Collagen membranes for host-implant integration: a pilot clinical study

Saminathan Suresh Nathan, Edwin Ravanzo Guerzon, Kishore Bhavanam, Lay Hong Tan, Khin Zarchi, Barry Pereira
Department of Orthopedic Surgery, National University of Singapore, Singapore

ABSTRACT

Purpose. To evaluate host-implant integration with collagen membranes in 14 patients who underwent limb salvage surgery for musculoskeletal oncological disease.

Methods. 8 females and 6 males aged 10 to 69 (mean, 30) years underwent limb savage surgery with collagen membranes (Tutomesh; Tutogen Medical, Germany) for osteosarcoma (n=7), chondrosarcoma (n=3), giant cell tumour (n=1), malignant fibrous histiocytoma (n=1), arteriovenous malformation (n=1), and pigmented villonodular synovitis (n=1). The procedures performed were proximal humeral resection (n=3), partial scapulectomy (n=1), proximal femoral resection (n=2), total femoral resection (n=2), proximal tibial resection (n=3), and wide resection of soft tissues of the knee (n=3). In addition, 10 patients underwent endoprosthesis reconstruction. Reconstruction of musculoskeletal defects was classified into type I (intercalary, n=2), type II (joint, n=4), and type III (both, n=8). Graft incorporation and local recurrence were monitored. Clinical outcome measures entailed the Short Form-36, Toronto Extremity Salvage Score (TESS), and Musculoskeletal Tumor Society Score (MSTS).

Results. Two patients with proximal tibial resection and one with total femoral resection had wound healing problems. No patient had any infection or any foreign body reaction necessitating implant removal. Eight patients with type II or III reconstruction were followed up for a mean of 11 (range, 1–23) months. Their scores in the Short Form-36, TESS, and MSTS were similar to those who had undergone reconstructions without the membrane, with the exception of type II reconstructions for which the membrane conferred good results.

Conclusion. The Tutomesh membrane facilitated host-implant integration and provided a feasible anatomic reconstruction for ligaments in the shoulder, knee, and hip.

Key words: collagen; limb salvage; membrane; tissue engineering
INTRODUCTION

Resection of tumour with adequate margins minimises local recurrence. Nonetheless, this results in problems for soft-tissue coverage, wound closure, and functional morbidities. Autografts and allografts have limited application to joints, and often leads to arthrodesed joints. Endoprosthesis for joint reconstruction may result in large segments of biologically inanimate fillers without reliable soft tissue–implant integration. Biological incorporation of soft tissues and implant while maintaining joint mobility is important.

Resorbable or bioabsorbable membranes are either animal-derived (e.g. porcine and bovine) or synthetic polymers (e.g. polyacetic or polyglycolic acid). These avoid surgical retrieval after implantation and minimise contamination. We evaluated host-implant integration with collagen membranes in 14 patients who underwent limb salvage surgery for musculoskeletal oncological disease.

MATERIALS AND METHODS

Between November 2005 and October 2008, 8 females and 6 males aged 10 to 69 (mean, 30; standard deviation [SD], 19) years underwent limb salvage surgery with resorbable membranes (Tutomesh; Tutogen Medical, Germany) for osteosarcoma (n=7), chondrosarcoma (n=3), giant cell tumour (n=1), malignant fibrous histiocytoma (n=1), arteriovenous malformation (n=1), and pigmented villonodular synovitis (n=1). The procedures performed were proximal humeral resection (n=3), partial scapulectomy (n=1), proximal femoral resection (n=2), total femoral resection (n=2), proximal tibial resection (n=3), and wide resection of soft tissues of the knee (n=3). In addition, 10 patients underwent endoprosthesis reconstruction involving cemented or cementless techniques (Table 1). Cemented implants provided an extra-cortical porous-coated section. Cementless or press-fit implants were made of titanium alloy with plasma-sprayed stem and hydroxyapatite coating.

Reconstruction of musculoskeletal defects was classified into 3 types. Type I reconstruction (n=2, Fig. 1) entailed bone and intercalary reconstruction and musculeattachment (i.e. endoprosthetic replacement). Type II reconstruction (n=4, Fig. 2) entailed joint capsule reconstruction and periarticular soft-tissue reattachment (the menisci and collateral ligaments

<table>
<thead>
<tr>
<th>Sex/age (years)</th>
<th>Diagnosis/site involved</th>
<th>Procedure</th>
<th>Surgery type</th>
<th>Membrane size (cm)</th>
<th>Follow-up (months)/status</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/13</td>
<td>Osteosarcoma/total femur</td>
<td>Total femoral resection &amp; endoprosthesis</td>
<td>I</td>
<td>12x16</td>
<td>38/living</td>
<td>Pressure sores</td>
</tr>
<tr>
<td>M/55</td>
<td>Malignant fibrous histiocytoma/total femur</td>
<td>Total femoral resection &amp; endoprosthesis</td>
<td>I</td>
<td>12x16 (x2)</td>
<td>32/living</td>
<td>Seroma</td>
</tr>
<tr>
<td>F/17</td>
<td>Pigmented villonodular synovitis/knee posterior compartment</td>
<td>Wide resection &amp; endoprosthesis</td>
<td>II</td>
<td>12x16</td>
<td>41/living</td>
<td>-</td>
</tr>
<tr>
<td>M/32</td>
<td>Arteriovenous malformation/knee posterior lateral corner</td>
<td>Wide resection &amp; reconstruction</td>
<td>II</td>
<td>12x16</td>
<td>34/living</td>
<td>-</td>
</tr>
<tr>
<td>F/37</td>
<td>Chondrosarcoma/scapula</td>
<td>Partial scapulectomy</td>
<td>II</td>
<td>12x16 (x2)</td>
<td>45/living</td>
<td>-</td>
</tr>
<tr>
<td>F/40</td>
<td>Chondrosarcoma/knee medial ligamentous complex</td>
<td>Wide resection &amp; reconstruction</td>
<td>II</td>
<td>4x5</td>
<td>37/living</td>
<td>-</td>
</tr>
<tr>
<td>M/10</td>
<td>Osteosarcoma/proximal humerus</td>
<td>Proximal humeral resection &amp; endoprosthesis</td>
<td>III</td>
<td>12x16</td>
<td>45/living</td>
<td>-</td>
</tr>
<tr>
<td>F/14</td>
<td>Osteosarcoma/proximal humerus</td>
<td>Proximal humeral resection &amp; endoprosthesis</td>
<td>III</td>
<td>12x16</td>
<td>41/living</td>
<td>-</td>
</tr>
<tr>
<td>F/17</td>
<td>Osteosarcoma/proximal tibia</td>
<td>Proximal tibial resection &amp; endoprosthesis</td>
<td>III</td>
<td>12x16</td>
<td>54/living</td>
<td>-</td>
</tr>
<tr>
<td>M/18</td>
<td>Osteosarcoma/proximal femur</td>
<td>Proximal femoral resection &amp; endoprosthesis</td>
<td>III</td>
<td>12x16</td>
<td>49/living</td>
<td>-</td>
</tr>
<tr>
<td>M/18</td>
<td>Osteosarcoma/proximal tibia</td>
<td>Proximal tibial resection &amp; endoprosthesis</td>
<td>III</td>
<td>12x16, 4x5</td>
<td>50/living</td>
<td>-</td>
</tr>
<tr>
<td>F/25</td>
<td>Osteosarcoma/proximal femur</td>
<td>Proximal femoral resection &amp; endoprosthesis</td>
<td>III</td>
<td>12x16</td>
<td>34/living</td>
<td>-</td>
</tr>
<tr>
<td>M/58</td>
<td>Chondrosarcoma/proximal humerus</td>
<td>Proximal humeral resection &amp; endoprosthesis</td>
<td>III</td>
<td>12x16</td>
<td>51/living</td>
<td>-</td>
</tr>
<tr>
<td>F/69</td>
<td>Giant cell tumour/proximal tibia</td>
<td>Proximal tibial resection &amp; endoprosthesis</td>
<td>III</td>
<td>12x16</td>
<td>35/living</td>
<td>Wound dehiscence</td>
</tr>
</tbody>
</table>

Table 1

Patient characteristics and outcomes
in the knee and the iliofemoral ligament in the hip). Type III reconstruction (n=8, Fig. 3) necessitated both segmental bone and joint reconstruction.

Prior to application, the membranes were soaked in normal saline solution containing gentamicin for half an hour. 15 pieces of 12x16 cm and 2 pieces of 4x5 cm membranes were used. The endoprostheses were wrapped by a membrane as a sleeve. Soft tissues were attached to the prosthesis through the membrane with absorbable sutures. Musculoskeletal defects were covered with the membranes.

Graft incorporation and local recurrence was monitored using magnetic resonance imaging. Whether the membrane provided durable patellar stability for those with patellar ligament reattachment was evaluated using lateral radiographs; the Insall-Salvati ratio and Blumensaat’s line provided an indication of patella alta or baja.2

Clinical outcome was evaluated using the Short Form-36,3 Toronto Extremity Salvage Score (TESS),4 and Musculoskeletal Tumor Society Score (MSTS).5 Comparisons were made with a control group of

![Figure 1](image1.png)  
**Figure 1** A 13-year-old girl undergoing a total femur reconstruction: (a) type I reconstruction of the intercalary, (b) resection of the entire femur and all soft-tissue attachments, and (c) the endoprosthesis is wrapped with the Tutomesh membrane and attached to spared muscles and tendons.

![Figure 2](image2.png)  
**Figure 2** A 17-year-old man undergoing wide resection of soft tissues of the knee: (a) type II reconstruction of the joint, (b) resection of the joint capsule along with nearby muscles and ligaments, (c) defect in the popliteal fossa and posterior leg compartment leading to exposure of the joint space and instability of the menisci and posterior ligaments, and (d) the capsular defect is covered with the Tutomesh membrane, and adjacent soft tissues (mainly the posterior meniscus) are secured onto the membrane with absorbable sutures.

![Figure 3](image3.png)  
**Figure 3** A 10-year-old boy undergoing proximal humeral reconstruction: (a) type III reconstruction of the intercalary and joint, (b) en bloc resection of the proximal humerus, and (c) the endoprosthesis is wrapped with the Tutomesh membrane encompassing the glenohumeral joint to enable dynamic muscle transfer around the shoulder.
8 patients who had undergone endoprosthesis reconstruction without membranes, and another control group of 8 patients who had undergone chemotherapy for acute lymphoblastic leukaemia without extremity surgery.

The Short Form-36 measures overall health status, functional status, and health-related quality of life. Its use for patients with sarcoma is questionable, because its subscales differentiate physical function of upper from lower extremity poorly; a score of 50 was defined as average, 0 to 49 as below average, and 51 to 100 as above average.

The self-evaluated TESS measures physical function (disability) in terms of limitations in activity related to decreased body movement and restrictions in mobility, self-care, and performing activities of daily living (ADL). It had been used in 97 patients with bone or soft tissue sarcoma in the lower extremity. It was superior to the other scales in evaluating physical function/disability.3

The MSTS measures functional outcomes of both upper and lower extremity. Each extremity is evaluated by 6 factors; each factor is graded 0 to 5. A maximum score of 30 (5x6) indicates best outcome for each extremity. Outcome is reported as a percentage of the maximum score and reflects the clinician’s rather than the patient’s assessment of functional outcome.4

RESULTS

Coverage of the endoprosthesis and musculoskeletal defect was adequate. No graft was torn in the course of joint motion. Two patients with proximal tibial resection and one with total femoral resection had wound healing problems. In the former, repeated debridements exposed the membrane, which was resolved with flap closure, and the membrane was eventually incorporated. In the latter, a seroma over the femoral reconstruction was drained and excised at week 6. Part of the membrane (2x2 cm) was removed without compromising wound closure or function, and subjected to haematoxylin and eosin,

<table>
<thead>
<tr>
<th>Haematoxylin &amp; eosin staining, x40</th>
<th>Masson's trichrome staining, x40</th>
<th>Immunohistochemical staining with CD3, x40</th>
<th>Immunohistochemical staining with ED1, x40</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>(b)</td>
<td>(c)</td>
<td>(d)</td>
</tr>
</tbody>
</table>

Figure 4  A 55-year-old man having drainage and excision of a seroma and removal of part of the membrane at week 6: (a) no acute inflammatory cells or invasion of the xenograft with polymorphs is noted, (b) integrity of the collagenous construct is maintained but remodelling is continuing. The membrane is histologically fragmented and mostly incorporated with the implant. (c) Graft infiltration with T-lymphocytes and (d) a preponderance of macrophages are noted.

(a) (b) (c) (d)

Figure 5  A 40-year-old woman undergoing wide resection of soft tissues of the knee and reconstruction of the medial ligamentous complex: (a) at month 3, the patient has a good range of motion, with no instability or complication; (b) at month 6, remnants of the membrane (arrows) and remodelling of the medial ligamentous complex are evident.
Masson’s trichome, and immunohistochemical (CD3 and ED1) staining (Fig. 4). No acute inflammatory cells or invasion of the xenograft with polymorphs was noted. Integrity of the collagenous construct was maintained but remodelling was continuing. The membrane was histologically fragmented and mostly incorporated with the implant. Graft infiltration with T-lymphocytes and a preponderance of macrophages were noted.

No patient had any infection or any foreign body reaction necessitating implant removal; only a slight increase in regional warmth was noted. In a patient having wide resection of knee soft tissues, sequential magnetic resonance images showed stiffness, erythema, and swelling of the knee that peaked at week 6 and subsided by week 12, with no sign of inflammation (Fig. 5). At month 6, knee motion was painless throughout its range of motion, and the swelling had resolved. There was a subjective sensation of instability although only mild lateral laxity was evident clinically. The patient developed intense oedema over the graft site but the meniscocapsular reattachment remained stable.

Durability of the 3 cases of proximal tibial reconstruction was evaluated. Proximal tibial resection results in detachment of the extensor mechanism from the tibial tubercle. Attempts at reattachment of the extensor mechanism to the prosthesis have been ineffective. Therefore, the proximal tibia was wrapped by a membrane, which was secured to the patellar ligament (Fig. 6). In a patient with 3 years of follow-up, no extensor lag was noted and the patellofemoral anatomic relationship was normal. The mean Insall-Salvati ratio in the 3 patients was 1.07 (SD, 0.05). No patella alta was noted.

Eight patients with type II or III reconstruction were followed up for a mean of 11 (SD, 7; range, 1–23) months (Table 2). Their SF-36 physical scores were below average and not significantly different. Nonetheless, patients with type II reconstruction fared significantly better in mental scores. Regarding the MSTS, patients with type II reconstruction had good-to-excellent scores, whereas those with type III reconstruction had fair-to-good scores. Of the 5 patients with upper extremity involvement, one with type II and 2 with type III reconstruction had good and 2 with type III reconstruction had fair scores. Of the 3 patients with lower extremity involvement, one with type II reconstruction had excellent and 2 with type III reconstruction had fair results. Regarding TESS, patients with type II reconstruction performed better than those with type III reconstruction in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD</th>
<th>Toronto Extremity Salvage Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short Form-36 score</td>
<td>Musculoskeletal Tumor Society Score (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical health</td>
</tr>
<tr>
<td>Type II reconstruction (n=4)</td>
<td>39.2\pm3.7</td>
<td>51.8\pm18.5</td>
</tr>
<tr>
<td>Type III reconstruction (n=8)</td>
<td>37.0\pm9.0</td>
<td>48.0\pm6.0</td>
</tr>
<tr>
<td>Surgical controls without membrane (n=8)</td>
<td>39.0\pm11.8</td>
<td>51.0\pm10.1</td>
</tr>
<tr>
<td>Non-surgical controls (n=8)</td>
<td>53.7\pm6.8</td>
<td>55.3\pm2.4</td>
</tr>
</tbody>
</table>

Figure 6 A 17-year-old girl undergoing proximal tibial resection and endoprosthesis reconstruction: (a) resection of the proximal tibia and detachment of the patellar tendon, (b) the resected proximal tibia with the extensor mechanism removed, (c) extensor mechanism reconstruction using a membrane and a medial gastrocnemius flap, (d) at year 3, the Insall-Salvati ratio (lines) is normal (1.08), and the inferior pole of the patella is below the Blumensaat’s line (dashed line).
difficult activities, but the latter fared better in performing important activities. These scores were similar to those who had undergone reconstructions without the membrane, with the exception of type II reconstructions for which the membrane conferred good results (Table 2).

**DISCUSSION**

The use of prosthetic meshes as a fascial substitute or reinforcement in abdominal wall defect surgeries has been reported. The results were unfavourable owing to foreign body reaction and infection. The use of the Tutomesh for abdominal wall reconstruction has been more favourable, with low rates of infection.

Ligamentous allografts and xenografts are rapidly remodelled and incorporated into host connective tissue. They are superior to synthetic materials, as they enable wound healing by reforming original matrix material instead of remaining as inert devices that may form nidi of infection. When infected, they do not possess the immunological mechanisms for defence. Remodelling of such organic grafts occurs within 4 months of implantation. This is consistent with our findings in the retrieval study and radiological evaluation.

Long-term applications of the Tutomesh achieved good clinical results, with no secondary infection or allergic reaction. It provides a scaffold for tissue ingrowth and remodelling within 12 months, depending on implant site and patient status. It is soft and elastic with high pull-out force, enabling easy manipulation and handling. It also provides multidirectional strength and adapts smoothly to surface contours. Fixation is achieved with suturing, gluing, clipping or stapling. In addition, the membrane-like structure replicates the anatomic condensations of the joint. In our study, the Tutomesh also had good biocompatibility in patients with limb salvage surgeries for musculoskeletal oncological disease.

Interface membranes enable integration of bone grafts onto skeletal defects. Interface membranes protect the defect from in-growth of soft tissue cells and enable bone progenitor cells to develop within a blood clot that is formed beneath the interface membrane. In this process, inhibitory factors outside the defect are excluded and growth factors inside are preserved, thus preventing graft resorption. In our study, when an endoprosthesis was used, the auto- or allografts were laid over the implant-bone interface to bridge the gap. The implant and interface were then wrapped with the membrane and secured with absorbable sutures. The bone grafts were tightly sutured within pockets created in the membrane to prevent it from migrating into the immediate joint space. Union at the implant-bone interface without lysis was noted.

A limitation of this study was the small number of cases. Given the rarity of the condition and the relatively high risk of infection, the membrane should be used cautiously. Considering its good biocompatibility and durable construct, further evaluation is warranted.

**REFERENCES**


