Health-related Quality of Life Evaluation in Patients Undergoing Cavernous Nerve Reconstruction During Radical Prostatectomy

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Objective: Nerve-grafting surgery after resection of neuro-vascular bundles during radical prostatectomy is one of the promising resolutions for dilemma between cancer control and functional preservation. The objective of this study is to evaluate the effect of nerve-grafting surgery on health-related quality of life (HRQOL) in localized prostate cancer patients with special interest in the influence of sexual dysfunction on mental status.

Methods: A total of 88 patients followed for a minimum of 12 months after surgery with a median follow-up of 48 months were enrolled in this study. Of those, 24 patients underwent unilateral nerve-sparing with contralateral nerve-grafting or bilateral nerve-grafting and 64 patients underwent prostatectomy without nerve-sparing procedure. HRQOL assessed with the Japanese version of Extended Prostate Cancer Index Composite (EPIC) and Medical Outcomes Study 8 Items Short Form Health Survey (SF-8TM) was analyzed cross-sectionally.

Results: Patients in nerve-grafting group who recovered potency demonstrated higher sexual function scores compared with those without nerve-sparing procedure ($P = 0.022$ and $0.001$ in 25–48 and 49 months or later, respectively). However, sexual bother scores in nerve-grafting group who recovered potency were lower than those without nerve-sparing procedure throughout the observation periods ($P = 0.012$ in 49 months or later).

Conclusions: Cavernous nerve reconstruction provided recovery of erectile dysfunction in substantial proportion of patients, which resulted in favorable physical HRQOL. Majority of these patients, however, did not seem to be satisfied with their sexual function, which caused sustained sexual bother feeling.

Key words: prostate cancer – radical prostatectomy – quality of life – nerve graft – EPIC

INTRODUCTION

With increment of early-stage prostate cancer in younger generation due to the spread of the prostate-specific antigen (PSA) testing in Japan, patients who desire to preserve potency after treatment are increasing. In patients with early-stage prostate cancer, long survival after treatment is usually guaranteed. Within this context, quality of life (QOL) after treatment has recently become higher priority endpoint especially for early-stage prostate cancer patients.

The early-stage shifting in Japan, however, is still less prominent than in the USA because >90% of men older than 50 years have not been exposed to PSA checking in their lifetime. This means that smaller proportion of Japanese patients can enjoy bilateral nerve-preservation without compromising cancer control than American patients. On the other hand, potency outcome after unilateral nerve-preservation so far reported is still unsatisfactory, which is ranging from 47% to 58% (1–3). Autologous nerve-grafting has been developed aiming to restore erectile function in patients who inevitably undergo bilateral cavernous nerve resection at prostatectomy or to enhance potency in patients who undergo unilateral nerve-preservation. Our previous analysis and other reports on nerve-grafting surgery have revealed substantial effect on restoring erectile function (4–8). Physical and mental health QOL after nerve-grafting surgery, however, remains to be investigated. Our preliminary investigation suggests discrepancy between sexual function and sexual bother, which was assessed with UCLA-Prostate Cancer Index, in patients who underwent...
nerve-grafting surgery (4). In this study, general health-related QOL (HRQOL) in patients who underwent nerve-grafting radical prostatectomy (RP) was assessed with the Japanese version of Extended Prostate Cancer Index Composite (EPIC) (9) and the Medical Outcomes Study 8 Items Short Form Health Survey (SF-8™) with reference to those who underwent RP without any attempt to preserve potency.

PATIENTS AND METHODS

Patients

Radical retropubic prostatectomy (RRP) was carried out in 124 patients with localized prostate cancer at Kagawa University Hospital during the period between June 2001 and December 2006. Ninety-three patients underwent RRP without any attempt to preserve erectile function. Seven patients underwent RRP with unilateral or bilateral nerve-sparing procedure without nerve-grafting. Twenty-four patients underwent RRP with bilateral nerve-grafting (n = 8) or unilateral nerve-grafting combined with contralateral nerve-sparing (n = 16). Interposition of sural nerves was carried out according to the method described elsewhere (10) with some modifications (4). In this study, 93 patients without any attempt to preserve potency (designated as Group N) and 24 patients who underwent nerve-grafting RRP (designated as Group G) were encouraged to respond to self-descriptive assessment for their sexual function and HRQOL as described below. Patients in Group G who recovered potency were subclassified as Group Ga.

All patients in Group G were informed of the risk related to nerve-sparing and nerve-grafting surgery (i.e. relatively increasing blood loss, prolongation of operation time and pain or sensory deficit of the lateral aspects of the foot, neuroma formation at the nerve donor site) prior to obtaining written consent. Pre-operative erectile function was subjectively assessed using the validated questionnaires. These assessments proved that all Group G patients had an adequate ability to maintain spontaneous erection and intercourse.

Instruments for QOL Assessment

Cross-sectional analysis of disease-specific and general HRQOL was conducted with Japanese version of EPIC and the Japanese version of SF-8™, respectively. Validity and reliability of the Japanese version of both instruments have already been confirmed, which was described elsewhere (11). Each domain score of EPIC was scaled from 0 to 100, with higher scores representing better HRQOL status. SF-8 comprises eight subscales (PF, physical functioning; RP, role physical; BP, body pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; and MH, mental health) which are compatible with SF-36™. In this study, physical health component summary score (PCS) and mental health component summary score (MCS) were measured using the norm-based scoring (NBS) method, which was based on a large-scale population study conducted in Japan (12). The validity of Japanese version SF-8™ in early prostate cancer patients in Japan was already reported (13). Sexual function was assessed using questionnaires about erectile condition and the sexual domain of EPIC.

Every patient who agreed to participate in this study received a self-administrated questionnaire, an informed consent form and a prepaid envelope for returning the questionnaire.

Assessment of QOL

In this study, patients were assessed for sexual function, sexual bother, urinary function and urinary bother using EPIC, and general HRQOL using SF-8™ with horizontal analysis. Furthermore, we investigated the erectile condition and the capability of vaginal penetration using questionnaires.

Patients were divided into three groups based on an observation period after surgery (12–24, 25–48 and over 49 months) to analyze the differences in scores over time after surgery.

Statistics

We assessed differences in demographic characteristics (age and PSA value) and the EPIC and SF-8™ scores between the two groups with the use of the Mann–Whitney rank sum test. Scores for patient-reported outcomes, as measured by EPIC and SF-8™, were calculated as described previously (12,14). A value of $P < 0.05$ was considered to be statistical significant.

RESULTS

All patients (24 patients) in Group G responded for questionnaires, whereas in Group N, 64 of 93 patients (68.8%) responded for questionnaires. Overall response rate was 77.4%.

Follow-up periods for Groups G and N ranged from 13 to 79 months (median = 48 months). Until now, 9 patients in Group G (37.5%) and 29 patients in Group N (45.3%) have shown a biochemical failure, defined as a single PSA $> 0.4$ ng/ml or it did not decrease to $< 0.1$ ng/ml post-operatively 3 months later. Patients age ranged from 50 to 77 (average = 62.5) in Group G and 59–78 (average = 69.9) in Group N. The mean age of Group-G was significantly younger than that of Group N ($P < 0.001$). Initial PSA ranged from 2 to 22 ng/ml (median = 7.5 ng/ml) in Group G and 4.1–69.6 ng/ml (median = 10.6) in Group N ($P = 0.124$) as shown in Table 1. Seven patients in Group G (29.2%) have used the phosphodiesterase-5 inhibitors.
Erectile Function after Nerve-Grafting

Sixteen of 24 patients (66.7%) in Group G and 4 of 64 patients (6.3%) in Group N have been observed erection in this observation period. Vaginal penetration was observed in 12 (50%) and 2 patients (3.1%) in Groups G and N, respectively. Elapsed time to erection in each patient is shown in Fig. 1. The duration to erectile function recovery ranged from 1 to 24 months after surgery. There was no patient who recovered erectile function in 24 months later within follow-up periods in this study.

Comparison of Sexual Function and Sexual Bother after Surgery

Sexual function and sexual bother domains assessed with EPIC were compared between Groups Ga and N stratified with observation periods (Fig. 2a and b). According to the observation periods, patients were divided into three groups, i.e. 12–24, 25–48 and 49 months later after surgery. The patients in Group Ga demonstrated a high sexual function score compared with those in Group N (non-nerve-sparing/non-nerve-grafting group). (a) Sexual function assessed with Extended Prostate Cancer Index Composite (EPIC). The patients in Group Ga (nerve-grafting group) demonstrated a high sexual function score compared with those in Group N (non-nerve-sparing/non-nerve-grafting group). (b) Sexual bother assessed with EPIC. Sexual bother scores in Group Ga were lower than those in Group N throughout the observation periods.

Table 1. Patient profiles of the nerve-grafting group (Group G) and the non-nerve-sparing/non-nerve-grafting group (Group N)

<table>
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<th>Group G</th>
<th>Group N</th>
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<tr>
<td>No. of patients</td>
<td>24</td>
<td>64</td>
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<tr>
<td>Age (years)</td>
<td>62.5 (50–77)</td>
<td>69.9 (59–78)</td>
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<td>Follow-up (months)</td>
<td>52 (13–76)</td>
<td>40 (14–79)</td>
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<td>Initial PSA (ng/ml)</td>
<td>2–22 (med. 7.5)</td>
<td>4.1–69.6 (med. 10.6)</td>
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<tr>
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<tr>
<td>T2a</td>
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PSA, prostate-specific antigen; GS, Gleason score.
group, \(P = 0.012\). Also we compared sexual bother scores between Groups G and N, the same as the results of comparison between Groups Ga and N, sexual bother scores in Group G were lower than those in Group N throughout the observation periods. Statistical significance between Groups G and N was observed in 49 months later group (\(P\) value: 0.006) (data not shown).

**Comparison of Urinary Function and Urinary Bother after Surgery**

No significant differences in urinary function and urinary bother domain were observed between Groups Ga and N throughout the follow-up time in the current study (Fig. 3a and b).

**Comparison of Physical and Mental Health after Surgery**

The PCS in Group Ga was higher than that in Group N throughout the follow-up period with significant difference at 24–48 months after surgery (\(P = 0.043\)). There was no significant difference in each SF-8 subscale score (data not shown). On the other hand, no significant differences in MCS were observed in any observation periods between Groups Ga and N (Fig. 4a and b).

**DISCUSSION**

Nerve-grafting technique after resection of neuro-vascular bundles (NVBs) during RP is one of the promising resolutions for dilemma of cancer control and functional preservation. Relatively good outcomes from bilateral nerve-grafting have been demonstrated by several investigators (7,8,15). Sim et al. (8) reported that men who had undergone unilateral nerve-sparing prostatectomy with contralateral sural nerve interposition graft repair of a cut cavernosal nerve had a greater rate of return of erectile function than men undergoing unilateral nerve-sparing prostatectomy alone. On contrary, recent report showed that contralateral sural nerve interposition graft did not improve potency (16). However, the usefulness of contralateral nerve-grafting remained to be an elucidated issue. The aim of this study is to evaluate the implications of nerve-grafting on HRQOL including sexual function and its psychological burden in localized prostate cancer patients. EPIC was developed as a tool to measure prostate cancer-specific QOL and has been utilized in several HRQOL surveys (17–19). Nevertheless, there are few studies analyzing the impact of nerve-grafting during RP on HRQOL assessed with EPIC.

The first interesting result in this study was the dissociation of sexual function and sexual bother after nerve-grafting. The comparison between nerve-grafting and bilateral resection groups in sexual function showed positive
impact with nerve-grafting; however, negative impact was observed on sexual bother in nerve-grafting patients. Discrepancy between sexual function and sexual bother was observed in nerve-grafting patients. Similar tendency has already been found in a small cohort with shorter observation period (4). In the present study, the psychological burden relating sexual function impairment was confirmed. It can be explained that Group G patients, even if their erectile dysfunction was recovered, have not satisfied with their sexual function status. Careful informed consent prior to operation and persistent counseling during follow-up seem to be important in order to avoid patient’s excessive expectation for nerve-grafting surgery. Another explanation is that sexual desire and drive were low enough not to feel any bother feeling as to sexual function in Group N patients, because mean age of Group N was significantly higher than that of Group G.

It was also interesting that the physical and mental health evaluations were different between nerve-grafting and non-nerve-grafting groups assessed with SF-8™. To our knowledge, this is the first study to assess general HRQOL using SF-8™ after nerve-grafting procedure. The physical health scores in nerve-grafting patients assessed with SF-8™ were higher than those in bilateral nerve resection patients throughout the follow-up period. However, no significant differences were observed in mental health between both groups within any observation periods. There are several studies that evaluate the general HRQOL of patients who underwent nerve-grafting using SF-36. Our previous study showed in longitudinal study after nerve-grafting assessed with SF-36 that there was no difference in the change of general HRQOL over time between nerve-grafting and non-nerve-grafting patients (4). In the present study, the significant differences were observed in physical health between nerve-grafting and non-nerve-grafting groups. In comparison with our previous study, the number of cases was somewhat added in this study and median observation period was longer than that in previous report (29 vs. 48 months). In this study, we used SF-8 for general HRQOL assessment and not SF-36 as in the previous study. We assumed that for these reasons, the different results in general HRQOL were observed.

It still remains controversial whether nerve-sparing contributes to urinary continence after RP. Namiki et al. (5) reported the impact of nerve graft on sexual function and urinary function assessed with UCLA-PCI and concluded that the nerve-grafting procedure may contribute to the recovery of urinary function as well as sexual function after surgery. Singh et al. (20) also indicate the positive impact of unilateral interposition sural nerve-grafting on recovery of urinary function assessed with UCLA-PCI. Eastham et al. (21) showed that unilateral nerve preservation was associated with less post-operative incontinence than bilateral NVB resection. Continence after RP is multifactorial, and the mechanism or relationship between NVB and continence is under investigation. In this study, positive impact was observed on sexual function in nerve-grafting group; however, there was no significant difference in urinary function between nerve-grafting and non-nerve-grafting groups assessed with EPIC. The improvement in surgical technique may be one of the reasons of high urinary function or bother scores and there were no differences between both groups.

Another interesting result in this study is that the recovery of erectile function yielded by nerve-grafting may occur until 24 months after surgery. There was no patient who recovers the erectile function 24 months later. Kim et al. (6) reported the erectile outcomes after bilateral nerve-grafting during RP, the results were shown that tumescence was not reported until at least 5 months after surgery, slow improvement was observed from 8 to 12 months post-operatively and accelerated improvement was identified at 12–18 months post-operatively. Only minimal improvement was identified in the 18- to 24-month post-operative period. It is assumed that the erectile function recovery depends on nerve-grafting may occur within 24 months after surgery. Because the majority of nerve-grafting patients do not recover erectile function as early as urinary continence, patients should be well informed of the fact that it takes a substantial period to recover erectile function, even if the cavernous nerve can be reconstructed.

It is well known that a substantial proportion of patients with clinically localized prostate cancer who undergo radical surgery will experience a biochemical relapse. In the present study, there was no significant difference in biochemical failure rate between nerve-grafting and bilateral nerve resection groups. It therefore can be said that nerve-grafting technique did not compromise cancer control in this study, although the number of nerve-grafting patients is still small. Moreover, there were no serious complications during or after the operation depend on the nerve-grafting procedure in this study.

CONCLUSION

It was demonstrated that nerve-grafting procedure during RP contributes to improvement of sexual function and physical QOL. However, patients felt sexual burden in spite of substantial recovery of sexual function, because they expected to recover much more than they did. Careful informed consent prior to operation and persistent counseling during follow-up seem to be important in order to avoid patient’s excessive expectation for nerve-grafting surgery.

Conflict of interest statement

None declared.

References


