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## **Reconstructive techniques in musculoskeletal tumor surgery : management of pelvic and extremity bone tumors**

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# Chapter 11

## **General Discussion**

## General Discussion

During recent decades, limb-salvage surgery has replaced amputation as the treatment of choice for musculoskeletal tumors of the appendicular skeleton and pelvis<sup>1,2</sup>. This transition is largely attributable to the advent of effective adjuvant treatment and concomitant sophistication of imaging and surgical techniques<sup>1,3,4</sup>. Simultaneously, five-year survival rates increased from less than 20% before the 1970s, to approximately 55 to 70% nowadays<sup>1,4,8</sup>. The preponderance of limb salvage surgery and increased patient survival resulted in an increased demand for durable reconstructions with favorable and predictable clinical results and functional outcome.

In this thesis, we evaluated the clinical outcomes of various reconstructive techniques in musculoskeletal tumor surgery. This thesis aimed to assess clinical outcome in terms of complications and reconstruction survival rates, and to identify risk factors for complications and impaired survival. Therewith, we ultimately aim to improve outcomes for patients with bone tumors. Part I of the thesis focused on management of pelvic bone tumors, part II focused on reconstructions of the appendicular skeleton.

In 2011, Henderson *et al* proposed a failure mode classification for tumor endoprostheses, with the aim to facilitate understanding of endoprosthetic failures and to stimulate uniform reporting<sup>9</sup>. They classified five different modes of failure: soft-tissue failure (type 1), aseptic loosening (type 2), structural failure (type 3), infection (type 4) and tumor progression (type 5). Throughout the majority of the studies in this thesis, we have used this system to classify failures. In addition, we have attempted to classify complications that did not result in reconstruction failure. Therewith, we aimed to stimulate more uniform reporting on clinical results, in order to gain further insight in the outcomes of these complex reconstructions. Below, we will systematically discuss current concepts, complications and surgical strategies in management of pelvic (part I) and extremity (part II) bone tumors. Additionally, we will propose a number of modifications to the Henderson classification system, with the aim to further improve registration and comparability of complication and failure rates.

### Part I - Management of Pelvic Bone Tumors

Tumors of innominate bone are some of the most challenging conditions to treat for orthopaedic oncologists<sup>10-12</sup>. Pelvic tumors may present with vague

abdominal complaints and, because they are located deep in the body, are often large at the time of diagnosis<sup>13</sup>. As a result, they are difficult to access surgically and often demonstrate close proximity to major neurovascular, urinary, and intestinal and reproductive organ structures. Therefore, it can be challenging to obtain an adequate resection margin<sup>14</sup>. Nevertheless, limb-salvaging internal hemipelvectomies are nowadays the standard of care for patients with a pelvic bone tumor, if a clear margin can be achieved<sup>2</sup>.

Internal hemipelvectomy gained favor over hindquarter amputation because of obvious cosmetic, psychological and functional advantages<sup>2, 15, 16</sup>. According to Enneking's classification of pelvic resections<sup>12</sup>, a type 1 or type 3 internal hemipelvectomy (i.e., isolated resection of the ilium or pubis) does not compromise the anatomic weight-bearing axis and therefore, these resections generally do not necessitate reconstruction<sup>17, 18</sup>. However, if the periacetabular bone has to be resected (type 2 internal hemipelvectomy) and femorosacral continuity is disrupted, a particular reconstructive challenge arises<sup>19</sup>.

After a type 2 internal hemipelvectomy, one strategy is to leave the defect alone, producing a flail hip ("super Girdlestone")<sup>20, 21</sup>. This however results in instability of the iliofemoral joint and severe shortening of the affected side. Others prefer to perform an iliofemoral arthrodesis or pseudarthrosis, either to obtain solid fusion or as primary pseudarthrosis<sup>19, 22</sup>. These procedures may provide moderate but durable long-term functional results<sup>22</sup>. On the other hand, failure to obtain fusion occurs in up to 50% of primary pseudarthroses, potentially resulting in a painful reconstruction with poor function<sup>19</sup>. Another alternative is transposition of the hip, a procedure which serves to produce a neo-joint at the level of iliac resection rather than reconstruct the weight-bearing axis or acetabulum<sup>23</sup>. Although transposition of the hip generally results in reasonable and predictable functional outcome<sup>21, 23, 24</sup>, it may cause significant shortening of the affected limb<sup>10</sup>. This may be corrected during a secondary lengthening procedure; however, these operations are associated with a significant risk of major complications, especially in inexperienced hands<sup>25</sup>.

Other techniques aim to restore the native situation as much as possible. Allografts, either as a structural pelvic allograft or as part of an allograft-prosthetic composite reconstruction, have been commonly used<sup>15, 26-30</sup>. Acceptable long-term results have been reported<sup>29, 30</sup>, although many surgeons prefer to avoid the use of allografts because they are considered to be associated with high rates of infection and mechanical complications, including graft fracture, nonunion of allograft-host

junctions, and allograft resorption on the long term<sup>28, 31</sup>. Furthermore, structural allograft reconstructions are technically demanding as it is often difficult to obtain an adequate fit between the allograft and host bone<sup>32, 33</sup>. In addition, in some countries, widespread use of allografts might be restricted by limited availability and concerns about transmission of infectious diseases<sup>33</sup>.

Endoprosthetic devices, on the other hand, allow for relatively easy, quick and durable reconstruction<sup>10</sup>. The first endoprosthesis that was commonly used for reconstruction of pelvic tumor defects was the saddle prosthesis<sup>17, 34, 35</sup>. This implant requires the surgeon to create a notch in the remnant iliac wing, to match the curved shape of the saddle prosthesis<sup>36</sup>. The saddle prosthesis lacks modularity and may require additional resection of the iliac wing to be implanted<sup>37, 38</sup>.

Various authors consider stemmed implants the state of the art for periacetabular reconstruction<sup>39-41</sup>. Others prefer to use custom-made or hemipelvic prostheses<sup>42-44</sup>. Although comparative studies between stemmed and hemipelvic implants are lacking, hemipelvic implants have a number of inherent disadvantages. Most importantly, they lack the possibility of intraoperative adjustment. This may cause problems when greater resection is needed than was anticipated preoperatively<sup>45</sup>. In addition, custom-made implants may cause delay in treatment and are costly to manufacture<sup>46, 47</sup>.

Although recent developments have greatly increased the possibilities and clinical outcome after treatment for pelvic bone sarcoma, these large reconstructions are still fraught with complications.

### ***1.1 Soft-tissue failure and instability***

Resections of pelvic bone tumors often require extensive surgical approaches, and frequently leave large dead spaces and poorly vascularized soft-tissue flaps, resulting in a substantial risk of wound dehiscence and deep infection<sup>14, 48-50</sup>. The true incidence of wound dehiscence is however uncertain because many authors fail to mention superficial wound problems<sup>21, 39, 51</sup>. Apart from the risk of wound problems and deep infection, the extensive soft tissue resections also lead to poor muscular support around the neo-joint, and thus contribute to the high risk of prosthetic dislocation, especially for saddle prostheses<sup>34, 38, 50</sup>. In our retrospective study on periacetabular reconstruction with the (monobloc) pedestal cup endoprosthesis, we found that 16% of patients had experienced recurrent dislocations during follow-up<sup>10</sup>.

A number of factors should be considered. During pelvic resection, patients are positioned in the lateral decubitus position, allowing them to be rotated to nearly prone or supine positions. As a result, during reconstruction, it can be hard for the surgeon to adequately assess how the implant should be inserted. It was hypothesized that modularity of the implant would resolve part of these difficulties, because it would allow for adjustment of acetabular cup orientation – even after the stem has been implanted. With the LUMiC prosthesis, modularity was introduced in the field of pelvic reconstruction. In our study on the short-term clinical results of LUMiC endoprosthetic reconstructions, we found that recurrent dislocations occurred in four out of 47 patients (9%), one of whom had a first dislocation after resection of an extensive recurrence<sup>40</sup>. Although results are difficult to compare because of inherent heterogeneity in terms of the extent of resection and surgical approach, modularity in our experience made it easier to adequately position the cup. Cup position has been reported as an important factor for prosthetic dislocation risk, functional outcome and polyethylene wear in studies on total hip arthroplasty<sup>52,53</sup>.

Additional factors may help to further improve cup positioning in pelvic tumor reconstructions. First, computer-assisted surgical techniques can be used for adequate intraoperative visualization of prosthetic orientation. Second, modification of prosthetic design may allow for further intraoperative adjustment: although the acetabular cup can be rotated with reference to the stem, the acetabular cup-stem angle is fixed in the LUMiC. The exact influence of acetabular cup positioning on outcome of pelvic reconstructions should be determined in future studies.

In an attempt to further reduce the risk of dislocation, the possibility of dual-mobility articulation was introduced for the LUMiC prosthesis. Previously, it was reported that dual-mobility cups can be effective in treatment of recurrent instability in total hip replacements or instability encountered during hip revision arthroplasty<sup>54</sup>. Interposition of a mobile polyethylene component increases the effective head diameter and allows greater movement of the femoral head before subluxating or dislocating<sup>55,56</sup>. Indeed, we found that the risk of dislocation was significantly lower in reconstructions with a dual-mobility cup, as compared with conventional acetabular cups. We are of the opinion that any internal hemipelvectomy for a primary tumor should be reconstructed with a dual-mobility cup to reduce the risk of dislocation.





## 1.2 Aseptic loosening

Aseptic loosening is one of the major modes of failure for endoprosthetic reconstructions in orthopaedic oncology, especially for reconstructions around the knee<sup>57,58</sup>. The high risk of loosening for knee replacements has been ascribed to several factors, including the torque acting on the stem-bone interfaces<sup>59,60</sup>. As opposed to knee replacements, reconstructions of polyaxial joints allow for a certain degree of movement between prosthetic parts and therefore, less torque acts on these stem-bone interfaces. Irrespective of the limited torque acting on pelvic implants, we found that three of 19 patients (16%) had aseptic loosening of their uncemented porous-coated pedestal cup endoprosthesis<sup>10</sup>. Although the reported incidence of loosening is closely correlated with duration of follow-up, and results are therefore difficult to compare, previous authors reported comparable rates of loosening for saddle (12%) and hemipelvic prostheses (16%)<sup>17,61</sup>. Factors that contribute to the risk of loosening of pelvic implants include the high mechanical stresses as a result of great resection length and extensive soft tissue dissection. Moreover, because of the flat morphology of the ilium, there is limited initial contact between the implant and cortical bone.

In keeping with results reported for reconstructions of the appendicular skeleton, it was hypothesized that hydroxyapatite (HA) coating of the iliac stem would stimulate bony ingrowth and thus reduce the risk of loosening<sup>62</sup>. In our study on reconstructions with the LUMiC prosthesis, we found that two patients with uncemented HA-coated iliac stem (2/45, 4%) experienced loosening. Further analysis showed that both patients had inadequate primary fixation of the stem (one due to an intraoperative fracture, one due to fixation in a previous structural allograft), while primary stability is a prerequisite for ingrowth of HA-coated implants<sup>63</sup>. An alternative modern pelvic implant, the "ice-cream cone prosthesis" (Stanmore Implants Worldwide, United Kingdom), relies on a combination of HA-coating and bone cement for stem fixation<sup>39</sup>. Cement may be useful to obtain adequate primary stability and thus allow for bony ingrowth in the HA-coating. On the other hand, cement fragmentation and foreign body reaction to wear debris may result in late periprosthetic osteolysis and loosening<sup>64</sup>. Excellent results have been reported for tumor implants with hybrid fixation, although the number of patients included and follow-up were limited in the studies on pelvic reconstructions<sup>39,65-68</sup>.

Other advantages of cementing are that it allows for immediate weight-bearing, especially in case of extensive bony destruction, and the possibility to add

local antibiotics. Therefore, cemented implants may be preferable for patients with radiotherapy or those at high risk of developing postoperative deep infection<sup>39</sup>. We prefer uncemented fixation with HA-coated stems for patients with a reasonable prognosis and sufficient bone quality, mainly because these implants are at a lower risk of loosening once bony ongrowth has taken place<sup>58, 69</sup>.

### **1.3 Structural failure**

Structural failure is common for pelvic allograft reconstruction, either due to primary fracture or due to graft resorption<sup>15, 70</sup>. Saddle prostheses also frequently fail due to structural complications, including prosthetic dissociation and fractures of the remnant ilium<sup>38</sup>. With modern endoprosthetic production quality and design, implant fractures are rare; no structural implant failures were reported in recent studies on the pedestal cup, LUMiC and ice-cream cone endoprostheses<sup>10, 39, 40</sup>. Periprosthetic iliac fractures, however, still occur. Two types of iliac fractures should be distinguished. First, intraoperative crack fractures, which cause minimal displacement and generally heal without major interventions<sup>10, 40</sup>. Obvious risk factors for intraoperative fractures include the use of uncemented press-fit iliac stems, poor bone quality, and revision procedures; in these cases, extra caution is warranted<sup>71</sup>. And second, postoperative fractures of the iliac wing. The saddle prosthesis has been associated with a substantial risk of fracture of the remnant iliac wing, in addition to the risk of cranial migration of the saddle component (up to 7%)<sup>17, 22, 34, 72, 73</sup>. A possible explanation for these structural failures lies in the fact that the saddle prosthesis anchors laterally from the natural femorosacral weight-bearing axis, where the anteroposterior dimension of the ilium is limited and the iliac cortices are thin; therefore, adequate supportive bone stock is lacking<sup>17, 34, 35, 38, 74, 75</sup>. Consequently, more cranial migration has been reported when larger resection of the iliac wing is required<sup>17, 35</sup>. Cranial migration of the implant in turn causes limb length discrepancy and recurrent dislocations, compromising function of the affected side<sup>34</sup>. Moreover, the eccentric position of the artificial hip center allows only limited range of motion<sup>76</sup>. Several more modern implants, including the Mark II saddle (Link, Hamburg, Germany) and the PAR prosthesis (Stryker Howmedica, NJ, USA), still have these unfavorable features<sup>37, 72</sup>.

Conversely, so-called “stemmed acetabular” or “inverted ice-cream cone” prostheses anchor in the medial ilium, adjacent to the sacroiliac joint<sup>10, 39, 40</sup>. There, a thick bar of bone extends from the sacroiliac joint down to the acetabulum, along the natural weight-bearing axis. This allows the implant to be seated well



between the anterior and posterior cortices<sup>10,74,77</sup>. In a number of these stemmed implants, the stem is tapered, which causes the implant to anchor itself as a result of axial loading along the weight-bearing axis<sup>10,40</sup>. Theoretically, this type of fixation should not only reduce the risk of iliac fractures and cranial migration, but also of aseptic loosening<sup>40</sup>.

It is for these reasons that additively manufactured (3D-printed) pelvic prostheses, in our opinion, should be met with caution. Although these hemipelvic implants are superior for restoring iliac crest anatomy, they typically lack adequate fixation in the weight-bearing axis. Mechanical complications, including loosening, cranial migration and component breakage, can therefore be expected; in that regard, custom hemipelvic implants are much like hemipelvic allografts.

### **1.4 Infection**

Pelvic tumor resections are notorious for the high risk of postoperative infection (18-32%), irrespective of the reconstructive technique used<sup>14, 23, 50, 75, 78, 79</sup>. Deep infections can be devastating, necessitating multiple surgical debridements, removal of implants or even – although rarely – hindquarter amputation<sup>14</sup>. The high risk of infection can be attributed to the length and complexity of the surgical procedure, creating a large dead space and leaving large soft tissue defects, and the immunocompromised status of patients, due to co-treatment with chemotherapy<sup>38, 80-82</sup>. A validated deep infection risk score for endoprosthetic reconstructions is currently lacking, and should be developed in future research to allow surgeons to better identify patients at risk for developing surgical site infection. Given the influence of operative time on the risk of infection, we feel that further centralization of care for patients with pelvic bone tumors should be considered.

Numerous precautions have been taken in an attempt to reduce the rate of infection, including the administration of prophylactic antibiotics – which are given for a duration of up to five days postoperatively<sup>82</sup>. To date, solid evidence to support the use of a specific antibiotic protocol is lacking. Currently, there is an international randomized controlled study (the PARITY trial) ongoing to determine the optimal antibiotic regimen (one or five days) following endoprosthetic reconstruction for bone tumor resection<sup>83</sup>.

Other strategies to reduce the risk of deep infection focus on implant surface modifications to minimize adhesion of bacteria, inhibit the formation of a biofilm, and provide bactericidal action<sup>84</sup>. In recent years, silver coating of endoprostheses

has been one of the most discussed techniques<sup>85-87</sup>. Silver coating of various medical materials, such as cardiac and urinary catheters, previously proved to reduce the risk of infection<sup>85</sup>. Studies demonstrated that silver coating of MUTARS endoprostheses (implantcast, Buxtehude, Germany) effectively reduced the risk of infection in a rabbit model, and that the use of silver coating is free of side-effects<sup>85,86</sup>. Furthermore, two retrospective clinical studies showed that silver coating may increase the likelihood of successful revision surgery in case of endoprosthetic infection, and of being able to retain an implant in case it gets infected<sup>87,88</sup>. It should be noted, however, that the number of patients included in these studies were limited, while other studies were not able to detect a significant difference<sup>40,58</sup>. Furthermore, comparative studies between coated and uncoated implants are lacking and thus, there is currently no solid evidence to support the idea that silver coating reduces the risk of infection of primary endoprosthetic reconstructions for bone tumors. One may therefore question whether coated implants should be used routinely. A cost-benefit analysis will have to be conducted to answer this question.

More recently, researchers from Japan reported excellent results for iodine coating of titanium endoprostheses for preventing and treating periprosthetic infection<sup>89,90</sup>. Future studies are needed to assess the beneficial effect and potential complications of the use of different coatings in endoprosthetic reconstructions<sup>84</sup>. This should include analysis of a potential effect on implant fixation. Meanwhile, patients with coated implants should be followed on a regular basis and surgeons should be alert for side effects, such as clinical evidence of argyria in patients with silver coated implants<sup>84</sup>.

The use of myocutaneous flaps, to cover implants with well-vascularized soft tissue and to eliminate dead space, also gained attention during recent years. Some centers use a rectus abdominis myocutaneous flap as a standard of treatment for patients with a pelvic reconstruction<sup>68,91</sup>. These techniques however necessitate large contralateral dissection, usually take long and often require extensive blood transfusion<sup>91</sup>. Regardless of the use of such extensive flaps, the risk of wound problems remained high in a study on pelvic reconstructions<sup>68</sup>. In addition, the use of extensive flaps undermines the integrity of the abdominal wall and has a risk of herniation<sup>92</sup>. Therefore, we are of the opinion that surgeons should be hesitant to perform a myocutaneous flap rotation during the primary procedure in treatment of pelvic tumors. Omentoplasty is an alternative technique that may be used to cover pelvic reconstructions, although there are currently no studies to

support the idea that this reduces the risk of deep infection. It has, however, been shown that omentoplasty can be used to successfully fill a large cavity and cover an infected structure (bronchopleural fistula)<sup>93</sup>.

Filling the dead space with large amounts of antibiotic-loaded bone cement is another technique to reduce the risk of deep infection<sup>39</sup>. On the other hand, the exothermic reaction of polymethylmethacrylate (PMMA) bone cement may cause further damage to surrounding soft tissues<sup>94</sup>. Furthermore, multi-resistant microorganisms may evolve. Alternatives for delivering large amounts of antibiotics locally include Garacol® (EUSA Pharma, Hemel Hempstead, United Kingdom) and Septopal® (Zimmer Biomet, Warsaw, IN, United States), although there is no evidence to support the use of these agents in large tumor defects. Future research should be directed at developing and evaluating the efficacy of bactericidal materials that can be used to fill the dead space after tumor resection.

## **Part II: Management of Extremity Bone Tumors**

Primary bone tumors of the appendicular skeleton most commonly affect the epimetaphyseal regions of the distal femur, proximal tibia, proximal humerus and proximal femur<sup>95,96</sup>. Many studies therefore focused on reconstructions of the knee, hip, and shoulder. Three techniques can be used to reconstruct a functional joint following articular tumor resection: transplantation of an osteoarticular allograft, implantation of an endoprosthesis, or a combination of the two (allograft-prosthetic composite, APC)<sup>97-100</sup>. Although these techniques have greatly improved possibilities and functional outcomes for sarcoma patients, joint replacements for bone tumors are still associated with relatively high complication and revision rates<sup>57</sup>. Intercalary reconstructions salvage the native joint, lack moving components, are easier to perform, and are generally associated with a lower risk of late mechanical failure<sup>33,101</sup>. Therefore, we prefer these joint-sparing resections whenever oncologically safe. In an attempt to further improve mechanical results of intercalary reconstructions, our center pioneered with hemicortical resection of tumors with limited cortical and intramedullary involvement<sup>102</sup>.

Below, complications and failure modes of different biological and endoprosthetic techniques will be discussed, based on the Henderson classification<sup>9</sup>. Furthermore, comments will be made on controversies in surgical strategies for reconstructions after lower-extremity bone tumor resection.

## 2.1 *Soft-tissue failure*

Two types of soft-tissue failures can be distinguished: either related to function (“limited function owing to insufficient musculo-ligamentous attachment”), or related to coverage (aseptic wound dehiscence). Few studies explicitly mentioned soft tissue problems as a cause of failure for reconstructions of the extremities, presumably because most soft-tissue complications ultimately either result in infection, or can be managed with a skin graft or myocutaneous flap.

Adequate soft-tissues are of essential importance for optimal functioning of reconstructions of polyaxial joints; a lack of support results in subluxation or recurrent dislocation<sup>103</sup>. It is, however, difficult to assess the influence of the extent of soft tissue resection on functional outcome of intercalary reconstructions or knee replacements. On the other hand, we know that muscular support reduces the loads on the adjacent joint<sup>104</sup>, and extensive soft tissue resection therefore may result in an increased risk of mechanical failure<sup>105</sup>. The TLEMsafe project, which is currently ongoing, aims to combine a computerized model of the musculoskeletal system and innovative imaging techniques to predict functional effects of a specific resection<sup>106</sup>. Although this model is not able to account for compensatory function of salvaged muscles and it may be questioned whether such a prediction would actually affect clinical practice, it would be interesting to use such models to calculate mechanical stresses on implants, to predict mechanical failure and, ultimately, to manufacture implants that are optimized to withstand the relevant mechanical stresses.

Loss of extensor mechanism function is a particular concern after tumor resections around the knee<sup>105</sup>. Osteoarticular allografts have a theoretical advantage over endoprotheses because they offer the possibility to reconstruct the extensor mechanism and may thus result in a less severe extension lag<sup>107, 108</sup>. On the other hand, synthetic materials may be used to reconstruct the extensor mechanism when using an endoprosthesis. Early synthetic (Terylene) ligaments were abrasive to local tissues and eventually ruptured<sup>109</sup>. Modern synthetic materials, such as the MUTARS trevira tube<sup>58</sup> and LARS tube<sup>110</sup> (LARS, Arc-Sur-Tille, France), however demonstrated satisfactory results in the first clinical studies<sup>58, 110, 111</sup>. Future studies will have to show whether there is a difference in outcomes between biological and modern synthetic materials for reconstructions of the extensor mechanism.

## ***2.2 Aseptic loosening and graft-host nonunion***

As discussed in paragraph 1.2, endoprostheses around the knee were notorious for the risk of aseptic loosening. With the introduction of hydroxyapatite (HA) coating for uncemented implants and HA collars for cemented implants, the risk of failure due to aseptic loosening decreased from 25-40% to approximately 5% at 10 years follow-up for primary implants<sup>58, 65, 66</sup>. The risk of loosening has been ascribed to a number of factors, including the torque acting on the stems<sup>59, 60</sup>. Endoprostheses of the knee originally had a fixed hinge without rotational freedom, which resulted in excessive stress transfer at the implant-bone or cement-bone interface<sup>112</sup>. Modern hinges allow for a certain degree of axial rotation, thereby theoretically reducing mechanical stress at the interface and thus lowering the risk of loosening. Clinical studies that compared outcomes of fixed and rotating hinges concluded that rotating hinges appeared to reduce the risk of loosening<sup>65, 66</sup>, although results may have been biased by concomitant modifications in endoprosthetic design (including the introduction of HA coating and collars) and increasing surgical experience.

Whereas the incidence of type 2 failure of endoprostheses has greatly been reduced during recent decades, graft-host nonunion is still among the main complications for allograft reconstructions. Even though the risk of reconstruction failure is limited (5-7%), up to 40% of patients require operative intervention to facilitate union<sup>33, 113</sup>. We demonstrated that plate fixation and cortical contact at the junction are important prognostic factors in union of allograft-host junctions. Although the number of patients included in our study on allograft-host junctions was limited, we found that all junctions with plate fixation and radiographic cortical continuity on the first postoperative radiograph united without further surgical intervention. These results shine new light on the dilemma whether to use an allograft or a vascularized fibular graft (VFG) for reconstruction of intercalary defects.

The superior biological potential of VFGs is one of the reasons why some surgeons prefer to use a VFG<sup>114</sup>. However, if the risk of nonunion of allograft-host junctions can be eliminated, there presumably is no advantage of using a VFG over an allograft for defects with a length of less than eight to 10 centimeters. A virtual bone bank system and computer-assisted surgery may prove useful to obtain superior fit between host bone and the allograft<sup>115, 116</sup>. For larger defects, VFGs may be preferable because of the increased risk of complications in large allograft reconstructions<sup>113</sup>. Reconstruction length was not associated with complication

rates in one study on VFGs<sup>114</sup>. Nevertheless, initial stability is an important concern in VFG reconstructions, especially when reconstructing large defects in heavy adults. VFGs however have the potential of hypertrophic growth; although patients will have to accept a long period of partial weight-bearing, gradual increase in weight-bearing may result in a durable construct of living bone. Interposition of a joint-sparing implant is another promising technique for reconstruction of intercalary long-bone defects, and allows for early weight-bearing<sup>117</sup>. Modern additive manufacturing techniques may be used to produce patient-specific joint-sparing implants with optimal three-dimensional fit. Future comparative studies are needed to definitively determine what is the best technique for reconstruction of (large) intercalary defects.

### 2.3 Structural failure

For endoprostheses, structural complications can be divided into (1) implant breakage or wear, and (2) periprosthetic osseous fractures. Breakage of stems is rare, occurring in approximately 2% of knee endoprostheses<sup>57, 118</sup>. Obvious risk factors for stem fractures include greater resection length and the use of small-diameter stems<sup>58, 118</sup>. Failure of the polyethylene and PEEK-OPTIMA (Invibio Ltd, Thornton-Cleveleys, United Kingdom) locking mechanisms has been a particular concern for the MUTARS system<sup>119</sup>. With the introduction of a metal-on-metal locking mechanism, the risk of structural failure has been eradicated. In vitro studies and close follow-up of patients are indicated to assess the amount of wear debris released, the risk of adverse reactions, and thus the long-term safety of these locking mechanisms.

Periprosthetic fractures can be divided into intraoperative crack fractures without displacement and 'true' (or late) periprosthetic fractures. The occurrence of intraoperative crack fractures is associated with the use of uncemented press-fit stems<sup>120</sup>. As they generally require little or no further surgical treatment and mostly heal uneventfully<sup>58, 121</sup>, we do not consider this a contraindication for the use of uncemented stems. Management of late periprosthetic fractures, on the other hand, is problematic, but their incidence is low<sup>69</sup>. These fractures are presumably associated with periprosthetic osteolysis (bone resorption) and aseptic loosening of implants<sup>122</sup>. The occurrence of resorption has been ascribed to stress shielding; if osseointegration of the stem occurs over a longer trajectory, stresses in the outer cortex are reduced, and resorption may occur<sup>69</sup>. To reduce the low-stress region in the outer cortex, Blunn *et al* suggested that the region of HA-coating should



be reduced to one-third of the stem length. MUTARS stems are coated for more than one third. Although resorption of the outer cortex is often evident following uncemented fixation, particularly in the zone nearest to the reconstructed joint, we did not observe this as a reason for implant failure in our long-term follow-up study<sup>58</sup>. This supports our idea that this process stabilizes over time, and therefore, the clinical relevance of the phenomenon remains unclear.

For biological reconstructions, structural complications can be divided into (1) osteosynthesis material breakage leading to construct instability, and (2) fractures through the graft. The most common cause of osteosynthesis material breakage is metal fatigue. The occurrence of fatigue fractures is likely associated with diastasis at the osteotomy junction and delayed or nonunion; repetitive mechanical stresses on the osteosynthesis materials will eventually lead to failure. Fractures are a serious complication of segmental allograft reconstructions, occurring in 16-29% of patients<sup>33, 101, 113, 123</sup>. Its treatment is problematic because the fracture site is generally composed of non-vascular bone tissue. Several techniques have been described for treatment of allograft fractures, including the addition of a vascularized fibular graft or new allograft at the fracture site, or the application of recombinant bone morphogenetic protein-2<sup>124-126</sup>. The chance of successful healing is limited and most surgeons therefore prefer to revise the entire allograft. Vascularized grafts offer an obvious advantage over allografts in this regard.

## **2.4 Infection**

Strategies to reduce the risk of infection after endoprosthetic reconstruction are discussed in paragraph 1.4; most of these also apply to reconstructions in the appendicular skeleton. The overall rate of deep infection after endoprosthetic or allograft reconstruction for extremity bone tumors is approximately 10%<sup>82, 127</sup>. Reconstructions of the proximal tibia are associated with a higher rate of infection (up to 36% in early series on endoprostheses)<sup>109</sup>. Some surgeons started to routinely perform a gastrocnemius muscle flap rotation, and reported that the risk of infection had reduced to 12% by doing so<sup>109</sup>. Later studies demonstrated that the effect was less profound than was initially believed<sup>65</sup>. Moreover, dissection of the medial gastrocnemius muscle may impair functional outcome. We therefore prefer to perform a gastrocnemius muscle flap only in high-risk cases, when soft-tissue coverage is poor. Further follow-up will have to prove if this approach is equally effective.

## General conclusions

During recent decades, there has been a tremendous improvement in treatment possibilities for bone tumors of the pelvis and extremities. Nevertheless, functional outcomes vary greatly between patients, in part owing to the frequent occurrence of complications. We therefore set out to assess complications of various reconstructive techniques and to identify risk factors for those complications, with the ultimate aim to improve outcomes for patients with musculoskeletal tumors.

Treatment of pelvic bone tumors is associated with a high risk of complications, regardless of the reconstructive technique used. The design principle of modern stemmed acetabular implants for reconstruction after periacetabular resections is comparable to those of decades ago. However, due to improvements in production processes and modifications in implant design, including the introduction of modularity, coatings, and dual-mobility articulation, their reliability and durability has improved dramatically. At present, they can be used for the vast majority of pelvic tumor reconstructions and the reconstruction itself has become less technically demanding. The main issues that remain to be solved are the high risk of instability and infection, and it appears that the occurrence of these complications is closely tied to the extent of surgery. Future research should be directed at prevention and adequate treatment of these complications.

Fortunately, complications are less frequent in treatment of extremity bone tumors. During the early years of limb-salvage surgery, allografts were the preferred method of reconstruction in many large European sarcoma centers. As with any surgical procedure, the outcome is dependent on the right indication. It however appears that this especially holds true for allografts: they offer a reliable, durable and elegant option when they are being used for meticulous reconstruction of defects of limited size in younger patients. On the other hand, when they are being used for reconstruction of extensive osseous defects in older patients with poor healing potential and their fitting is suboptimal, the risk of complications is extremely high and the reconstruction is likely to fail. During the last few decades, endoprostheses have largely replaced allografts as the technique of choice for reconstruction of extremity bone tumor defects. Again, improvements in production and design of these implants have caused an enormous increase in reliability and long-term stability. The challenge for the orthopaedic oncologist is to choose the right technique for the specific patient and tumor type. Apart from introducing new techniques, it is extremely important to be aware of risk factors for complications of existing techniques. In the end, the outcome of any

surgical procedure is dependent on the right indication and a precise technique of execution.

### General considerations

The vast majority of clinical articles in orthopaedic journals are single center observational case series on a surgical technique<sup>128</sup>, leading to a substantial risk of selection bias and heterogeneity. A systematic review demonstrated that 92% of studies published on surgical management of lower extremity bone tumors are level IV or V studies<sup>129</sup>. The overall quality of reporting is generally poor, and studies are therefore prone to confounding bias, sampling bias and recall bias<sup>129</sup>. Furthermore, studies on surgical techniques often report single-center results from a highly specialized center – commonly one that was involved in the development of the technique – and thus may overestimate clinical outcome. Reasons for the lack of higher level of evidence studies include the rareness of diseases, heterogeneity in presentation and surgical approaches, loss of follow-up due to patient mortality, and ethical considerations. International cooperation is key to obtaining sufficient patient numbers, although differences in expertise, treatment protocols and surgeon preferences may introduce other types of bias. In that regard, it is essential that uniform definitions are employed and that standard reporting guidelines, such as the STROBE statement, are applied as much as possible<sup>130</sup>.

The classification of failure modes as described by Henderson *et al* was one of the first widely supported classification systems that aimed to stimulate uniform reporting<sup>9</sup>. Although the authors must be applauded for their initiative, there are a number of flaws in the classification. First, the system only classifies failures, not complications. As a result, isolated revision of the bushing is counted as a failure – while many authors consider this routine maintenance<sup>57, 58</sup>. On the other hand, servicing procedures result in secondary deep infection in approximately 5% of cases<sup>58</sup> and we therefore encourage striving for an implant system that is free of the need of maintenance. Second, to distinguish early from late infections, the Henderson classification system uses a cutoff point of two years for endoprostheses, and six months for biological reconstructions. Rather than the time from primary surgery to the onset of symptoms, a classification system should distinguish infections with an acute onset from delayed or chronic infections; this dictates the treatment strategy and the probability of being able to retain the implant<sup>40, 131</sup>. Third, the Henderson classification did not include massive bone resorption

around endoprostheses, nor resorption of grafts, while this is an important issue in larger biological reconstructions<sup>98, 127</sup>. Fourth, the classification system did not distinguish breakage of implants from breakage of supportive hardware (i.e., a supportive screw), while the clinical implications of the two are materially different. We present a modified version of the Henderson classification (tables 1 and 2), aiming to further improve reporting of complications and failures and comparability of different surgical strategies and reconstructive techniques. Future collaborative studies are indicated to optimize the classification system based on factors that are relevant for clinical outcome.

Careful evaluation of functional outcome, not just complications and failures, should be included in future studies to offer further insight in clinical outcome of various reconstructive techniques. Currently, two systems are widely accepted for assessment of functional outcome. The MSTS (MusculoSkeletal Tumor Society) score was developed in the 1980s and is currently the most commonly used<sup>132</sup>. The system is a physician-reported outcome that assigns numerical values (0-5) for six domains, producing an overall numerical score that can be used to calculate a percentage rating. The TESS (Toronto Extremity Salvage Score), on the other hand, is a patient-reported questionnaire that was developed in the 1990s<sup>133</sup>. The TESS questionnaire assigns numerical values (1-5) for 30 activities of daily living. Although the questionnaires demonstrate reasonable agreement, the subjective satisfaction and acceptance of physical impairment are generally higher than the objective score<sup>134</sup>. In addition, we are of the opinion that the scoring systems offer little discriminative value. Data of large cohort studies should be used to develop a novel, easy-to-use system for assessment of functional outcome. A recent study concluded that the vast majority of functional improvement can be expected during the first two years after surgery, suggesting that long-term follow-up studies are not necessarily needed to assess functional outcome<sup>135</sup>.

Apart from evaluating functional outcomes, we are of the opinion that innovative surgical techniques should be introduced in a regulated manner, ensuring the safety and effectiveness of novel techniques. The IDEAL consortium proposed a five-stage model that was based on the phased approach for drug development<sup>136</sup>. It should be taken into account, however, that well-regulated introduction of novel treatment strategies and implants in orthopaedic oncology is complicated. Because of the rarity of disease, combined with the heterogeneity in localizations, disease extent, use of co-treatments, and patient characteristics, it is extremely difficult to adequately compare the outcomes of different techniques.

To some extent, however, roentgen stereophotogrammetric analysis (RSA) may be used to compare implants<sup>137</sup>. This technique is able to accurately measure three-dimensional implant migration (up to 0.1mm for translations and 0.1 degree for rotations). RSA has been shown to have early predictive properties for implant failure, and may be used in the process of adequate phased introduction of new implants<sup>137</sup>.

Although there have been tremendous improvements over the years, challenges remain in effective treatment of musculoskeletal tumors and in optimization of reconstructive techniques. Again, (inter-)national collaborative studies are needed, aiming for a golden era of cancer therapy, when, in the words of Gordon-Taylor, "gross mechanical destruction of disease and cruel mutilation of tissue shall be no more"<sup>138</sup>.

**Table 1.** Classification of complications for endoprosthetic reconstructions in orthopaedic oncology.

Category	Type	Subtype	Description	Time of diagnosis <sup>1</sup>	No. of patients affected <sup>2</sup>	No. of patients needing a re-intervention	No. of implants removed as a result
Mechanical	Type 1: Soft tissue	1A. Functional	Instability or dislocations (including dislocations treated with closed or open reduction)				
		1B. Coverage	Superficial wound problems, including aseptic wound dehiscence and superficial necrosis				
	Type 2: Aseptic loosening	N/A	Radiographic or clinical signs of loosening in the absence of infection				
	Type 3: Structural failure	3A. Periprosthetic fracture	Fracture of periprosthetic bone				
		3B. Structural hardware breakage	Breakage of stem or locking mechanism				
Non-mechanical	Type 4: Infection <sup>3</sup>	3C. Supporting hardware breakage or wear	Breakage of liner or screw				
		3D. Wear	Wear of liner or insert				
		3E. Bone resorption	Massive periprosthetic bone resorption				
		4A. Acute	<6 weeks after implantation				
		4B. Late or chronic	>6 weeks after implantation				
	Type 5: Tumor progression	4C. Secondary acute	<6 weeks after secondary procedure				
		5. Local tumor relapse	Recurrence or progression of tumor				

<sup>1</sup> Report the median time (and range) from surgery to diagnosis of the complication, in months. Does not apply for type 3D (wear of liner or insert) and 3E (bone resorption) complications

<sup>2</sup> Report the total number of patients who were affected by the complication, also those who did not need surgical re-intervention

<sup>3</sup> All deep infections, including those treated with implant retention

**Table 2.** Classification of complications for biological reconstructions (allograft, autograft) in orthopaedic oncology

Category	Type	Subtype	Description	Time of diagnosis <sup>1</sup>	No. of patients affected <sup>2</sup>	No. of patients needing a re-intervention	No. of grafts removed as a result
Mechanical	Type 1: Soft tissue	1A. Functional	Instability or dislocations (including dislocations treated with closed or open reduction)				
		1B. Coverage	Superficial wound problems, including aseptic wound dehiscence and superficial necrosis				
	Type 2: Nonunion	2A. Hypertrophic	Hypertrophic nonunion of the allograft-host junction, defined as the lack of continuity in three cortices at the junction one year after surgery				
		2B. Atrophic	Atrophic nonunion of the allograft-host junction, defined as the lack of continuity in three cortices at the junction one year after surgery				
	Type 3: Structural failure	3A. Fracture	Fracture of graft or fracture through graft-host junction				
Non-mechanical	Type 4: Infection <sup>3</sup>	3B. Hardware breakage	Breakage of osteosynthesis material				
		3C. Graft collapse or massive resorption	Collapse of the graft, of massive resorption of the graft				
		4A. Acute	<6 weeks after implantation				
		4B. Late or chronic	>6 weeks after implantation				
		4C. Secondary acute	<6 weeks after secondary procedure				
Type 5: Tumor progression	5. Local tumor relapse	Recurrence or progression of tumor					

<sup>1</sup> Report the median time (and range) from surgery to diagnosis of the complication, in months. Does not apply for a type 2 complication (nonunion)

<sup>2</sup> Report the total number of patients who were affected by the complication, also those who did not need surgical re-intervention

<sup>3</sup> All deep infections, including those treated with graft retention

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