Laparoscopic total mesorectal excision for rectal cancer
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MALE SEXUAL FUNCTIONING AND
LOWER URINARY TRACT SYMPTOMS AFTER
LAPAROSCOPIC TOTAL MESORECTAL EXCISION;
A PROSPECTIVE STUDY.

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Submitted
Abstract

Background: In this prospective study we investigated sexual functioning and the prevalence of lower urinary tract symptoms (LUTS) in male patients with rectal cancer after short-term radiotherapy and laparoscopic total mesorectal excision (LTME) by physical and psychological measurements.

Methods: Sexual functioning and LUTS were assessed by questionnaires (International Index of Erectile Function (IEFF), International Prostate Symptom Score (IPSS)), pharamaco duplex-ultrasonography of the cavernous arterial blood flow and nocturnal penile tumescence and rigidity monitoring (NPTR). All investigations were done before start of preoperative radiotherapy and 15 months after surgery.

Results: Nine patients (mean age 60 years) participated. Erectile function was maintained in 71%, and ejaculation function in 89%. Compared with pre-operative scores on the IEFF, patients reported a significant deterioration in intercourse satisfaction only (7.9 vs 10.3, p=0.042).

The NPRT parameters (duration of erectile episodes, duration of tip rigidity ≥ 60%, tumescence activity units of the tip and TAU base) had decreased. Patients reported a deterioration in micturition frequency (2.0 vs 1.0, p=0.034) and quality of life due to urinary symptoms (8.0 vs 1.8, p=0.018).

Conclusion: Fifteen months after short-term radiotherapy and LTME in males with rectal cancer, objectively assessed sexual dysfunction was considerable, but overall sexual satisfaction had not changed.
Introduction

Erectile dysfunction (ED), ejaculatory dysfunction (EJD) and lower urinary tract symptoms (LUTS) are well known problems after open total mesorectal excision (OTME) for rectal cancer. Besides iatrogenic surgical injury to pelvic autonomic nerves, preoperative radiotherapy may induce as well as nerve damage\(^1\,^2\).

Laparoscopic total mesorectal excision (LTME) offers short-term advantages, like earlier return of normal diet, less postoperative pain, less narcotic use and shorter hospital stay\(^3\,^4\,^5\). Magnification enhances excellent exposure of the pelvic cavity and facilitates sharp dissection of the lateral, anterior, and presacral spaces, all being autonomic nerve locations. However, the technical demands of LTME may just predispose to nerve injury\(^6\).

Until now, very little is known concerning sexual functioning and lower urinary tract symptoms after LTME on the long term\(^6\,^7\). A retrospective, questionnaire based study showed an ED incidence of 47% and an EJD incidence of 40%\(^7\). Another questionnaire based study showed a nonsignificant trend towards more sexual dysfunction after LTME\(^6\). These two studies showed no differences with regard to LUTS after LTME or OTME.

In this prospective study, we assessed sexual functioning by an international validated questionnaire, the International Index of Erectile Function (IIEF), repeated pharmaco duplex-ultrasonographic investigations of the cavernous arteries and nocturnal penile tumescence and rigidity (NPTR) monitoring. Lower urinary tract symptoms were assessed by the International Prostate Symptom Score (IPSS).

Patients and methods

The study was performed between July 2003 and January 2006. All patients underwent an elective LTME at Medical Centre Leeuwarden\(^8\). The patients were included if they were heterosexually active and if the LTME had a curative intention.

Patient with advanced T3 (cT3b) or T4 carcinoma diagnosed on magnetic resonance imaging (MRI) were excluded. A tumour-free circumferential resection margin of at least 2.0 mm is defined as a R0-resection\(^9\) and can be predicted with a high degree of certainty when the distance on MRI is at least 6.0 mm\(^10\). An advanced T3 tumour was defined when the MRI distance was less than 6.0 mm. According to the national Dutch protocol all patients received a short preoperative course of 5 x 5 Gy radiotherapy.

The above mentioned investigations (questionnaires, duplex ultrasonography of the cavernous arterial blood flow at rest and after intracavernous injection of vasoactive substances, and nocturnal erections monitoring) were done just before the start of the preoperative radiotherapy and at fifteen months follow-up. At that time the late side-effects of radiotherapy and the natural restore of both psychological as surgical factors reach their plateau phase.

The study was approved by the Committee on Medical Research Ethics and all patients provided written informed consent.
Questionnaires

The patients completed two questionnaires: the International Index of Erectile Function (IIEF)\textsuperscript{11} and the International Prostate Symptom Score (IPSS)\textsuperscript{12}.

The IIEF was used to assess male sexual function in short. In this questionnaire fifteen items are checked, including erectile frequency, erection firmness, penetration ability, maintenance frequency, maintenance ability, intercourse frequency, intercourse satisfaction, intercourse enjoyment, ejaculation frequency, orgasm frequency, desire frequency, desire level, overall satisfaction, relationship satisfaction, and erection evidence. The IIEF can only been used for heterosexual males.

The scoring systems are from 0 to 5 (0: not at all, 1: less than 1 time in 5, 2: less than half the time, 3: about half the time, 4: more than half the time and 5: almost always) on the first 10 items and from 1 to 5 (1, very low; 2, low/ a few; 3, moderate; 4 most/high; very high/ almost always) on the last 5 items.

The IIEF is subdivided into 5 response domains (erectile function, orgasmic function, intercourse satisfaction, sexual desire, overall satisfaction). The domain scores are computed by adding the scores of individual items in each domain.

Complete ED is defined as an erectile function domain score < 10 and partial ED as a score < 17 but ≥10.

The international validated IPSS was used to assess bladder function. The IPSS is subdivided into 7 items: which include incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. The scoring system is based on a 0 to 5 scale, as follows: 0, not at all, 1 less than 1 time in 5, 2, less than half the time, 3 about half the time, 4, more than half the time; and 5, almost always. The total score is calculated by adding the item scores. Quality of life is also classified on the IPSS and ranges from delighted to terrible 0: delighted, 1: pleased, 2: mostly satisfied, 3: mixed about equally satisfied and dissatisfied, 4: mostly dissatisfied, 5: unhappy, 6: terrible).

Duplex-ultrasonography of the cavernous arteries

Peak flow velocities within the cavernous arteries were measured by duplex-ultrasonography before and at one, five, 10, and 15 minutes after injection of 0.25 ml Androskat\textsuperscript{®} (3.75 mgr papaverinehydrochloride plus 0.125 mgr phentolamine; Byk, Zwanenburg, The Netherlands). All investigations were performed by the same examiner, using a 5 MHz pulsed Doppler linear array transducer with B-mode colour images and pulsed wave doppler. The Doppler angle correction-cursor was adjusted to match the correct axis of flow. The average systolic peak flow of left and right cavernosal artery was used for further analysis.

Nocturnal penile tumescence and rigidity (NPTR) measurements

To assess erectile function nocturnal penile tumescence and rigidity (NPTR) were measured at home during two consecutive nights using the RigiScan (RigiScan\textsuperscript{®}, Dacomed Corp, Minneapolis, USA). The RigiScan recorded changes in penile tumescence and radial rigidity during the whole duration of each night. At the end of the study data were analysed with the new Rigiscan Plus\textsuperscript{®} software (version 4.0, Urohealth Co, USA). Analysis of the recordings was focused on the following
parameters: 1) number of erectile episodes, 2) duration of erectile episodes, 3) duration of erectile episode with ≥ 60% tip rigidity\textsuperscript{13}, and 4) rigidity activity units (RAU) and tumescence activity units (TAU) of both tip and base. These two units, TAU and RAU, were developed by Urohealth Co to facilitate the interpretation of the time-dependent nature of rigidity and tumescence. RAU is a time-intensity measurement that represents the area under the rigidity curve during a qualified event. The Rigidity Activity Unit is calculated by summing the rigidity values for the duration of a qualified event and dividing by 2 times 100. The value 2 is used because there are two rigidity samples taken per minute, and the value 100 is used to remove the percent. TAU is a time-intensity measurement that represents the area under the tumescence curve above the baseline during qualified events. It is proportional to the percent increase in tumescence over baseline. The Tumescence Activity Unit is calculated by summing the tumescence values minus the baseline tumescence and dividing by 4 times the baseline. The value 4 is used in the calculation because there are four tumescence samples taken per minute.

RAU and TAU for both tip and base measurements are calculated and evaluated separately\textsuperscript{14}.

Statistics
The IIEF and IPSS questionnaires were scored according to the guidelines. Scale scores are presented as means with standard deviations. Differences in systolic blood flow velocities were analyzed with the Wilcoxon signed rank test, comparing postoperative score to preoperative score. The comparison of questionnaires and NPTR before and after LTME was also assessed by the Wilcoxon signed rank test.

Erectile dysfunction scored on IIEF was compared with parameters of NPTR testing using Mann-Whitney U test. Differences were considered to be statistically significant when p < 0.05.

Results
Nine patients were included. Table 1 shows the characteristics of the patients, their treatments and histopathological tumour staging.

After treatment eight out of the nine patients (88%) regained their sexual activities. According to the IIEF, two of the nine patients (22%) already demonstrated complete ED in the pre-treatment phase (defined as domain score <10), none demonstrated partial ED (a score <17 and ≥ 10) in this phase. According to the IIEF scores erectile function was maintained in 5 out of the 7 (71%) patients at 15 months follow-up, so there were 2 “new” patients with ED. However, the differences between preoperative and postoperative scores were not significant (Table 2).

Only one of the nine patients was unable to ejaculate, but that problem already existed preoperatively. Intercourse satisfaction significantly had decreased from 10.3 preoperatively to 7.9 postoperatively (p=0.042).

Total mean IPSS score was 7.7 ± 5.9 preoperatively versus 10.9 ± 5.1 postoperatively (p>0.05) (Table 3). Quality of life due to urinary symptoms significantly decreased after LTME (p=0.018). With regard to specific symptoms, only frequency
significantly worsened (p=0.034). All other IPSS scores (incomplete bladder emptying, intermittency, urgency, weak stream, straining, and nocturia) did not show significant changes at 15 months follow-up (Table 3).

No statistical significant differences were observed comparing the individual systolic peak flow velocities pre- and postoperatively.

With regard to the NPRT parameters at 15 months follow-up the duration of
erectile episodes (56 vs 87, p=0.012), duration of tip rigidity ≥ 60% (14 vs 31, p=0.036), tumescence activity units of the tip (TAU tip 11 vs 28, p=0.012) and TAU base (18 vs 33, p=0.017) were all decreased (Table 4). Figure 1 shows an example of NPTR measures before and after treatment.

Comparison of the IIEF erectile domain scores with NPTR parameters shows no significant differences (p>0.05).

<table>
<thead>
<tr>
<th></th>
<th>Preoperative mean</th>
<th>Standard Deviation</th>
<th>Postoperative mean</th>
<th>Standard Deviation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete emptying</td>
<td>0.6</td>
<td>0.9</td>
<td>0.7</td>
<td>0.7</td>
<td>0.739</td>
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<td>Frequency</td>
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<td>1.3</td>
<td>2.0</td>
<td>1.5</td>
<td><strong>0.034</strong></td>
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<td>Intermittency</td>
<td>1.1</td>
<td>1.3</td>
<td>1.7</td>
<td>1.7</td>
<td>0.262</td>
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<td>Urgency</td>
<td>0.4</td>
<td>0.7</td>
<td>0.6</td>
<td>1.0</td>
<td>0.914</td>
</tr>
<tr>
<td>Weak stream</td>
<td>1.3</td>
<td>1.7</td>
<td>1.6</td>
<td>1.2</td>
<td>0.726</td>
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<tr>
<td>Straining</td>
<td>1.6</td>
<td>2.0</td>
<td>0.9</td>
<td>1.6</td>
<td>0.336</td>
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<td>Nocturia</td>
<td>1.7</td>
<td>1.0</td>
<td>2.0</td>
<td>1.4</td>
<td>0.618</td>
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<td>Total IPSS</td>
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<td>5.9</td>
<td>10.9</td>
<td>5.1</td>
<td>0.312</td>
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<td>Quality of life due to Urinary symptoms</td>
<td>1.8</td>
<td>1.0</td>
<td>8.0</td>
<td>5.1</td>
<td><strong>0.018</strong></td>
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</tbody>
</table>

SD: standard deviation

<table>
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<tr>
<th></th>
<th>Preoperative mean</th>
<th>Standard Deviation</th>
<th>Postoperative mean</th>
<th>Standard Deviation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of erectile episodes</td>
<td>3.3</td>
<td>1.6</td>
<td>2.6</td>
<td>1.2</td>
<td>0.160</td>
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<td>Duration of erectile episodes (min)</td>
<td>87</td>
<td>52</td>
<td>56</td>
<td>52</td>
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<tr>
<td>Duration of tip rigidity ≥ 60%</td>
<td>31</td>
<td>26</td>
<td>14</td>
<td>14</td>
<td><strong>0.036</strong></td>
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<td>RAU tip</td>
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<td>18</td>
<td>17</td>
<td>18</td>
<td>0.263</td>
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<tr>
<td>TAU tip</td>
<td>28</td>
<td>27</td>
<td>11</td>
<td>15</td>
<td><strong>0.012</strong></td>
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<tr>
<td>RAU base</td>
<td>32</td>
<td>27</td>
<td>33</td>
<td>28</td>
<td>1.000</td>
</tr>
<tr>
<td>TAU base</td>
<td>33</td>
<td>26</td>
<td>18</td>
<td>20</td>
<td><strong>0.017</strong></td>
</tr>
</tbody>
</table>

SD: standard deviation
Discussion

Radiotherapy and TME can compromise both the vascular and the nervous system in the lower pelvis. To our knowledge this is the first prospective study assessing both somatic and psychological factors determining sexual functioning of male patients after LTME. In our view duplex ultrasonography of the cavernous arteries, NPTR and validated questionnaires offer the opportunity for a better understanding of specific causes of sexual dysfunction in these patients.

Fifteen months after treatment intercourse satisfaction, frequency of micturition and quality of life due to urinary symptoms were deteriorated. Although nearly all patients (8 out of 9) had resumed sexual activities we observed significant decrease of NPTR parameters. These findings suggest a partial parasympathetic nerve injury,

Figure 1. Rigiscan traces of nocturnal erections. A: nocturnal erections before LTME B: nocturnal erections after LTME.
corresponding with the results in patients with rectal cancer or inflammatory bowel disease undergoing open surgery\textsuperscript{15}.

The pelvic parasympathetic nerves may be damaged at a number of points during rectal surgery. Excessive traction on the rectum during posterior mobilization can result in neuropraxia or even avulsion of sacral roots 2, 3 and 4. The pelvic plexus itself is most at risk during lateral dissection at the level of the middle haemorrhoidal vessels, to which it is intimately related. In abdominoperineal resection neural injury may also occur during the perineal phase. After division of the rectourethralis muscle, the neurovascular bundles are visible in association with the lateral prostatic fascia and are vulnerable to trauma by excessive dissection or diathermy anterolateral to the rectum. Although the locations of the nerves are known, it is a misunderstanding that these tiny micro-sized nerves can be visualized directly intraoperatively. Even with the aid of an operation microscope this is seldom possible.

The concept of nerve mapping and possible decreased ED rates has been intriguing. If the nerves could really be identified intraoperatively by direct stimulation, they might be more likely to be preserved. Unfortunately, the applicability of this concept has fallen short of expectations, especially in urological surgery. For example, unlike in the dog and rat, the human penis does not respond reproducibly to electrical stimulation of the cavernous nerves\textsuperscript{16}. Although some men demonstrate a mild tumescence with pelvic nerve electrostimulation, others actually have a detumescence or no response. On the other hand a recent study shows that during OTME intraoperative nerve-stimulating may facilitate nerve identification and preservation\textsuperscript{17}.

According to prospective studies ED and EJD rates after OTME respectively vary from 4 to 28 % and 5 to 8\textsuperscript{18-21}, so the results with respect to postoperative sexual functioning vary widely between surgeons and institutions.

According to the IIEF scores erectile function was maintained in 5 out of our seven patients (71\%) of the patients, whereas EJD was reported by only one (11\%). Although sexually active two out of the nine patients already had ED before treatment, adequate vaginal intromission was almost never possible.

Our findings suggest that after LTME parasympathetic nerves are more at risk than sympathetic. Quah and co-workers, reporting on 15 males after LTME and 22 males after OTME found similar results concerning ED (33\%) but described just a very high EJD rate after LTME (40\%)\textsuperscript{7}. The EJD in their OTME patients was only 5 percent.

Based on IPSS scores our patients had high micturition frequencies and worse quality of life 15 months after treatment. Especially in the pre-treatment phase it was for logistic and emotional reasons obviously not possible to combine extended urodynamic investigations with duplex-ultrasonography and NPTR. In general, bladder dysfunction is difficult to assess in elderly men, who may have associated prostatic pathology, but extended urodynamic investigations may proof neurogenic bladder disease. In contrast with previous studies reporting on LTME, our results suggest that also with LTME the plexus hypogastricus is still at risk resulting in neurogenic bladder dysfunction\textsuperscript{6,7}.

The most recent studies reporting on OTME show at hospital discharge bladder dysfunction rates of 3.8 to 10.7 \%\textsuperscript{22,23}. Another study reporting about 6 months after OTME shows a percentage of ten\textsuperscript{21}.
Currently, pharmaco duplex-ultrasonography is generally accepted as the most sensitive method for evaluation of the functional status of the penile vascular system. Using this method, we found no relevant differences in cavernous arterial blood flow velocities before and after LTME. These results suggest no mayor vascular damage, neither due to the short-term preoperative radiotherapy nor to the LTME.

In most cases ED following TME and LTME is neurogenic in origin. However, ligation of the anterior division or distal branches of the internal iliac artery is sometimes necessary.

As all patients in our study received short-term radiotherapy we could not identify the contribution of each treatment component, radiotherapy or LTME, in the development of sexual or bladder dysfunction 15 months postoperatively.

Concerning the late side effects of preoperative short-term radiotherapy in TME patients, there are only few studies available. Recently data from the Dutch Colorectal Cancer Group analysed 990 patients (497 in the radiation + OTME group and 493 in the OTME only group) in terms of health-related quality of life and sexual function. The OTME group only reported more male sexual dysfunction than the irradiated patients, but this did not lead to significant worse overall quality of life.

Because of the very small number of non-consecutive patients and possible selection bias the results of our study must be evaluated with caution.

Despite these shortcomings our data suggest that in spite of better visualization of the autonomic nerves the occurrence of neurogenic sexual dysfunction and LUTS after LTME are comparable to those after OTME. This is in accordance with results of radial prostatectomy for prostate cancer in which no difference with regard to iatrogenic ED after the open and the minimal invasive approach have been observed.

Despite objectively assessed physical sexual deterioration our patients had unchanged overall sexual satisfaction. This corresponds with findings in patients treated for testicular cancer and with data of females treated for gynaecological cancer. This phenomenon can be explained by the so called “response shift”. This means that long term survivors develop a more positive appreciation of their sexual life.

Unlike in most patients who have ED in whom there is a gradual reduction in rigidity over many years, the loss of sexual functions in the post TME patient is initially sudden and in many cases total and definitive. Surgeons are left with the difficult task to counsel patients who preoperatively primarily were concerned with survival and cancer cure and who were left with the prospect of never achieving an adequate “natural” erection anymore.

If there is an iatrogenic ED, patients should be offered a phosphodiesterase 5 inhibitor, preferably in the early postoperative phase in close cooperation with the sexual partner. Her (or his) sexual interest and function is an important aspect of sexual rehabilitation. In general there is a good response (87%) but the effect of such a drug is dependent on, at least partially, intact cavernous nerves to produce nitric oxide. Therefore, if the cavernous nerves have been totally ablated, phosphodiesterase 5 inhibitors will be ineffective.

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Reference List


