Function, Disability, and Health-Related Quality of Life After Allograft-Prosthesis Composite Reconstructions of the Proximal Femur

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Background: Factors affecting function, disability and health-related quality of life after allograft-prosthesis composite reconstructions have been poorly studied.

Methods: Retrospective study of eighteen patients who underwent reconstruction with proximal femoral allograft-prosthesis composites and answered questionnaires to assess hip function (Postel and Merle d’Aubigné, self-reported Harris Hip Score), disability (Toronto Extremity Salvage Score), and health-related quality of life (SF-36).

Results: The median Toronto Extremity Salvage Score was 76 (IQR: 48–85), the median self-reported Harris Hip Score was 90 (IQR: 48–95) and the median Postel and Merle d’Aubigné score was 17 (IQR: 12–17). Older age, female gender, and presentation with a pathologic fracture were associated with increased disability and poorest function. The median Physical Component Summary score was 44 (IQR: 39–45) and Mental Component Summary scores were 49 (IQR: 46–56). Male gender and recurrence of disease were associated with poorer health-related quality of life. There was a high degree of correlation between function, disability scores and Physical Component Summary score.

Conclusions: Patients’ characteristics at presentation such as age, gender, and occurrence of a pathologic fracture play an important role in determining disability, function, and health-related quality of life after allograft-prosthesis composite reconstruction of the proximal femur.


KEY WORDS: bone tumor; tumor reconstruction; quality of life; function; disability

INTRODUCTION

Development of aggressive surgery and chemotherapy has permitted dramatic improvement of patient survival such that function and health-related quality of life are now central to patients, oncologists, and surgeons [1–6]. The two preferred reconstructive options in adults after bone tumor resection at the proximal femur are implantation of a megaprosthesis and allograft-prosthesis composite reconstruction [7–9]. The purported benefits of allograft-prosthesis composites over megaprosthesis include improved function, improved longevity, and restoration of bone stock [10]. Comparative studies have reported improvement in function for patients reconstructed with allograft-prosthesis composites compared to patients with megaprosthesis and their use after bone tumor resection at the proximal femur is currently favored by many [7–9,11,12].

However, factors affecting function and disability after allograft-prosthesis composite reconstructions at the proximal femur have not been sought in the past. Moreover, although health-related quality of life has become of great interest among cancer patients, surgeons, and oncologists, to the best of our knowledge, it has not been studied specifically for this reconstruction. The objective of the present retrospective study was to assess the results of the reconstruction in regard to function, disability, and health-related quality of life. We also sought for factors associated with these outcomes in order to improve patient care in the future. We have evaluated all patients alive at the time of study whether they had retained the allograft-prosthesis composite or not. Therefore, the results reported in the present work reflect the final outcome of an intention to treat with an allograft-prosthesis composite regardless of the outcome of the reconstruction.

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MATERIALS AND METHODS

Demographics

From 1987 to 2005, 34 patients underwent resection of a bone tumor at the proximal femur followed by reconstruction with an allograft-prosthesis composite in our department. At the time of the last follow-up, 21 patients (62%) were alive and disease-free, 4 (12%) were alive with recurrence of disease, and 9 (26%) had died from metastatic disease. Of the 25 patients alive at the time of last review 3 had returned to their home country and attempts to contact them failed, 2 were lost to follow-up, and 2 did not answer the questionnaires. Therefore, the present work reports the function, disability, and health-related quality of life of these 18 patients.

There were 13 male patients and five female patients with a median age of 44 years (range, 18–76 years), a median body weight of 67.5 kg (interquartile range (IQR), 63–69 kg), and a median height of 172 cm (IQR, 166–179 cm) at the time of surgery. The right limb was affected in seven patients. Eleven patients were grade 1 according to the American Society of Anaesthesiology [13]; six were grade 2; and one was grade 3. Three patients presented with a pathologic fracture at the time of surgery. The diagnosis was low-grade chondrosarcomas in 12 patients, high-grade osteosarcomas in 2, low-grade osteosarcoma, high-grade malignant fibrous histiocytoma of the bone, high-grade...
leiomyosarcoma of the bone, and aneurysmal bone cyst in one each. At the time of diagnosis no patient had metastatic disease and preoperative imaging did not show involvement of the joint. Neoadjuvant chemotherapy was used in five patients (patients diagnosed with osteosarcoma, malignant fibrous histiocytoma and leiomyosarcoma) and preoperative radiation therapy in none. Six patients had revision of a previous megaprosthesys implanted after bone tumor resection: three patients for tumor recurrence, and three for aseptic loosening.

Surgical Technique and Postoperative Care

All allografts were obtained from the institution’s bone bank. Eight allografts were sterilized by gamma radiation (25 kGy precisely controlled by dosimeters), and ten were fresh frozen allografts cryopreserved with addition of dimethyl sulfoxide and rifampicin; the institution’s policy in regard to bone allograft conservation changed in 1995 in favor of fresh frozen allografts. The allograft tendons were not retained on the specimens. All allografts were cultured before delivery and implantation.

The technique used in these patients has been described previously [7]. A lateral approach was used in all patients. The surgical technique involved resection of the tumor, or the previous megaprosthesys, and reconstruction of the joint. At the time of resection, eight patients had an abductor mechanism continuity preserved; of these, six had a trochanteric slide osteotomy and two had continuity preserved via the gluteus medius and vastus lateralis tendons by periosteal elevation. The abductor mechanism continuity was not preserved in ten patients: nine patients had the soft tissue detached from the proximal femur and one had a trochanteric osteotomy. The tumor resections conformed to principles for management of benign and malignant bone tumors: for benign tumors a marginal excision was performed; for malignant tumors a cuff of normal tissue was left with the tumor and the biopsy track was left in continuity with the specimen with a 2-cm margin. The distal femoral cut was horizontal.

Reconstruction was performed during the same surgery. Preferably, patients had a bipolar prosthesis implanted as it is considered more stable; however, the three patients who had a previous hip operation, the six patients who had a megaprosthesys revised, and the one last patient with radiologic signs of osteoarthritis preoperatively had a total hip replacement. We first prepared the allograft to match the length and shape of the skeletal defect. We then cemented the prosthesis into the allograft on a back table and performed a second trial after cement polymerization was complete. The composite was cemented into the host bone, and care was taken so that no cement was caught between the allograft and the host bone.

Abductor mechanism reconstruction was by different techniques: patients who had a trochanteric osteotomy (with or without continuity), had the trochanter reattached to the allograft; patients who had no trochanter left to be reattached to the allograft, had the gluteus medius and vastus lateralis tendons and the fascia lata sutured together; these tendons were not sutured to the allograft. Four patients had the reconstruction augmented with a biceps tendon plasty.

Postoperative second generation cephalosporins were administrated for 48 hr. Patients had traction in the department for 2 weeks during which they benefited from wound care and a spica cast for six other weeks to allow for a fibrous tissue to constitute around the hip.

Disability was evaluated with the Toronto Extremity Salvage Score [14]; the Toronto Extremity Salvage Score is a measure of physical disability developed specifically for the extremity tumor population and has proved to be reliable and valid [15]. It is constituted of 30 items reflecting patient’s ratings of the difficulty experienced in activities of daily living, including self-care, mobility and role functions; it ranges from 0 to 100, with 100 being the best score.

The function was evaluated with the self-reported modified Harris Hip Score [16], and the Postel and Merle d’Aubigné score [17]. The self-reported modified Harris Hip Score is a patient-based self-reported questionnaire derived from the Harris Hip Score; it has shown excellent concordance with the Harris Hip Score; it ranges from 0 to 100, with 100 being the best score [16]. The Postel and Merle d’Aubigné score is a clinician-rated measure of hip function; it ranges from 3 to 18 with 18 being the best score. This score is reported by the surgeon in charge of the patient at each follow-up and was retrieved from hospital records. These two questionnaires evaluate hip function in regard to pain, mobility, and type of support used.

The Rand 36-item Short-Form health survey (SF-36) was used to assess health-related quality of life [18]. The SF-36 is a validated health survey consisting of 36 questions that measure eight health concepts: (1) physical functioning; (2) role limitations due to physical health; (3) bodily pain; (4) role limitations due to emotional problems; (5) energy/fatigue; (6) social functioning; (7) pain; and (8) general health. Two summary scores, a Mental Component Summary score and a Physical Component Summary scores are calculated from these eight health concepts. Each of the eight domains is scored out of 100, with higher scores indicating better functioning. The Mental Component Summary score and Physical Component Summary score are standardized to a mean of 50 (SD = 10), with scores above and below 50 indicating above and below average functioning, respectively.

Univariate regression models were used to assess the effect on disability (Toronto Extremity Salvage Score) and function (self-reported modified Harris Hip Score, and Postel and Merle d’Aubigné score) of age, gender, history of previous hip replacement, presentation with a pathologic fracture, continuity of the abductor mechanism preserved at the time of resection, type of allograft used (irradiated versus fresh-frozen), and reoperation during follow-up. Univariate regression models were used to assess the effect on health-related quality of life (Mental Component Summary score and Physical Component Summary score) of age, gender, and recurrence of disease. In each model, the linear effect of age was assessed with splines. The estimates of each variable with 95% confidence interval (95% CI) are reported for each model. Correlation between function, disability, and health-related quality of life score was tested using the Pearson’s correlation coefficient.

Survival of the allograft-prosthesis reconstruction for the 34 patients was estimated using the cumulative incidence function to account for competing risks; this method has been shown to be a better estimator than the Kaplan–Meier method [19]. The event of interest considered was the revision of any part of the reconstruction (allograft, stem, or acetabular component) for mechanical reasons; revision for other reasons and death were considered as competing events. Median cumulative probabilities of events with the 95% CI were determined.

For quantitative variables (continuous variables), we report the median, first, and third quartile values. Categorical variables are reported as counts. All analyses were performed with R statistical software [20]. The conduction of the study was retrospective and the Local Ethics Committee gave his approval. All patients were included in the analysis, whether or not they had retained the allograft-prosthesis composite, and completed the forms specifically for this study.
RESULTS

Follow-up

The median duration of follow-up was 83 months (range, 25–232 months). Two patients (11%) had postoperative complications, which included: one hematoma with neurological signs of transient sciatic nerve palsy which required drainage; one stem was too long on the postoperative check radiographs with a supracondylar breach through the anterior cortex and was shortened with a diamond saw through an anterior cortical window. No postoperative deaths were related to the procedure. All patients contacted agreed to participate.

Function, Disability, and Health-Related Quality of Life

The median Toronto Extremity Salvage Score was 76 (IQR: 48–85; 1 missing value); three patients had a score of less than 40. The median self-reported Harris Hip Score was 90 (IQR: 48–95; 1 missing value) and the median Postel and Merle d’Aubigné score was 17 (IQR: 12–17). Older age, female gender, and pathologic fracture at presentation were preoperative factors associated with (significantly or with a tendency to significance) increased disability and poorest function; patients who had continuity of the abductor mechanism preserved at the time of resection and those who did not require reoperations during follow-up had less disability and better function than others; other factors did not seem to influence these outcomes (Table I; Fig. 1). The median Physical Component Summary score was 44 (IQR: 39–50; 3 missing values) for the whole group, 44 (IQR: 39–50) for males and 45 (IQR: 42–57) for females. The median Mental Component Summary score was 49 (IQR: 46–56; 3 missing values) for the whole group, 48 (IQR: 45–50) for males and 60 (IQR: 58–61) for females. Excluding the physical functioning health concept, female patients reported better scores than male patients (Table II). Female gender was associated with significantly better Mental Component Summary score and disease recurrence was significantly associated with worst Physical Component Summary score; older patient had a tendency to worst Physical Component Summary score (Table III).

There was a high degree of correlation between function, disability scores, and the Physical Component Summary score. However, there was no correlation between the Mental Component Summary score and other scores, including the Physical Component Summary score (Table IV).

Reoperations

In all, 17 repeat surgical procedures were performed in ten (56%) of the 18 patients. Five patients had the original allograft-prosthesis composite removed. Four patients had infection developed after a median follow-up of 35 months (range: 4–76) and one patient had the reconstruction exchanged for aseptic loosening of the acetabular component after 212 months. Reconstruction was by another allograft-prosthesis composite in two patients, and by a megaprosthesis in two others; one patient eventually required a Girdlestone procedure to eradicate infection.

Other reoperations included: cortico-spongiose bone autograft at the allograft-host bone junction (one patient); excision of soft tissue recurrence (one patient); biopsy for tumor recurrence (two patients; negative); wash-out procedure for infection (two patients cited above); reattachment of a ununited greater trochanter for nonunion (two patient); soft tissue plasty to improve abductor strength (one patient); exchange of an acetabular component with the allograft-prosthetic composite left in place (one patient). Three patients had a single postoperative dislocation each which was relocated with no further event.

The cumulative probability of revision for mechanical reason was 6.5% at 15 years (95% CI: 0–19%); at 15 years, the cumulative probability of revision for other reasons (always infection) was 22% (95% CI: 3.3–41%) and the cumulative probability of death before revision for any reason was 20% (95% CI: 5.3–34%) (Fig. 2).

DISCUSSION

Results in regard to function and disability in this series were good with a median Toronto Extremity Salvage Score of 76, a median self-reported Harris Hip Score of 90 and a median Postel and Merle d’Aubigné score of 17. Other authors have published good functional results after allograft-prosthesis composite reconstructions of the proximal femur with a mean Musculo Skeletal Tumor Society score (a measure of impairment) ranging from 64% to 87% in series ranging in size from 11 to 20 patients, and a median Toronto Extremity Salvage Score of 71 in 5 patients [8,9,12,21]. However, median scores should not hide from view that some patients yield poor functional results. In our series, four patients had a Toronto Extremity Salvage Score or a self-reported Harris Hip Score of less than 40 or a median Postel and Merle d’Aubigné score of less than 8, indicating important disability or poor function. Other authors have reported contrasting results after allograft-prosthesis composites: McGovern et al. [21] have reported that five patients of 13 evaluated

TABLE I. Univariate Models for the Self-Reported Harris Hip Score (HHS), Postel and Merle d’Aubigné Score (PMA), and Toronto Extremity Salvage Score (TESS)

<table>
<thead>
<tr>
<th>Covariates</th>
<th>TESS</th>
<th>HHS</th>
<th>PMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.3 (1.2–1.6)</td>
<td>1.5 (1.3–1.7)</td>
<td>1.2 (1.0–1.4)</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.2 (0.7–1.9)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>Previous hip replacement</td>
<td>1.2 (0.8–1.7)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>Radiation therapy (yes)</td>
<td>0.7 (0.5–0.9)</td>
<td>0.7 (0.5–0.9)</td>
<td>0.8 (0.6–1.0)</td>
</tr>
<tr>
<td>Pathologic fracture (yes)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>Cont. Abd. Mech. (preserved)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>Reoperation (yes)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.3 (1.0–1.6)</td>
</tr>
</tbody>
</table>

The values are given as the estimate with the 95% confidence interval (95% CI). Cont. Abd. Mech. = continuity of the abductor mechanism. The estimates should be interpreted respectively to the range of each score and the category of the covariate (continuous or binomial); for instance, a 70-year-old patient has a decrease in the TESS of 7.7 points (10 × 0.77), in the HSS of 7.4 points (10 × 0.74) and in the PMA of 0.94 points (0.094 × 10) when compared to a 60-year-old patient; a patient who presents with a pathologic fracture has a decrease in the TESS score of 24 points, in the HSS of 30 points and in the PMA of 4.2 points compared to someone who has no pathological fracture at presentation.

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yielded poor Musculo-Skeletal Tumor Society score; in contrast, Langlais et al. [12] and Donati et al. [11] both reported consistently fair to excellent results in series ranging from 11 to 22 patients evaluated. Although, the small number of patients evaluated across these series may explain these differences, other factors likely play an important role.

Older age at the time of surgery, presentation with a pathologic fracture and reoperation during follow-up to treat postoperative complications were associated with disability and poor function. Other authors in different settings have reported that older age and the occurrence of a postoperative complication were predictive of disability and impairment after treatment of lower extremity sarcomas [2,4,6]. In our series, of the four patients with important disability or poor function, three were more than 65 years old at the time of surgery, two presented with a pathologic fracture and all underwent reoperations to treat postoperative complications (infection in three and tumor recurrence in one). For the whole group, the median age at the time of surgery was 44, 17% of the patients presented with a pathologic fracture (3 of 18) and 56% underwent reoperations to treat postoperative complications (10 of 18).

Similarly, in the series by McGoveran et al. [21], patients underwent allograft-prosthesis composite reconstructions at the proximal femur at a mean age of 51 and 50% patients (8 of 16) required reoperation to treat postoperative mechanical complications (10 of 18).

Table II. Health Concepts and Component Summary Scores of the SF-36 for Women, Men, and the Whole Group

<table>
<thead>
<tr>
<th>SF-36 items</th>
<th>Male</th>
<th>Female</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>65 (45–80)</td>
<td>58 (49–69)</td>
<td>65 (48–78)</td>
</tr>
<tr>
<td>Role limitations due to physical health</td>
<td>75 (38–88)</td>
<td>100 (94–100)</td>
<td>75 (63–100)</td>
</tr>
<tr>
<td>Role limitations due to emotional problems</td>
<td>100 (83–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
</tr>
<tr>
<td>Energy/fatigue</td>
<td>50 (48–63)</td>
<td>68 (63–74)</td>
<td>60 (50–65)</td>
</tr>
<tr>
<td>Emotional well being</td>
<td>60 (56–74)</td>
<td>86 (81–88)</td>
<td>72 (56–80)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>75 (56–86)</td>
<td>100 (100–100)</td>
<td>88 (63–100)</td>
</tr>
<tr>
<td>Pain</td>
<td>78 (55–90)</td>
<td>85 (68–90)</td>
<td>80 (55–90)</td>
</tr>
<tr>
<td>General health</td>
<td>55 (45–70)</td>
<td>73 (64–81)</td>
<td>60 (48–70)</td>
</tr>
<tr>
<td>Physical Component Summary score</td>
<td>44 (39–50)</td>
<td>45 (42–47)</td>
<td>44 (39–50)</td>
</tr>
<tr>
<td>Mental Component Summary score</td>
<td>48 (45–50)</td>
<td>60 (58–61)</td>
<td>49 (46–56)</td>
</tr>
</tbody>
</table>

Values are reported as median (first quartile–third quartile).
younger age (38 and 32 years old respectively), had fewer pathologic fracture at presentation (one and none reported respectively) and underwent fewer reoperations to treat postoperative complications (15% and 38% respectively). Therefore patients’ characteristics and follow-up events seem to have more importance in determining disability and function than surgical technique per se.

The health-related quality of life score was poorly correlated with measures of function and disability indicating that the actual condition of the limb operated on or the difficulty experienced in activities of daily living by the patient have little importance in regard to his or her perception of general health. This has been previously reported in the literature between amputees and limb sparing surgery where little or no differences in health-related quality of life measurements have been demonstrated [1,4,5]. It is argued that differences between amputation and limb sparing for lower extremity sarcomas are experienced at the level of handicap (limitation in or prevention of a role that is normal) and less so at the level of disability [1]. Similarly, Schreiber et al. [6] in a study of 100 patients who were treated for extremity soft-tissue sarcomas reported that impairment and activity limitations affect the daily activities of a patient can perform, but it is the restriction in participation of life roles and situations that has the greatest effect on patient health related quality of life. Therefore, factors that would be predictive of poor function and disability would not necessarily influence health-related quality of life negatively.

In the present work, female gender was associated with improved Mental Component Summary score. It has been previously reported that female patients did not cope similarly to male patients in cancer studies. Healey et al. [22] in a study of 201 surgically treated patients with lower extremity tumors reported that women noted more frequently good friends, ability to function, helping people, raising children and being able to travel as important, while men noted having a good job, engage in sports/recreation, social activities, and financial security. Znajda et al. [23] in a study of 10 patients treated with extremity soft-tissue sarcoma reported that if physical symptoms were common to men and women, women adapted more easily with explanations; women feared loosing life, family role and relationships and needed repeated information from several sources along with reassurance and increased social support, whereas men preferred the minimum of social support, requiring instead independence and extra attention to physical limitations. Schreiber et al. [6] reported that only gender was significantly correlated with quality of life with female patients having better scores.

Recurrence of disease and older age had a negative impact on the Physical Component Summary score after allograft-prosthesis composites of the proximal femur. The negative effect of recurrence on quality of life has been previously reported in patients treated for colorectal cancer [24].

This study has several limitations. First, the number of patients included in this series is small and factors possibly associated with function, disability, and health-related quality of life may have been overlooked due to the limited power of the analyses [25]; conversely, factors that appeared to be associated with these outcomes are likely to play an important role. Second, the series presented is heterogeneous with regard to patient’s characteristics, allografts used and surgical techniques employed and possibly a more homogeneous series will yield better results; nonetheless, this series is consecutive and the results are representative of the differences in patient’s characteristics treated for bone tumor and of the evolution of surgical technique with time. Third, patients who returned to their home country, those lost to follow-up, those who did not answer the questionnaires, and those dead at the time of study are a risk for biases [26]. It is generally thought that patients who do not come to their follow-up appointments have worse results than others although we are not aware of any study having demonstrated this in the context of limb salvage surgery. At last, all patients, whether or not they have retained the allograft-prosthesis composite at the time of the study, were included in the analyses and the results presented include the results of the failed reconstruction; this “intention-to-treat” analysis is more representative of the true results of the procedure.

**CONCLUSION**

Patients’ characteristics at presentation such as age, gender, and occurrence of a pathologic fracture play an important role in determining disability, function, and health-related quality of life after allograft-prosthesis composite reconstruction of the proximal femur and patients should be informed accordingly before surgery. Patients should be informed that results after allograft-prosthesis

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**TABLE IV. Correlation Coefficient (CC) Between the Disability Score (Toronto Salvage and Extremity Score (TESS)), the Function Scores (Self-Reported Harris Hip Score (HHS) and Postel and Merle d’Aubigné Score (PMA)) and the Heath-Related Quality of Life Mental Component Summary (MCS) and Physical Component Summary (PCS) Scores (SF-36)**

<table>
<thead>
<tr>
<th>Scores</th>
<th>TESS</th>
<th>HHS</th>
<th>PMA</th>
<th>SF-36-PCS</th>
<th>SF-36-MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC (95% CI)</td>
<td>CC (95% CI)</td>
<td>CC (95% CI)</td>
<td>CC (95% CI)</td>
<td>CC (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>TESS</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HHS</td>
<td>0.94 (0.84–0.98)</td>
<td>&lt;0.0001</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PMA</td>
<td>0.91 (0.75–0.97)</td>
<td>&lt;0.0001</td>
<td>0.98 (0.96–0.99)</td>
<td>&lt;0.0001</td>
<td>-</td>
</tr>
<tr>
<td>SF-36-PCS</td>
<td>0.89 (0.69–0.96)</td>
<td>&lt;0.0001</td>
<td>0.81 (0.48–0.94)</td>
<td>0.00050</td>
<td>0.79 (0.46–0.93)</td>
</tr>
<tr>
<td>SF-36-MCS</td>
<td>-0.35 (−0.73–0.20)</td>
<td>0.20</td>
<td>-0.35 (−0.74–0.22)</td>
<td>0.22</td>
<td>-0.36 (−0.74–0.18)</td>
</tr>
</tbody>
</table>
composite of the proximal femur are good in general, but that reoperation and recurrence of disease during follow-up put them at risk of decreased function and health related quality of life, and important disability.

REFERENCES


