A systematic approach to the surgical treatment of patients with long bone tumors using bone segmental alloimplants

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The most common techniques for the replacement of post-resection bone defects in patients with tumors are modular and individual endoprosthetics and bioreconstructive interventions. The following issues require solution: improvement and development of techniques for fixation of segmental allograft and recipient bone, study of bone remodeling processes in conditions of bone allograft and cytostatics (chemotherapy drugs) action, improvement of segmental allograft quality. Objective. To determine the indications for allograft replacement of post-resection defects of long bones (and its types) in patients with malignant bone tumors. Methods. Experimental studies were carried out to study morphological, biomechanical, biochemical changes in experimental rats after bone allograft under different conditions. Using the finite element method, the tensely deformed conditions in the «allograft – recipient-bone – endoprosthesis» system were assessed to determine the most effective fixation technique of the bone allograft and recipient bone in imitation of a bone regenerate in different terms after surgery. Results. The effectiveness of allograft prosthesis composite technique with a step-cut osteotomy and additional bone autoplasty in the contact zone of the allograft and the recipient bone was proven. It was determined that the use of radiation-sterilized bone allograft in combination with systemic administration of cytostatics leads to inhibition of bone formation. We developed an algorithm-scheme of surgical treatment of patients with tumors of long bones using segmental allograft and proposed methods of replacement of post-resection bone defects for each localization of tumor lesions. Clinical approbation was performed. Conclusions. Segmental bone allograft of large post-resection defects of long bones at their tumorous affection remains an actual and perspective technique of one bioreconstruction. Clear adherence to the indications for this technique will help to prevent complications and repeated operations.

Найпоширенішими методиками заміщення післярезекційних дефектів кісток у пацієнтів із пухлинами є модульне й індивідуальне ендопротезування, біореконструкційні втручання. Потребують вирішення питання: удосконалення й розроблення методик фіксації сегментарних алопластвів і кістки реципієнта, вивчення процесів реконструкції кісткової тканини за умов кісткової алопластики та дії цитостатиків (хіміотерапевтичних препаратів), поліпшення якості сегментарних алопластвів. Мета. Визначити показання до алопластичного заміщення післярезекційних дефектів довгих кісток (та його видів) у пацієнтів зі злоксієнними пухлинами кісток. Методи. Проведено експериментальні дослідження для вивчення формально-деформованих станів в системі «алопласт – кістка реципієнта – ендопротез» для визначення найефективнішої методики фіксації алопластики й кістки реципієнта за умов імітування кісткового регенерату на різних термінах після операції. Результати. Доведено ефективність застосування методики алопластичного ендопротезування зі ступінчастою остеотомією та додатковою кістковою автопластикою в зоні контактної алопластіці й кістки реципієнта. Визначено, що використання сегментових алолімплантатів, стерилізовані з γ-випромінюванням, у комплексі з системним введенням цитостатиків призводить до пригнічення кісткоутворення. Розроблено алгоритміза-нову схему хірургічного лікування хворих із пухлинами довгих кісток зі застосуванням сегментарних алолімплантатів і запропоновано методику заміщення післярезекційних дефектів кісток для кожної локалізації пухлинних уражень. Проведено клінічну апробацію. Висновки. Сегментарна кісткова алопластика великих післярезекційних дефектів довгих кісток у разі їхнього пухлинного ураження залишається актуальною та перспективною методикою біореконструкції кісток. Чітке дотримання показань до цієї методики допомагатиме збільшити ефективність і повторні операції. Ключові слова. Злоксієнні кісткові пухлини, кісткова алопластика, хірургічне лікування злоксієнних пухлин кісток.
Key words. Malignant bone tumors, bone allograft, surgical treatment of malignant bone tumors

Introduction

The surgical stage of treatment of patients with malignant tumors is very important with oncological and functional results depending on its success. One of the main tasks during surgical treatment is bone restoration after tumor removal. There are many methods of replacing post-resection defects of long bones but modular, individual endoprosthetic repair and bioreconstructive interventions are the most widespread [1, 2]. The latter include auto- and alloplasty of post-resection bone defects and their various combinations [3]. Segmental bone alloplasty has a number of advantages over modular endoprosthetics, one of them being the restoration of bone tissue and muscle and tendon attachment zones. A method of alocomposite endoprosthetic repair has been developed in order to reduce the number of complications after the use of alloplasty or endoprosthetic repair alone, combining these approaches [4]. The use of segmental alloimplants is accompanied by a number of complications typical for this method of replacing post-resection defects of long bones [5, 6]. The most frequent of them are absence of fusion of the bone of the recipient and the alloimplant, its lysis and fractures, and instability of the endoprostheses in alocomposite endoprosthetic repair [7, 8].

An important issue in alocomposite endoprosthetic repair is the reliability of the method of segmental alloimplant fixation and the recipient bone. It has been proven that the stable fixation of the alloimplant and its close adherence to the bone of the recipient allows achieving fusion between them. There are several methods of bone fixation during alocomposite endoprosthetic repair: the use of long legs of endoprostheses, a combination of short legs of endoprostheses and osseous osteosynthesis with plates or cerclage sutures, the use of intramedullary blocked rods [9]. There are also different types of osteotomy, such as oblique, stepped, S-shaped, transverse, with transverse being the most currently used due to its simplicity [10]. However, it is during the use of transverse osteotomy that the most cases of non-fusion of the alloimplant with the bone of the recipient are observed. Another aspect of bone alloplasty of post-resection defects of long bones that is relevant today is the improvement of the quality of bone alloimplants [11]. According to the literature, segmental bone alloimplants sterilized with γ-radiation are characterized by a violation of mechanical properties, resulting in their fractures [12, 13]. The use of alloimplants sterilized by deep freezing not infrequently leads to infectious complications [14]. Taking into account this data, the improvement of methods of sterilization of alloimplants continues. A very important risk factor for the development of complications in the use of segmental alloimplants in patients with malignant bone tumors subject to chemotherapy is the effect of cytostatics on the processes of osteoregeneration, which lead to immunosuppression and can affect the processes of bone remodeling [15, 16]. Therefore, segmental bone alloplasty of bone defects in patients with malignant tumors requiring chemotherapeutic treatment can lead to complications (violation of the fusion of the alloimplant and the recipient's bone). This issue has not been thoroughly studied.

Thus, the main problems that need to be solved are the improvement and development of methods of fixation of segmental alloimplants and the bone of the recipient, the study of bone tissue remodeling processes under the conditions of bone alloplasty and the effect of cytostatics (chemotherapeutic drugs) on these processes, as well as improving the quality of segmental alloimplants.

Purpose: to determine the indications for alloplastic replacement of post-resection defects of long bones (and its types) in patients with malignant bone tumors.

Material and methods

To achieve the established purpose, we conducted a number of experimental studies that allow us to study morphological, biomechanical and biochemical changes in experimental animals (rats) after bone alloplasty under different conditions. The stress-strain state in the «alloimplant-recipient’s bone-endoprosthesis» system was also studied theoretically (using the finite element method) to determine the most effective method of fixing allogeneic bone material and recipient bone under the conditions of imitating bone regeneration at different times after surgery. Each of these experimental studies is thoroughly described in our previous publications [17–21]. We present a brief description of the studies and their results, which made it possible to create a scheme, i.e. determination of indications for surgical interventions in tumor lesions of long bones with the use of segmental bone alloimplants.

In order to determine the most effective method of fixation of the segmental alloimplant and the recipient's bone, models of alocomposite endoprosthetics...
were proposed for in vivo study (rats). Experimental models were developed according to three methods (1st — transverse osteotomy of the femur with implantation of an allocomposite endoprosthesis; 2nd — stepped osteotomy of the femur with implantation of an allocomposite endoprosthesis; 3rd — transverse osteotomy of the femur with implantation of an allocomposite endoprosthesis and autoplasty of the zone of union of the alloimplant with the bone) and a histological and biomechanical study of the zone of union of the recipient's bone and the bone alloimplant was carried out at the departments of the State Institution «Professor M. I. Sytenko Institute of Spine and Joint Pathology of the National Academy of Sciences of Ukraine» [17].

The stress-deformed state of the model «alloimplant-recipient's bone-endoprosthesis» in femur resection by transverse and stepped osteotomy was studied. Along the line of resection, the presence of bone regenerate was simulated by introducing a thin layer, which was given two different values of the modulus of elasticity to simulate the state of the regenerate 3 and 6 months after surgery [18, 19].

In the experiment, the processes of bone remodeling after the implantation of alloosseous implants, sterilized by various methods (γ-radiation or antibiotic saturation), and the effect of a cytostatic drug (cisplatin) on them were evaluated with the help of morphological and biochemical studies [20].

The study materials were approved by the local Bioethics Committee (Protocols No. 204 of 15.06.2020, No. 209 of 30.11.2020).

**Results and their discussion**

**Assessment of experimental study results**

Morphological study of the femurs of rats showed that in an increase in the plane of contact of the alloimplant with the recipient's bone due to stepped osteotomy, the processes of remodeling and vascularization of the alloimplant were more evident. In experimental and control animals 6 and 9 months after endoprosthetic repair, the formation of a tight connection «ceramic coating of the endoprosthesis leg-bone tissue» was noted, which gives hope for a more stable fixation [17].

According to the statistical data of the results of biomechanical study of rat femur samples, the strength of bones in transverse osteotomy was lower than that of bones in stepped osteotomy both 3 and 6 months after surgery [18].

Thus, the use of stepped osteotomy with subsequent fixation of the bone alloimplant to the recipient’s bone makes it possible to reduce the risk of complications of surgical interventions and improve the conditions for reparative osteogenesis in the contact zone of the alloimplant and the bone of the recipient. The use of an intramedullary leg of an endoprosthesis with a ceramic coating contributes to its better fixation in the channel of the alloimplant and the bone of the recipient and allows to avoid cement fixation.

Mathematical assessment using the finite element method showed that stepped osteotomy of the femur can reduce the level of mechanical stresses in the osteotomy zone by half. The study established that with time (3, 6 months after surgery) strength indicators improved, as the regenerate between the alloimplant and the recipient's bone acquired greater density.

Reconstruction of an allogeneic bone implant was studied depending on the method of its sterilization (γ-radiation or antibiotic saturation), as well as on the use of cisplatin in the postoperative period [20]. The study showed that the drug inhibited proliferation and stimulated apoptosis of bone marrow progenitor cells, which are one of the sources for bone regeneration. The highest content of bone tissue (58.09 %) was found in application of an antibiotic-sterilized alloimplant without the administration of cytostatics, and the lowest one in replacement of the defect with an alloimplant sterilized with γ-radiation, secondary to administration of cytostatics.

According to the indicators of the biochemical study of the blood of experimental rats, the highest activity of acid phosphatase indicators was observed in the groups where cisplatin was used, indicating a violation of remodeling processes and the predominance of resorption over bone formation. Assessment of the mineralization index in the experimental and control groups showed a significant decrease in the animals treated with cisplatin [21].

All the studies proved the effectiveness of the technique of allocomposite endoprosthetic repair with stepped osteotomy and additional bone autoplasty in the area of contact between the alloimplant and the recipient's bone, which made it possible to develop and justify the technique of allocomposite endoprosthetics repair [22]. A study of the impact of γ-radiation for sterilization of bone alloimplants in combination with systemic administration of cytostatics showed suppression of bone tissue remodeling processes.

All studies, including those involving patients, were carried out in compliance with international ethical requirements; their plan was discussed and approved at a meeting of the Bioethics Committee at the State Institution «Professor M. I. Sytenko Institute of Spine and Joint Pathology of the National...
Academy of Sciences of Ukraine» (Protocol No. 204 of 15.06.2020).

**Development of a scheme of a differentiated approach regarding the determination of indications for bone alloplasty with segmental implants in the case of post-resection defects of long bones**

These experimental studies were conducted with the aim of identifying indications for segmental bone alloplasty in the case of treating patients with long bone tumors (especially malignant ones) in order to achieve the best result and reduce the risk of developing complications. Based on the analysis of the indicators of the performed studies, we have developed an algorithmized scheme of surgical treatment of patients with tumors of long bones with the use of segmental alloimplants. Based on it, a differentiated approach to the choice of surgical treatment methods was created. Thus, in the case of a malignant bone tumor or an aggressive benign tumor (Stage 3), which requires only surgical treatment, it is recommended to perform a segmental resection of the bone with replacement of the post-resection defect with a segmental alloimplant sterilized by γ-radiation. In the case of a malignant tumor, which requires combined treatment of polychemotherapy (PCT) and surgery, it is recommended to perform segmental resection and replacement of the post-resection bone defect with an alloimplant, sterilized by antibiotic saturation, or bone reconstruction using an individual or modular endoprosthesis (Fig. 1).

For each localization of tumor lesions, methods of replacing post-resection defects of long bones using segmental bone alloimplants have been developed. In particular, in the case of tumor localization in the metaepiphyses of long bones, it is recommended to replace the post-resection defect with an allocomposite endoprosthesis (a segmental alloimplant fixed to the recipient's bone using stepped osteotomy with the addition of bone autoimplants in the bone contact zone, as well as an individual endoprosthesis). Under conditions of localization of the tumor in the diaphysis of the long bone, a segmental bone alloimplant fixed to the recipient bone using stepped osteotomy...
(on both sides, proximally and distally), an auto-bone graft inserted intramedullary and fixed with a plate should be used. In localization of a pathological focus in the distal part of the tibia, it is possible to use two methods of segmental alloplasty: an articulating bone alloimplant or formation of a supracalcaneal-tibial arthrodesis with fixation by an intramedullary blocked rod, as well as fixation of alloimplants with the recipient bone using stepped osteotomy and additional plastic repair with autografts. The choice of the form of the bone alloimplant (articulating or without preservation of the articular surface for the formation of an arthrodesis) depends on the length of the bone defect. For large alloimplants, preference should be given to arthrodesis surgery (Fig. 2).

According to the developed scheme, 10 patients were operated on. Among them, 6 with localization of the process in the distal part of the tibia, 2 in the diaphysis of the femur, 2 in the proximal part of the femur. Complications were as follows: 1 (14 %) recurrence of the tumor (adamantinoma), which led to amputation of the limb at the level of the lower third of the thigh; 1 (14 %) ischemic necrosis of soft tissues in the area of the lower third of the lower leg, which was removed, the wound was closed with the help of skin grafting and the alloimplant was preserved. The functional results were evaluated according to the scales of MSTS — (71 ± 14) %, which were interpreted as good, and TESS — (73 ± 16) %.

A clinical example of the application of the developed scheme of a differential approach to the surgical treatment of patients with tumors of long bones

A 68-year-old patient S. was treated in the bone oncology clinic of the State Institution «Professor M. I. Sytenko Institute of Spine and Joint Pathology of the National Academy of Sciences of Ukraine». Diagnosis: undifferentiated pleomorphic sarcoma of the distal part of the right tibia T2N0M0 stage II, clinical group II (Fig. 3, a). The diagnosis was established following a comprehensive examination (radiography, CT-oncoscreening, laboratory, histological examination of biopsy material). Considering the malignant nature of the tumor, according to the treatment protocols of this nosology, it was necessary to carry out neoadjuvant PCT, surgical intervention and adjuvant PCT.

According to the developed scheme of indications for segmental bone alloplasty, the following surgical intervention was chosen: removal of the tumor en block, wide segmental resection, replacement of the post-resection defect of the lower third of the tibia with a segmental bone alloimplant (sterilized by antibiotic saturation), fixation of the recipi-
ent bone and alloimplant with an intramedullary blocked rod, bone autoplasty of the connection zone of the alloimplant and the bone of the recipient. Taking into account the localization of the tumor process and the length of the alloimplant (resection length 20 cm), a decision was made to perform an arthrodesis of the supraclecal-tibial joint (Fig. 3, b). Six months after the operation and PCT, bone remodeling was noted in the contact zone of the recipient's bone and the segmental alloimplant (Fig. 3, c).

A negative example of the use of segmental alloplasty

A 51-year-old patient K. was admitted with pain in the right thigh area. Following comprehensive examination he was diagnosed with osteogenic sarcoma of the middle lower third of the right femur T2N0M0, stage II, clinical group II (Fig. 4). According to the treatment protocols of this nosology, combined treatment (polychemotherapy, surgery) was recommended. The patient underwent neoadjuvant PCT, surgical intervention (removal of the tumor en block, wide segmental resection, replacement of the post-resection defect of the middle lower third of the right femur with a segmental alloimplant with fixation to the recipient bone with a plate) (Fig. 5, a). The alloimplant was sterilized using γ-radiation. After surgery, the patient received adjuvant polychemotherapy. One year after the surgical intervention, radiography showed a satisfactory position of the alloimplant and the metal plate during the follow-up examination, but no signs of bone remodeling were detected (Fig. 5, b). Two years after treatment, the patient developed a varus deformity of the lower third of the right femur, X-rays showed a fracture of the screws in its distal part and the absence of fusion of the alloimplant with the recipient's bone (Fig. 5, c).

The clinical case presented by us is a vivid example of a negative result of the use of segmental bone alloplasty.

The use of an alloimplant sterilized by γ-radiation in a patient scheduled for PCT increased the risk of disruption of bone remodeling processes. The combination of such factors as γ-radiation and cytostatics in this case led to absence of fusion of the bone alloimplant with the bone of the recipient, which led to repeated surgical interventions.

Thus, the use of the bone alloplasty technique to replace large post-resection defects of long bones has specific features, and following clear indications for its implementation contributes to obtaining good results in the treatment of patients with long bone tumors.

Conclusions

Segmental bone alloplasty of large post-resection defects of long bones remains a relevant and promising method of bioreconstruction of bones in case of their tumor damage. It is the application of this technique according to clear indications that will prevent the development of complications and repeated surgical interventions.

As a result of the conducted experimental studies, the effectiveness of the use of segmental bone alloplasty with the use of stepped osteotomy has been proven.

Sterilization of alloimplants with antibiotics has been proven to give the best results of their incorporation compared to sterilization with γ-radiation.

Indications and an algorithmized scheme for the use of segmental bone alloimplants have been developed. Approbation of the proposed methods of surgical treatment of tumor patients using segmental alloimplants was carried out.