, Paterson JM, Magill N, Norman-Taylor F. Proximal femoral resection for the painful dislocated hip in cerebral palsy: does indomethacin prevent heterotopic ossification? *J Pediatr Orthop.* 2014;34(3):295–299. DOI: 10.1097/BPO.0000000000000146
66. Borgeat A, Ofner C, Saporito A, et al. The effect of nonsteroidal anti-inflammatory drugs on bone healing in humans: a qualitative, systematic review. *J Clin Anesth.* 2018;49:92–100. DOI: 10.1016/j.jclinane.2018.06.020
67. Stover SL, Hahn HR, Miller JM 3rd. Disodium etidronate in the prevention of heterotopic ossification following spinal cord injury (preliminary report). *Paraplegia.* 1976;14(2):146–156. DOI: 10.1038/sc.1976.25
68. Teasell RW, Mehta S, Aubut JL, et al.; SCIRE Research Team. A systematic review of the therapeutic interventions for heterotopic ossification after spinal cord injury. *Spinal Cord.* 2010;48(7):512–521. DOI: 10.1038/sc.2009.175
69. Spielman G, Gennarelli TA, Rogers CR. Disodium etidronate: its role in preventing heterotopic ossification in severe head injury. *Arch Phys Med Rehabil.* 1983;64(11):539–542.
70. Banovac K. The effect of etidronate on late development of heterotopic ossification after spinal cord injury. *J Spinal Cord Med.* 2000;23(1):40–44. DOI: 10.1080/10790268.2000.11753507
71. Shafer DM, Bay C, Caruso DM, et al. The use of eidronate disodium in the prevention of heterotopic ossification in burn patients. *Burns.* 2008;34(3):355–360. DOI: 10.1016/j.burns.2007.04.006
72. Thomas BJ, Amstutz HC. Results of the administration of diphosphonate for the prevention of heterotopic ossification after total hip arthroplasty. *J Bone Joint Surg Am.* 1985;67(3):400–403. DOI: 10.2106/00004623-198567030-00008
73. Ploumis A, Donovan JM, Olurinde MO, et al. Association between alendronate, serum alkaline phosphatase level, and heterotopic ossification in individuals with spinal cord injury. *J Spinal Cord Med.* 2015;38(2):193–198. DOI: 10.1179/2045772314Y.0000000213
74. Schuetz P, Mueller B, Christ-Crain M, et al. Amino-bisphosphonates in heterotopic ossification: first experience in five consecutive cases. *Spinal Cord.* 2005;43(10):604–610. DOI: 10.1038/sj.sc.3101761

ОБ АВТОРАХ

Владимир Александрович Новиков, канд. мед. наук;
ORCID: 0000-0002-3754-4090;
eLibrary SPIN: 2773-1027;
e-mail: novikov.turner@gmail.com

*** Алина Михайловна Ходоровская**, научный сотрудник;
адрес: Россия, 196603, Санкт-Петербург,
Пушкин, ул. Парковая, д. 64–68;
ORCID: 0000-0002-2772-6747;
eLibrary SPIN: 3348-8038;
e-mail: alinamyh@gmail.com

Валерий Владимирович Умнов, д-р мед. наук;
ORCID: 0000-0002-5721-8575;
eLibrary SPIN: 6824-5853;
e-mail: umnovvv@gmail.com

AUTHOR INFORMATION

Vladimir A. Novikov, MD, PhD, Cand. Sci. (Med.);
ORCID: 0000-0002-3754-4090;
eLibrary SPIN: 2773-1027;
e-mail: novikov.turner@gmail.com

*** Alina M. Khodorovskaya**, MD, Research Associate;
address: 64-68 Parkovaya str., Pushkin,
Saint Petersburg, 196603, Russia;
ORCID: 0000-0002-2772-6747;
eLibrary SPIN: 3348-8038;
e-mail: alinamyh@gmail.com

Valery V. Umnov, MD, PhD, Dr. Sci. (Med.);
ORCID: 0000-0002-5721-8575;
eLibrary SPIN: 6824-5853;
e-mail: umnovvv@gmail.com

* Автор, ответственный за переписку / Corresponding author

ОБ АВТОРАХ

Евгений Викторович Мельченко, канд. мед. наук;
ORCID: 0000-0003-1139-5573;
eLibrary SPIN: 1552-8550;
e-mail: emelchenko@gmail.com

Дмитрий Валерьевич Умнов, канд. мед. наук;
ORCID: 0000-0003-4293-1607;
eLibrary SPIN: 1376-7998;
e-mail: dmitry.umnov@gmail.com

AUTHOR INFORMATION

Evgenii V. Melchenko, MD, PhD, Cand. Sci. (Med.);
ORCID: 0000-0003-1139-5573;
eLibrary SPIN: 1552-8550;
e-mail: emelchenko@gmail.com

Dmitriy V. Umnov, MD, PhD, Cand. Sci. (Med.);
ORCID: 0000-0003-4293-1607;
eLibrary SPIN: 1376-7998;
e-mail: dmitry.umnov@gmail.com