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Changes in the sexual function of male patients with rectal cancer over a two-year period from diagnosis to 24-month follow-up: A prospective, multi-center, cohort study

Running Title: Male sexual function and rectal cancer

Authorship

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The authors declare no conflicts of interest directly relevant to the content of this article.

Ethics

The study protocol was approved by the ethics committee of the Kyoto University and

each participating hospital. Written informed consent was obtained from all participants.

Availability of data

Data available on request due to privacy/ethical restrictions

Synopsis for Table of Contents: This prospective study was performed to analyze sexual function in males with rectal cancer from the point of diagnosis to 24 months postoperatively. Sexual function was found to deteriorate following surgery, with recovery occurring until 12 months post-surgery; however, it did not significantly improve from 12 months to 24 months postoperatively.

Abstract

Background and Objectives

This prospective study aimed to identify long-term changes in sexual function of men with rectal cancer from point of diagnosis to 24 months postoperatively.

Methods

Male patients undergoing laparoscopic rectal cancer surgery were prospectively enrolled. International Index of Erectile Function (IIEF) Questionnaire scores were collected at diagnosis; first follow-up; and 6, 12, and 24 months postoperatively. Missing values were managed via multiple imputations using the propensity score method. Paired t-tests were applied to examine changes in IIEF scores over time.

Results

This study analyzed 115 patients. For erectile function, there were no significant changes in scores from point of diagnosis to first treatment (9.4 vs 9.8 as mean scores, $P = 0.227$). Scores deteriorated postoperatively and recovered until 12 months post-surgery, but did not improve significantly from 12 months to 24 months post-surgery (8.7 vs 8.2 as mean scores, $P = 0.440$). This pattern of change was observed in all other domains: orgasmic function, sexual desire, orgasmic satisfaction, and overall satisfaction.

Conclusions

Sexual function was not influenced by a rectal cancer diagnosis. Sexual function deteriorated following surgery and recovered until 12 months post-surgery; however, it did not significantly improve from 12 months to 24 months postoperatively.

Key words

"rectal neoplasms", "male erectile dysfunction", "sexual dysfunction, phycological", "quality of life"

Introduction

Recent advancements in cancer therapies and the earlier detection of tumors has led to improvements in the prognosis of patients with rectal cancer [1–3]. As the survival rates of rectal cancer patients improve, increased attention has been placed on the patient's quality of life, which encompasses sexual, urinary, and anal function [4–7].

Postoperative sexual dysfunction is a well-known sequala of rectal cancer surgery, with a reported incidence rate of 31–75% [8]. The risk factors for sexual dysfunction include age, poor psychological status, advanced cancer, preoperative radiotherapy, intraoperative pelvic nerve injury, and abdominoperineal resection [4,9]. Since men usually have a narrow pelvis, they are considered to be at risk of intraoperative pelvic autonomic nerve injury and postoperative sexual dysfunction [10].

Most previous studies focused on the perioperative and postoperative sexual function of patients over a 12-month, postoperative, follow-up period [11–15]. However, no reports discussed intrinsic sexual function prior to a cancer diagnosis. Further, longitudinal reports regarding sexual dysfunction after surgery are limited [16–18]. In addition, some studies investigated sexual function using unvalidated scales [9].

This prospective study aimed to examine the sexual function of male patients with rectal cancer from the point of diagnosis of rectal cancer to 24 months after the surgery using one of the most commonly used validated scales, the International Index of Erectile

Function (IIEF) Questionnaire.

Materials and Methods

Patients

This was a prospective multi-center observational study conducted across eight leading hospitals affiliated with the Kyoto University Hospital. The study protocol was approved by the ethics committee of Kyoto University and each participating hospital. The eligibility criteria were as follows: 1) aged 20 to 80 years, 2) male patient, 3) resectable rectal cancer, 4) elective surgery, 5) Eastern Cooperative Oncology Group Performance Status Scale score 0 to 2, and 6) providing written informed consent. Consecutive patients that met the eligible criteria between October 2011 and December 2014 were included. Patients who underwent rectal surgery previously were excluded.

Quality of life assessment

IIEF scores were collected at five timepoints: when rectal cancer was diagnosed (T1), when the first treatment was administered (T2), 6 months postoperatively (T3), at the 12-month postoperative follow-up (T4), and during the 24-month postoperative follow-up (T5). T1 was set as the baseline status of each patient in this study. The first treatment at T2 varied depending on the patient: preoperative chemotherapy, preoperative chemoradiotherapy, or surgery.

The IIEF is a validated, multidimensional, self-administered questionnaire comprising of five domains: erectile function (EF), orgasmic function (OF), intercourse satisfaction (IS), sexual desire (SD), and overall satisfaction (OS). Each domain has a maximum score of 30, 10, 10, 15, and 10, respectively, and a minimum score of 1, 0, 2, 0, and 2, respectively [19]. Additional quality of life scores such as the International Prostate Symptom score for urinary function [20] and the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire for global quality of life [21] were also evaluated and used to adjust for covariates.

Statistical analysis

Changes in the scores of each IIEF domain were statistically analyzed over time. Analysis sets were defined separately for each domain. Patients who completed the questionnaire at T1 and T2 were included in the analysis set. Patients who did not answer any questionnaire from T3 to T5 were excluded. If the missing IIEF scores at T3, T4, and T5 exceeded 5%, multiple imputation was conducted using the propensity score method in order to account for the missing variables [22]. Propensity scores, which indicated the probability of a missing observation, were calculated for T3, T4, and T5 based on the following covariates: age, pStage, Eastern Cooperative Oncology Group Performance Status Scale score, intraoperative pelvic nerve injury, the health-

related quality of life scores of the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire and the International Prostate Symptom Score at that timepoint, and all previous IIEF scores of that domain. Subgroup analyses based on age (<70 vs ≥70 years), preoperative treatment (with vs without preoperative treatment), and the EF domain score at baseline (<10 vs ≥10) were performed. The paired t-test was used to test the association between the IIEF scores at different timepoints. A *P*-value of less than 0.05 was defined as statistically significant. All statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA), and multiple imputation for missing values was conducted using SOLAS 4.02 (Statistical Solutions Ltd, Cork, Ireland).

Results

Patient characteristics

In total, 116 male patients were enrolled in this study; however, one patient was excluded because his tumor was located in the sigmoid colon. Clinical and surgical findings are shown in Table 1. The median age of patients was 64 (range, 36–79) years. Tumors were located in the upper rectum in 60 cases (52.2%) and in the lower rectum in 55 cases (47.8%). Fifty-five patients (47.8%) received preoperative chemotherapy and two (1.7%) received preoperative chemoradiotherapy. Anterior resection was performed

in nine patients (7.8%), low anterior resection was performed in 86 patients (74.8%), intersphincteric resection was performed in four patients (3.5%), and abdominoperineal resection was performed in 16 patients (13.9%). All surgical procedures were performed laparoscopically. Pathological stages were 0 in 10 patients (8.7%), one in 40 patients (34.8%), two in 22 patients (19.1%), three in 30 patients (26.1%), and four in 13 patients (11.3%). The number of analysis sets in each domain was 78 (EF), 85 (OF), 81 (SD), 82 (IS), and 73 (OS) (Supplemental figure).

IIEF Score Variations

Initially, changes in scores between adjacent timepoints were examined in order to evaluate the short-term tendency. It was considered that the change between T1 and T2 reflected the impact of notifying the patient of their rectal cancer diagnosis. The difference between T1 and T5 was assessed in order to examine whether the long-term IIEF score differed from the initial status. Finally, the difference between T3 and T5 was assessed in order to examine the long-term recovery. The rate of missing values at T3, T4, and T5 ranged from 7.3% to 14.1%, which was higher than the abovementioned criteria, in all 5 domains. Multiple imputation for missing values was conducted in all domains.

Erectile function

Seventy-eight patients were included in this analysis. The mean scores at T1, T2, T3, T4, and T5 were 9.4, 9.8, 8.1, 8.7, and 8.2, respectively (Figure 1). The score decreased at T3 and then increased slightly at T4. There were no significant differences in the changes between T1 and T2 ($P = 0.227$), T2 and T3 ($P = 0.174$), T3 and T4 ($P = 0.517$), and T4 and T5 ($P = 0.440$). No significant differences were observed between T1 and T5 ($P = 0.205$) and T3 and T5 ($P = 0.966$).

Orgasmic function

Eighty-five patients were included in this analysis. The mean scores at T1, T2, T3, T4, and T5 were 3.4, 3.4, 2.5, 2.7, and 2.7, respectively (Figure 1). There was no significant change in the scores between T1 and T2 ($P = 0.825$). The score decreased significantly from T2 to T3 ($P = 0.048$). The scores slightly increased after the surgery; yet, no significant differences were observed between T3 and T4 ($P = 0.731$) and T4 and T5 (P = 0.566). No significant differences were observed between T1 and T5 ($P = 0.199$) and T3 and T5 ($P = 0.404$).

Sexual desire

Eighty-one patients were included in this analysis. The mean scores of T1, T2, T3, T4, and T5 were 4.0, 3.9, 3.6, 4.0, and 3.8, respectively (Figure 1). There was no significant difference in the scores between T1 and T2 ($P = 0.369$). The score decreased from T2 to

T3 (P = 0.016) and then significantly increased from T3 to T4 (P = 0.017). The score decreased from T4 to T5, but changes in the scores were not significant (P = 0.551). No significant changes in the scores were observed between T1 and T5 (P = 0.186) and T3 and T5 (P = 0.332).

Intercourse satisfaction

Eighty-two patients were included in the analysis for this domain. The mean scores of each timepoint were 2.6, 2.7, 2.2, 2.6, and 1.9, respectively (Figure 1). There were no significant differences between T1 and T2 (P = 0.577) and T2 and T3 *(*P = 0.311). After surgery, the score slightly increased from T3 to T4 (P = 0.215); yet, it decreased from T4 to T5 (P = 0.040). There were no significant differences in the scores between T1 and T5 (P = 0.078) and T3 and T5 (P = 0.601).

Overall satisfaction

Seventy-three patients were included in this analysis. The mean scores of T1, T2, T3, T4, and T5 were 6.0, 6.1, 5.8, 5.9, and 5.9, respectively (Figure 1). There were no significant differences in the scores between T1 and T2 (P = 0.239), T2 and T3 (P = 0.158), T3 and T4 (P = 0.554), and T4 and T5 (P = 0.616). No significant differences were observed between T1 and T5 (P =0.595) and T3 and T5 (P = 0.204).

Subgroup analysis

The numbers of the patients in the non-elderly group (<70 years) ranged from 58 to 62 across all domains, and those in the elderly group (≥70 years) ranged from 15 to 21. The non-elderly group had higher scores in all domains except for OS. The mean score of the elderly group in the OS domain appeared slightly higher than that of the non-elderly group over the study period (Figure 2).

The number of patients in the preoperative treatment group ranged from 34 to 45 across all domains, and those in the non-pre-treatment group ranged from 37 to 38. The pre-treatment group demonstrated similar scores to the non-pre-treatment group until 12 months postoperative in all domains; however, the scores of the non-pre-treatment group recovered after 12 months postoperative in EF and IS domains, whereas the scores of the pre-treatment group did not (Figure 3).

The number of patients with high EF baseline scores (≥10) ranged from 21 to 22 across all domains, and those with low EF baseline scores (<10) ranged from 51 to 60. The high EF group had higher scores in comparison to the low EF group in all domains. The difference in scores between the high EF group and low EF group was especially small in the OS domain compared to that in other domains (Figure 4).

Discussion

This prospective observational study investigated male sexual function from the time of

diagnosis of rectal cancer until 24 months after the surgery. No significant differences were observed between the IIEF scores before and after diagnosis. The IIEF scores decreased following surgery and then recovered to some extent until 12 months postoperatively. The scores did not significantly increase from 12 months to 24 months after the surgery. This pattern of change in the scores was observed in all domains.

Sexual function following rectal cancer surgery is mostly examined in retrospective or cross-sectional studies [9]. When collecting more accurate data, prospective studies are preferable; thus, this investigation was based on prospective research. Previous prospective studies reported that the IIEF scores decreased following surgery and then recovered to some extent until 12 months after the surgery [10,18]. The findings of this investigation were consistent with the results of prior studies and contributed to the literature by demonstrating the changes in scores over an extended study period (i.e. from diagnosis to 24 months after the surgery).

Our previous study assessed the sexual function of male patients after total mesorectal resection and at 3, 6, and 12 months after surgery [23]. Some patients experienced a remarkably high recovery of EF more than 3 months after the surgery, regardless of intraoperative/perioperative nerve preservation. It was considered that the psychological effects of the cancer diagnosis may have temporarily worsened sexual function;

however, data on sexual function at diagnosis was not collected. Thus, this study investigated the impact of delivering a diagnosis of rectal cancer on sexual function. No such significant impact was shown in this study.

This study also focused on the long-term sexual function of patients who had undergone laparoscopic rectal cancer surgery. Previous studies have analyzed sexual function up to 12 months after surgery. During this period, patients with advanced disease often received adjuvant chemotherapy. It was, therefore, hypothesized that sexual function could continue to recover after completing adjuvant chemotherapy. Sexual function was assessed up to 24 months after surgery; however, mean IIEF scores did not increase from 12 months to 24 months postoperatively in any domain. This study focused on whether scores changed before and after the diagnosis and whether the score changed more than 12 months after surgery. Significant changes were not observed in either period. Thus, it may be unnecessary to investigate the IIEF scores before diagnosis and 24 months after the surgery in future studies.

Many studies reported that aging is a risk factor for postoperative sexual dysfunction; yet, some studies reported that age did not have a considerable impact on sexual dysfunction [24–26]. Aging progressively affects sexual function to the extent that every additional year of age causes a decline in sexual function. Therefore, a subgroup

analysis based on age was conducted, which revealed that elderly patients had lower overall sexual function than non-elderly patients; however, the impact of rectal cancer treatment did not differ between elderly and non-elderly patients. Another subgroup analysis based on the effects of preoperative chemotherapy was conducted. The scores of the pre-treatment group and non-pre-treatment group in the subgroup analysis were similar at 6 months after surgery; yet, the scores of the pre-treatment group had decreased more than that of the non-pre-treatment group following the 6-month measurement. The difference between the two groups became greater over time. Preoperative chemotherapy was considered to be a potential risk factor for long-term sexual dysfunction. The preoperative chemotherapy administered to patients in our cohort was mFOLFOX6 (5-Fluorouracil, leucovorin, and oxaliplatin). The neurotoxicity of oxaliplatin may cause damage to the pelvic plexus and affect long-term sexual function [27]. Finally, a subgroup analysis based on the EF score at diagnosis was conducted. Contrary to the hypothesis, the score of the low EF group did not increase dramatically after surgery.

This study collected subjective data prospectively and managed the missing values using multiple imputation. Additionally, this study evaluated the sexual function of male rectal cancer patients at numerous timepoints from diagnosis to 24 months

postoperatively.

This study had several limitations. Only a small number of patients who underwent preoperative radiotherapy were included. Receiving radiation therapies preoperatively can affect postoperative sexual dysfunction. Hence, the results of the current study should be carefully considered for patients undergoing radiotherapy. In addition, the rate of missing variables was high. The rate of missing variables should ideally be reduced by an appropriate study design; however, even a well-designed study cannot eliminate the problems caused by missing data, especially when examining sensitive patient reported outcomes [28]. Multiple imputation was used in this study to limit bias.

Conclusions

In conclusion, male sexual function was not influenced by the notification of a rectal cancer diagnosis. Sexual function recovered after 12 months following surgery but remained constant between the timepoints of 12 months and 24 months after surgery.

Acknowledgments

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Acronyms:

International Index of Erectile Function, IIEF; Erectile function, EF; Orgasmic function,

OF; Intercourse satisfaction, IS; Sexual desire, SD; Overall satisfaction, OS

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Figure legends

Fig. 1 Changes in the International Index of Erectile Function scores of each domain

Higher scores indicate better levels of functioning. Filled circles indicate mean scores. Error bars indicate 95% confidence intervals.

Fig. 2 Subgroup analysis: elderly (≥ 70 years) vs non-elderly (<70 years) patients

Higher scores indicate better levels of functioning. Filled triangles indicate mean scores of elderly patients, and filled circles indicate those of non-elderly patients. Error bars indicate 95% confidence intervals.

Fig. 3 Subgroup analysis: with and without preoperative treatment

Higher scores indicate better levels of functioning. Filled circles indicate mean scores of patients undergoing preoperative treatment, and filled triangles indicate those of patients who did not undergo preoperative treatment. Error bars indicate 95% confidence intervals.

Fig. 4 Subgroup analysis: low (< 10) vs high (≥10) erectile function score at baseline

Higher scores indicate better levels of functioning. Filled circles indicate mean scores of the low-score patients, and filled triangles indicate those of high-score patients. Error bars indicate 95% confidence intervals.

Supplemental figure Flowchart of the study

EF: erectile function, OF: orgasmic function, SD: sexual desire, IS: intercourse satisfaction, OS: overall satisfaction, T1: timepoint when rectal cancer was diagnosed, T2: timepoint when the first treatment was administered, T3: timepoint of the 6-month postoperative follow-up, T4: timepoint of the 12-month postoperative follow-up, T5:

timepoint of the 24-month postoperative follow-up

Table 1. Characteristic of participants (N=115)

Variable	n	%
Age, y[a]	64 (36-79)	
Sex		
Men	115	100.0
ECOG-PS		
0	74	64.3
1	24	20.9
2	17	14.8
3	0	0.0
Tumor location		
Upper Rectum	60	52.2
Lower Rectum	55	47.8
Preoperative treatment		
Chemotherapy	55	47.8
Chemoradiotherapy	2	1.7
Surgical approach		
Laparoscopy	115	100.0
Type of surgery		
Anterior resection	9	7.8
Low anterior resection	86	74.8
Intersphincteric resection	4	3.5
Abnominoperineal resection	16	13.9
Lateral lymph node dissection	6	5.2
Autonomic nerve injury	11	9.6
Tumor depth		
pT0 to pTis	10	8.7
pT1	15	13.0
pT2	30	26.1
pT3	46	40.0
pT4	14	12.2
Nodal stage		
pN+	40	34.8
pStage		
0	10	8.7
I	40	34.8
II	22	19.1
III	30	26.1
IV	13	11.3
Overall survival, days[b]	738 (734-742)	

[a]Values are median (range)

[b]Values are mean (95% confidence interval)

Figure 1

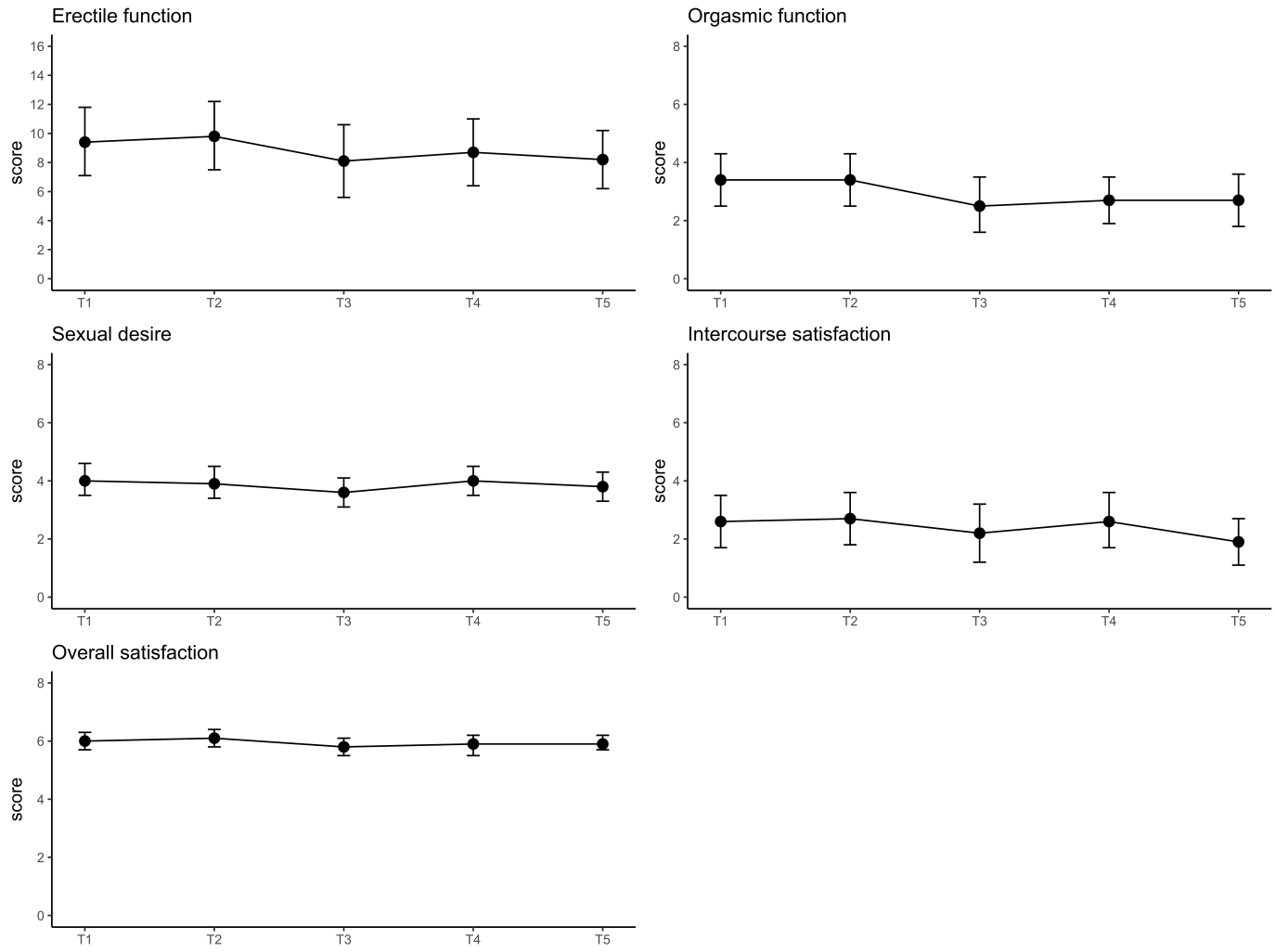

Erectile function
Orgasmic function
Sexual desire
Intercourse satisfaction
Overall satisfaction
score
T1
T2
T3
T4
T5

Figure 2

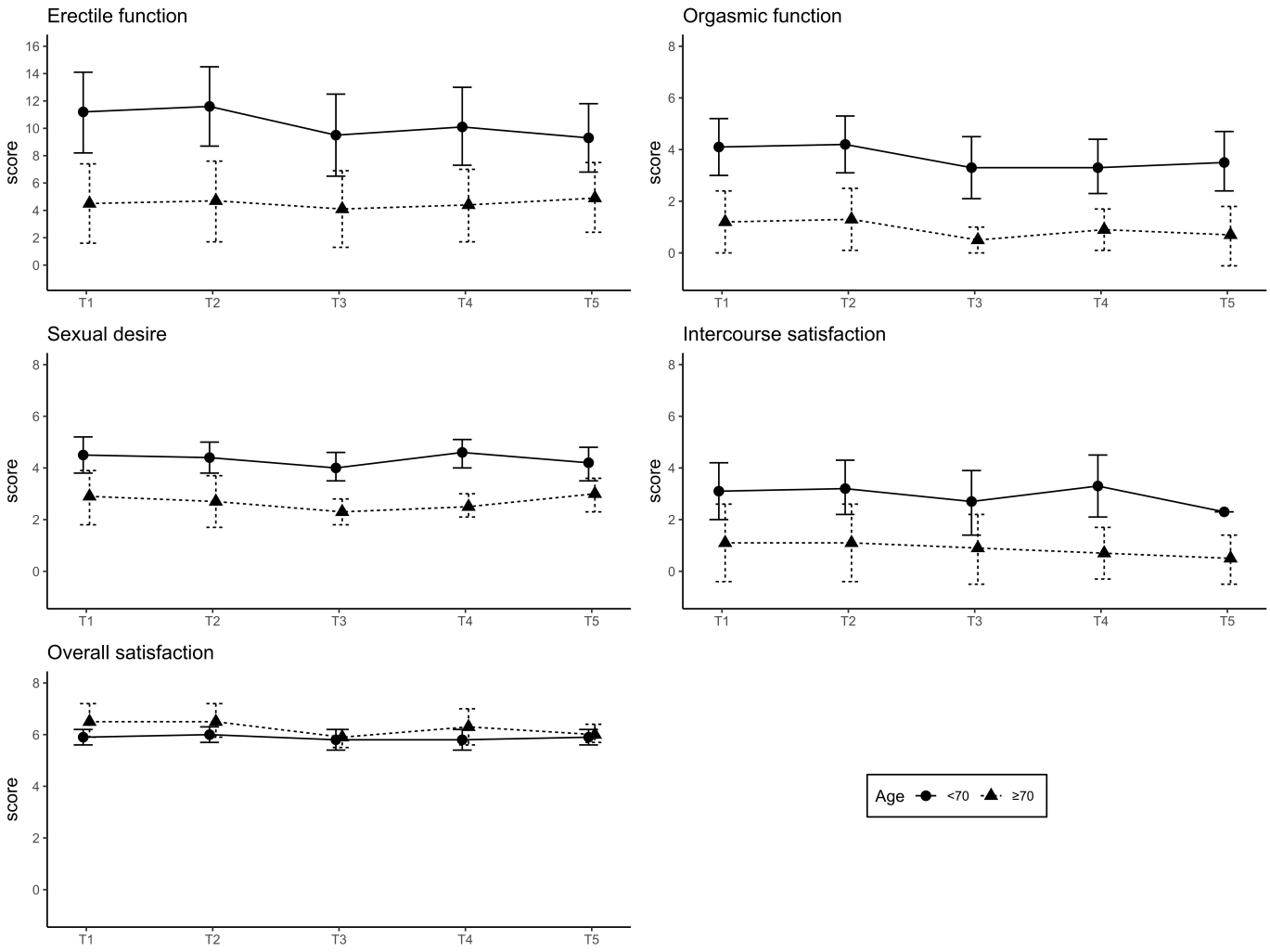

Erectile function
Orgasmic function
Sexual desire
Intercourse satisfaction
Overall satisfaction
score
T1
T2
T3
T4
T5
Age
<70
≥70

Figure 3

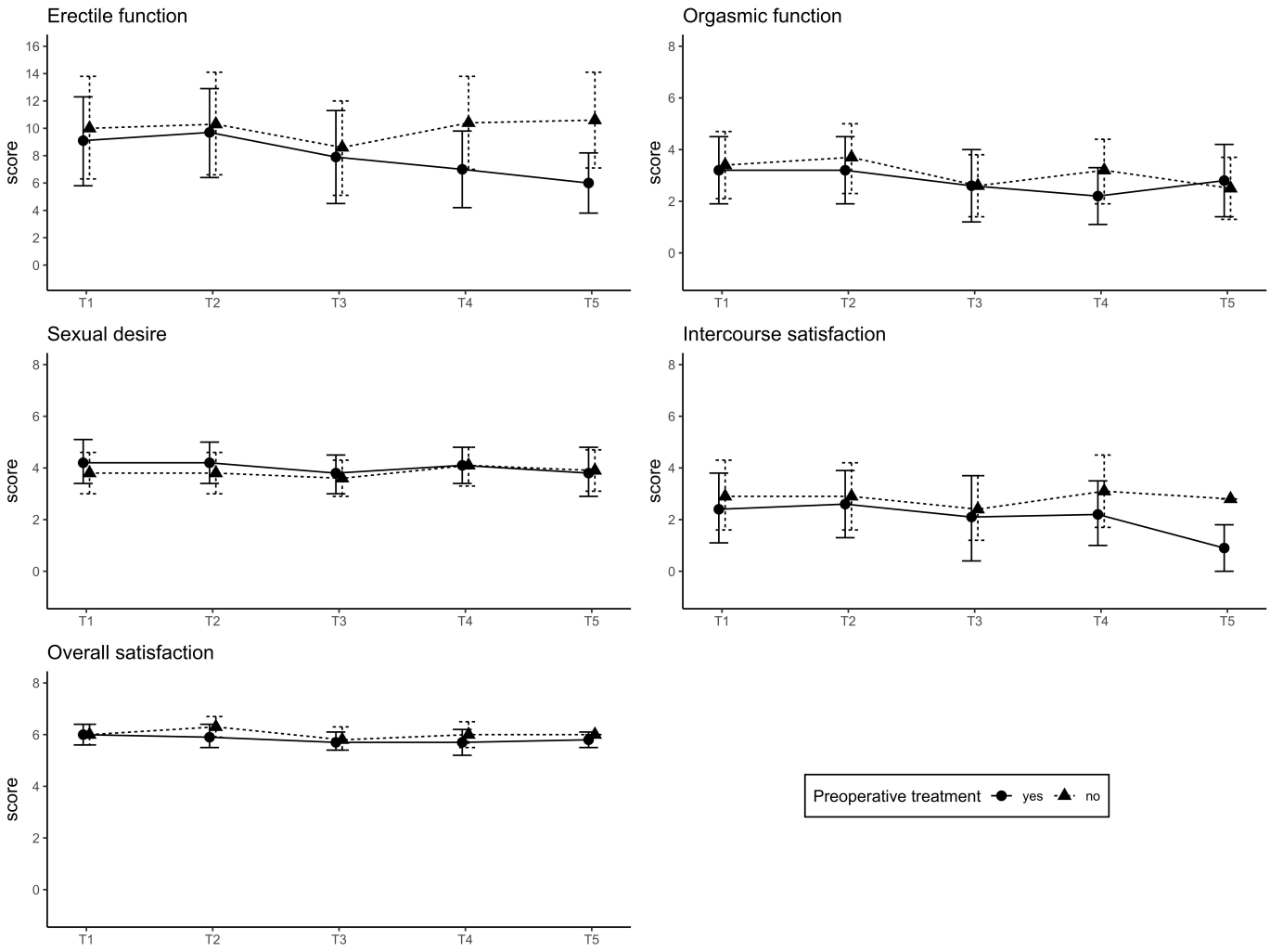
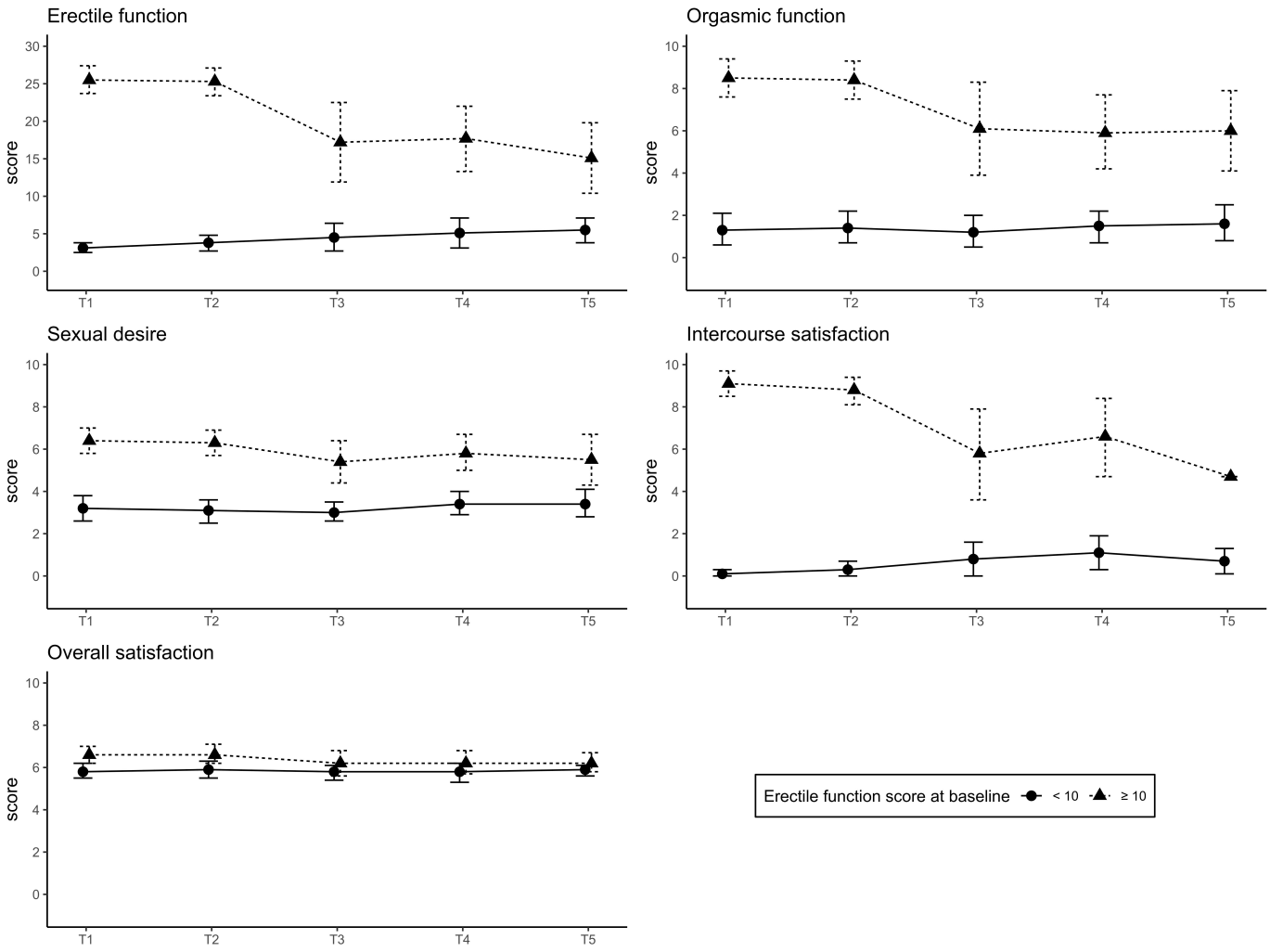

Erectile function
Orgasmic function
Sexual desire
Intercourse satisfaction
Overall satisfaction
score
T1
T2
T3
T4
T5
Preoperative treatment
yes
no

Figure 4


Erectile function
Orgasmic function
Sexual desire
Intercourse satisfaction
Overall satisfaction
score
T1
T2
T3
T4
T5
Erectile function score at baseline
< 10
≥ 10

Supplemental figure