

# Adjuvant Radiotherapy Is Associated With Increased Sexual Dysfunction in Male Patients Undergoing Resection for Rectal Cancer

## A Predictive Model

Alexander G. Heriot,\*† Paris P. Tekkis,\*† Victor W. Fazio,\* Paul Neary,\* and Ian C. Lavery, MB, BS\*

**Objectives:** The objectives of this study were to evaluate the effect of radiotherapy (RT) on sexual function in patients undergoing oncologic resection for rectal cancer, and to develop a mathematical model for quantifying the risk of sexual dysfunction through time for this group of patients.

**Methods:** Data were prospectively collected on patients undergoing proctosigmoidectomy (group 1: n = 101) or adjuvant radiotherapy (40–50 Gy) and resection (group 2: n = 100) for rectal cancer at a tertiary referral center between December 1998 and July 2004. Study end points were recorded at 7 time intervals (preoperatively, 4 months, 8 months, 1 year, 2 years, 3 years, and 4 years after surgery) and included: 1) ability to have an erection, 2) maintain an erection, 3) attain orgasm, 4) dry orgasm, and 5) whether they were sexually active. Multilevel logistic regression analysis for repeated measures was used to identify factors associated with the sexual dysfunction. A predictive model was developed and internally validated by comparing observed and model-predicted outcomes.

**Results:** Radiotherapy had an adverse effect on the ability to get an erection, maintain an erection, attain orgasm, and being sexually active in comparison with patients undergoing surgery alone (7.4%, 12.6%, 16.2%, and 13.7% reduction 8 months after surgery respectively;  $P < 0.05$ ). The effect of sexual dysfunction deteriorated with age (odds ratio for erectile function, 0.40 per 10-year increase in age; 95% confidence interval, 0.29–0.49;  $P < 0.001$ ). A significant variability in sexual function was present among the 7 time points with a maximal deterioration occurring at 8 months after surgery with subsequent slow but not complete recovery ( $P < 0.001$ ). The predictive model showed adequate discrimination on 4 of the 5 domains of sexual dysfunction (area under the receiver operating characteristic curve  $>0.70$ ).

**Conclusions:** Radiotherapy has an adverse effect on sexual function, the effect being maximal at 8 months after surgery. The risk of

sexual dysfunction can be quantified preoperatively using the proposed index and can assist patients in making better informed choices on the type of treatment they receive.

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There have been significant developments in the treatment of rectal cancer over the 20th century,<sup>1</sup> but the specter of local recurrence continues to cast a shadow over the management of this condition. Radiotherapy does appear to have an oncologic benefit<sup>2</sup> but is associated with long-term functional morbidity. A number of studies have reported impaired bowel function when compared with patients not receiving radiotherapy,<sup>3–5</sup> although heterogeneity of the studies and a lack of standardization of functional outcome make quantitative assessment difficult. There is a suggestion that sexual function is impaired by radiotherapy,<sup>6,7</sup> but function can also be affected by surgery alone, may be impacted on by other factors such as age,<sup>8</sup> and is difficult to study as a result of the sensitive nature of the topic. Assessment of impairment of sexual function resulting from radiotherapy is important, however, because potential oncologic benefit should not be considered in isolation, but should be balanced by possible functional impairment. Quantification and prediction of the degree of sexual function impairment would benefit both the clinician and the patient in making decisions over optimal management.

The aims of the present study were to evaluate the effect of radiotherapy (RT) on sexual function in male patients undergoing oncologic resection for rectal cancer and to thereby develop a mathematical model for quantifying the risk of sexual dysfunction through time for this group of patients.

## METHODS

### Data Sources

Patients undergoing surgery for colorectal cancer were identified through the Cleveland Clinic Colorectal Cancer Database initiated in 1976. The database was expanded in

From the \*The Department of Colorectal Surgery, Cleveland Clinic Foundation, Cleveland, Ohio; and †Imperial College London, Department of Surgical Oncology and Technology, St. Mary's Hospital, London, U.K. Reprints: Ian C. Lavery, MB, BS, Vice Chairman, Department of Colorectal Surgery/A30, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195. E-mail: laveryi@ccf.org.

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1998 to include prospective functional data. The database provided a comprehensive dataset consisting of patient symptoms, preoperative assessment, surgical treatment, postoperative course, pathology section, long-term complications, and functional outcomes. Functional outcome, including sexual function, was prospectively recorded at 7 time intervals: preoperatively, 4 months, 8 months, 1 year, 2 years, 3 years, and 4 years after surgery. Data validation was performed by requesting duplicate information from patient charts by a dedicated database officer. The study was approved by the Institutional Review Board.

### Inclusion and Exclusion Criteria

Prospective data were included on all male patients below 80 years old undergoing elective proctosigmoidectomy, and primary anastomosis for rectal cancer with and without the use of adjuvant radiotherapy. Patients who underwent emergency surgery, Hartmann's procedure, abdominoperineal excision of the rectum, or local resection of rectal cancer as their sole procedure were excluded from the study. All cancers above 15 cm from the distance from the anal verge were also excluded, as well as patients who underwent prior radiotherapy to the rectum or redone proctosigmoidectomy for recurrent disease.

All surgeons had received postgraduate training in the technique of total mesorectal excision (TME) and were practicing staff surgeons in a practice with a high volume of rectal surgery. Surgery was performed as described in previous reports from this institution<sup>9–11</sup> by sharp dissection of the mesorectum with its investing layer of fascia.

### Study End Points

The primary end point was male sexual dysfunction and was defined as 1) the ability to have an erection, 2) the ability to maintain an erection, 3) ability to attain orgasm, 4) presence of dry orgasm, and 5) whether the patient was sexually active. These were set as binary outcomes (yes/no) and were prospectively recorded at 7 time intervals: preoperatively, 4 months, 8 months, 1 year, 2 years, 3 years, and 4 years after surgery. Secondary end points included postoperative mortality, morbidity, readmission, or reoperation occurring within 30 days of the operative procedure and 5-year cancer-specific survival.

### Study Design

This was a nonrandomized, observational, case-control study that is based on a retrospective review of prospectively collected data comparing outcomes between 2 groups of patients undergoing surgery for rectal cancer: 1) group 1: patients undergoing proctosigmoidectomy without adjuvant radiotherapy and 2) group 2: patients undergoing proctosigmoidectomy with 40 to 50 Gy of neoadjuvant radiotherapy.

### Risk Factors

The patient and procedural risk-factors included: 1) age, 2) cancer site in accordance to the WHO International Classification of Diseases and Related Health Problems, 3) tumor height from the anal verge, 4) prior colorectal procedure (local resection of rectal cancer or prior colectomy), 5) surgical procedure categorized according to the OPCS4 sys-

tem,<sup>12</sup> 6) treatment intent classified as curative or palliative, 7) cancer staging according to the preoperative and intraoperative clinical findings and histologic TNM classification for colorectal cancer, 8) tumor grade, 9) tumor size at its maximum diameter, 10) distal or radial resection margin involvement, 11) the use of preoperative/postoperative radiotherapy, and 12) the use of preoperative/postoperative chemotherapy. Each risk factor was assessed at the time of surgery and assigned a "reference" category, which represents the subcategory with the lowest impact on in-hospital mortality (odds ratio of 1), eg, age  $\leq 65$  years for "age group."

### Statistical Analysis

Univariate multilevel logistic regression analysis for repeated measures was used to identify risk factors related to sexual dysfunction. Continuous variables such as age and tumor height from the anal verge were categorized into clinically relevant subgroups representing groups of increasing operative risk. Risk factors with a univariate *P* value of  $<0.25$  were included in the multivariate analysis. Chi-squared or Student *t* test was used to compare demographic factors between the 2 groups. Chi-squared test was used to assess the impact of radiotherapy on postoperative adverse events and outcome other than 5-year survival, which was assessed by log-rank test. The impact of radiotherapy on sexual function over time was assessed by chi-squared test for trend.

A 2-level logistic regression analysis was used to adjust for multiple risk factors and their interactions. The model used 2 levels of hierarchy, placing the individual patient-related risk factors at the second level and the repeat measures or occasions in level one. The between-subject variability was assessed by the level-2 variance, and the between-occasion within-subject variability was evaluated by the level-one variance, which was set to assume an extrabinomial distribution.<sup>13</sup> Each risk factor was manually entered into the model starting from the most relevant, smallest *P* value and adding each factor in turn. By observing the odds ratios, the 95% confidence intervals for each new factor, and the change in the log-likelihood statistic, we were able to ascertain whether each variable should remain in the model. The final variable selection was based on clinical relevance and statistical significance. The coefficients derived from the multivariate analysis were multiplied by 10 and used as weights in the nomogram for predicting sexual dysfunction after proctosigmoidectomy for rectal cancer.

### Model Validation

The initial model estimates were derived using a first-order penalized quaslikelihood estimation followed by a Bayesian method using Gibb's sampling to calculate confidence limits and to correct bias in the parameter estimation.<sup>13</sup> The models were internally validated on a random sample of 100 patients drawn from the original study population. There are 2 types of validation, internal and external. Internal validation can be performed using 3 different techniques: split sample validation, jack knife, and bootstrap resampling. Bootstrap resampling is thought to be the optimum technique of internal validation.<sup>14</sup> Internal validation was performed using a "bootstrap" technique of 50% of the study population

using 10,000 iterations. Model performance was evaluated by measures of calibration, discrimination, and subgroup analysis. Calibration or goodness-of-fit refers to the ability of the model to assign the correct probabilities of outcome to individual patients. The Hosmer-Lemeshow  $\hat{c}$  statistic was used to assess model calibration.<sup>15</sup> To obtain this statistic, we computed the estimated probability of an adverse outcome for each patient based on the model, ranked them into equal groups of ascending risk, and then statistically evaluated the expected and observed number of outcomes in each group. The statistic assumes that the model has a good fit, and therefore large statistic values and small corresponding *P* values are indicators of poor model fit. Model discrimination refers to the ability of the model to assign higher probabilities of sexual dysfunction to patients who actually have sexual dysfunction than those patients who do not; this was measured by the area under the receiver operator characteristic (ROC) curve. Values ranging from 0.7 to 0.8 represent reasonable discrimination and values exceeding 0.8 represent good discrimination.<sup>16</sup> Subgroup analysis was performed by comparing the observed and expected outcomes for individual procedures on the validation sample drawn randomly from the original population.

### Statistical Software

The following software packages were used: Intercooled STATA 6.0 for Windows (STATA Corp.) and Statistical Package for the Social Sciences version 11 for Windows (SPSS, Chicago, IL) for descriptive and univariate analysis and MLwiN Version 1.2 (University of London) for multi-level modeling.

## RESULTS

A total of 201 patients were identified from the colorectal cancer database who matched the inclusion criteria for the study period between December 1998 and July 2004. All patients underwent proctosigmoidectomy with a primary anastomosis by one of 9 staff who adopted a uniform protocol for use of neoadjuvant and adjuvant therapy. One hundred patients underwent proctosigmoidectomy without radiotherapy and were assigned to group 1, and 101 patients underwent proctosigmoidectomy with radiotherapy and were assigned to group 2. All patients who underwent external beam radiotherapy had a total of 40 to 50 Gy over 4 to 6 weeks by either 3 or 4 portals. All but 5 patients in group 2 underwent preoperative radiotherapy. The patient characteristics and disease presentation are shown in Table 1. There was no evidence of systematic underreporting of risk factors in the study population.

The 2 groups were similar with respect to treatment intent (palliative vs curative surgery), prior colorectal procedures, N-stage, M-stage, tumor grade, distal and radial margin involvement. A total of 10 patients underwent prior surgery; 5 patients underwent prior transanal excision of a rectal cancer, 4 in group 1 and one in group 2; 4 patients had prior colectomies, one in group 1 and 3 in group 2; and one patient had a defunctioning stoma before receiving radiotherapy. Significant differences were observed between the 2 groups in terms of age, tumor height above distance from the

**TABLE 1.** Demographic Characteristics of Patients With Rectal Cancer Undergoing Proctosigmoidectomy With or Without Adjuvant Radiotherapy

	No Radiotherapy Group (n = 100) (%)	Radiotherapy (n = 101) (%)	<i>P</i> Value
Age groups			0.002
<50 yr	18 (18.0)	30 (29.7)	
51–60 yr	32 (32.0)	41 (40.6)	
61–70 yr	33 (33.0)	21 (20.8)	
>70 yr	17 (17.0)	9 (8.9)	
Tumor height above anal verge	9.9 (2.9)	6.1 (2.4)	<0.001
Prior colorectal procedure	5 (5.0)	5 (5.0)	0.987
Treatment intent			0.816
Curative	92 (92.0)	92 (91.1)	
Palliative	8 (8.0)	9 (8.9)	
T-stage			<0.001
T <sub>1</sub>	20 (20.0)	5 (5.0)	
T <sub>2</sub>	39 (39.0)	24 (23.8)	
T <sub>3/4</sub>	41 (41.0)	72 (71.3)	
N-stage			0.340
N <sub>0</sub>	76 (76.0)	67 (66.3)	
N <sub>1</sub>	14 (14.0)	22 (21.8)	
N <sub>2–3</sub>	10 (10.0)	12 (11.9)	
M-stage			0.985
M <sub>0</sub>	93 (93.0)	94 (93.1)	
M <sub>1</sub>	7 (7.0)	7 (6.9)	
Adjuvant chemotherapy			<0.001
Preoperative	0 (0)	5 (5)	
Postoperative	25 (25)	96 (95.0)	
Tumor differentiation			0.877
Well/moderate	72 (72.0)	71 (70.3)	
Poorly	28 (28.0)	30 (28.7)	
Mean tumor size (SD)	4.0 (1.9)	2.6 (1.5)	<0.001
Distal/radial margin involvement	2 (2.0)	2 (2.0)	0.838

SD indicates standard deviation.

anal verge, depth of tumor penetration (preoperative T-stage), the mean tumor size, and the use of adjuvant chemotherapy. Patients undergoing radiotherapy were younger, the tumor was more often in the lower rectum, and the patients had a higher T-stage than patients not receiving radiotherapy (*P* < 0.01).

There were no significant differences in the postoperative adverse events, including surgical or medical complications, readmission rates, reoperation rates, and cumulative 5-year survival, as shown in Table 2. There were no postoperative deaths in any of the 2 groups. The 5 domains for sexual dysfunction were evaluated at fixed time intervals, the results of which are summarized in the Table 3. A significant variability in sexual function in the radiotherapy group was present among the 7 time points with deterioration to 8 months after surgery with subsequent slow but not complete recovery (*P* < 0.05). Radiotherapy had an adverse effect on the ability to get an erection, maintain an erection, attain

**TABLE 2.** Postoperative Adverse Events Between Patients Undergoing Proctosigmoidectomy (Group 1) or Adjuvant Radiotherapy and Resection (Group 2) for Rectal Cancer

	No Radiotherapy (n = 100) (%)	Radiotherapy (n = 101) (%)	P Value
30-d readmission	3 (3.0)	3 (3.0)	0.654
Reoperation rate	0 (0)	4 (4.0)	0.062
Cumulative 5-yr survival	75.9	73.6	0.711*
Medical complications (major)	3 (3)	4 (4)	0.654
Surgical complications			
Wound infection	3 (3.0)	6 (5.9)	0.498
Wound dehiscence	0 (0.0)	2 (2.0)	0.498
Bowel obstruction	4 (2.0)	2 (2.0)	0.445
Anastomotic leak	3 (3.0)	7 (6.9)	0.268
Small bowel fistula	0 (0.0)	1 (1.0)	0.502
Intraabdominal abscess	2 (2.0)	6 (5.9)	0.279
Bleeding	1 (1)	2 (2)	0.498

\*All analysis by chi-squared test other than 5-yr survival by log-rank test.

orgasm, and being sexually active in comparison with patients undergoing surgery alone (7.4%, 12.6%, 16.2%, and 13.7% reduction 8 months after surgery, respectively).

On univariate logistic regression analysis using the 5 domains of sexual dysfunction as the dependent variables, the patient's age, tumor grade, T-stage, N-stage, the use of radiotherapy, and patient follow up were found to be associated with various adverse sexual outcomes ( $P < 0.05$ ). Although 35 patients had tumors above 10 cm from the distance from the anal verge, of which 30 did not receive radiotherapy, the height of the tumor was not found to be a

significant predictor of sexual dysfunction on univariate or multivariate analysis. The effect of age on sexual dysfunction was evaluated further by regressing the patients' age and radiotherapy use as independent covariates in a multivariate logistic regression analysis. The ability to get an erection was an age-dependent process with 2.5-fold increase in the likelihood of sexual dysfunction per 10-year increase in age (odds ratio [OR] for erectile function, 0.40; 95% confidence interval [CI], 0.29–0.49;  $P < 0.001$ ). Having adjusted for age, patients receiving radiotherapy were 1.8 times more likely to have erectile dysfunction in comparison with patients who did not undergo radiotherapy (OR for erectile function, 0.57; 95% CI, 0.34–0.95;  $P < 0.001$ ).

The results of the multifactorial analyses of 4 of the 5 domains of sexual dysfunction are shown in Table 4. No independent predictors of dry orgasm were identified by the multivariate analysis except the time intervals that observations were made. With regard to the remaining 4 domains of sexual dysfunction, the following risk factors were found to be independent predictors of sexual dysfunction (shown as adjusted odds ratios with 95% confidence interval): the patient's age, the use of radiotherapy, T-stage (2 of the 4 domains), and the time intervals the observations were made. The between-subject (level 2) and the between-occasion within-subject variance (level 1) were significant across all 5 domains of sexual dysfunction.

A sensitivity analysis was performed to assess whether the differences in demographics between the 2 groups had any effect on the overall estimate. On multivariate analysis, all risk factors were considered that differed between the groups. This did not demonstrate any significant changes in the multivariate analysis and only significant variables were therefore included in the final model.

**TABLE 3.** Five Domains of Sexual Dysfunction Are Shown in Patients Undergoing Proctosigmoidectomy With or Without Adjuvant Radiotherapy at 7 Time Points\*

Sexual Function	Preoperative % (n)	4 Months % (n)	8 Months % (n)	1 Year % (n)	2 Years % (n)	3 Years % (n)	4 Years % (n)
Sexually active							
No radiotherapy	72.0 (100)	67.8 (90)	67.5 (80)	76.8 (82)	65.5 (55)	65.7 (35)	76.5 (17)
Radiotherapy†	75.2 (101)	52.1 (71)	53.8 (78)	59.1 (66)	60.5 (43)	40.0 (30)	52.2 (23)
Ability to have an erection							
No radiotherapy	84.4 (96)	78.9 (90)	70.2 (84)	75.0 (88)	72.1 (61)	80.0 (35)	75.0 (20)
Radiotherapy†	89.5 (101)	73.9 (69)	62.8 (78)	67.2 (67)	69.8 (43)	48.5 (31)	65.2 (23)
Ability to maintain an erection							
No radiotherapy	67.4 (95)	65.9 (88)	57.3 (82)	60.0 (85)	57.6 (59)	65.7 (35)	60.0 (20)
Radiotherapy†	80.6 (101)	57.4 (68)	44.7 (76)	54.7 (64)	57.1 (42)	32.3 (31)	50.0 (22)
Ability to attain orgasm							
No radiotherapy	87.4 (95)	80.0 (85)	77.2 (79)	82.5 (80)	78.6 (56)	85.7 (35)	80.0 (20)
Radiotherapy†	88.1 (101)	72.3 (65)	60.8 (74)	72.6 (62)	70.7 (41)	51.6 (31)	68.2 (22)
Dry orgasm							
No radiotherapy	8.7 (92)	17.9 (78)	19.7 (76)	21.9 (73)	16.4 (55)	20.0 (35)	15.8 (19)
Radiotherapy†	6.1 (99)	21.0 (62)	20.0 (70)	23.6 (55)	23.7 (38)	20.0 (30)	23.8 (21)

All analysis by chi-squared test for trend.

\*Values display percentages of total number of patients with the event. The total number of patients within each time interval is shown in parenthesis.

†Significance with a  $P$  value of  $<0.05$  using a chi-squared test for trend.

**TABLE 4.** Multivariate Analysis of Factors Associated With Sexual Dysfunction In Patients With Cancer Undergoing Proctosigmoidectomy

Risk Factor	Sexually Active		Getting an Erection		Maintaining an Erection		Attaining Orgasm		Dry Orgasm	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Groups										
No radiotherapy	1		1		1		1		1	
Radiotherapy	0.556	0.337–0.918	0.576	0.342–0.970	0.741	0.469–1.170	0.496	0.279–0.880	0.935	0.548–1.594
Age*	0.920	0.897–0.944	0.911	0.887–0.937	0.920	0.899–0.942	0.915	0.888–0.942		
T-stage										
T <sub>1</sub>	1						1			
T <sub>2</sub>	0.979	0.443–2.166					0.497	0.189–1.303		
T <sub>3/4</sub>	0.539	0.252–1.153					0.393	0.154–1.004		
Time interval										
Preoperative	1		1		1		1		1	
4 mo	0.470	0.327–0.676	0.391	0.263–0.579	0.457	0.322–0.648	0.414	0.273–0.628	2.759	1.625–4.684
8 mo	0.509	0.353–0.732	0.281	0.192–0.412	0.325	0.230–0.460	0.327	0.218–0.492	2.784	1.647–4.708
1 yr	0.759	0.520–1.108	0.346	0.234–0.513	0.440	0.309–0.627	0.488	0.318–0.749	3.327	1.952–5.670
2 yr	0.744	0.483–1.145	0.412	0.266–0.638	0.523	0.350–0.782	0.436	0.272–0.699	2.430	1.334–4.427
3 yr	0.560	0.338–0.928	0.391	0.235–0.650	0.446	0.277–0.718	0.411	0.240–0.701	2.411	1.228–4.731
4 yr	0.877	0.477–1.614	0.426	0.237–0.765	0.417	0.238–0.731	0.497	0.268–0.923	3.093	1.454–6.577
Constant	6.599	(0.855)	8.149	(0.981)	6.117	(0.746)	8.368	(1.040)	–2.406	(0.270)
Level 2 variance	3.045	(0.349)	3.622	(0.406)	2.743	(0.314)	3.758	(0.441)	3.239	(0.432)
Level 1 variance	0.490	(0.028)	0.422	(0.024)	0.456	(0.026)	0.452	(0.026)	0.553	(0.034)

OR indicates odds ratio; CI, confidence interval.

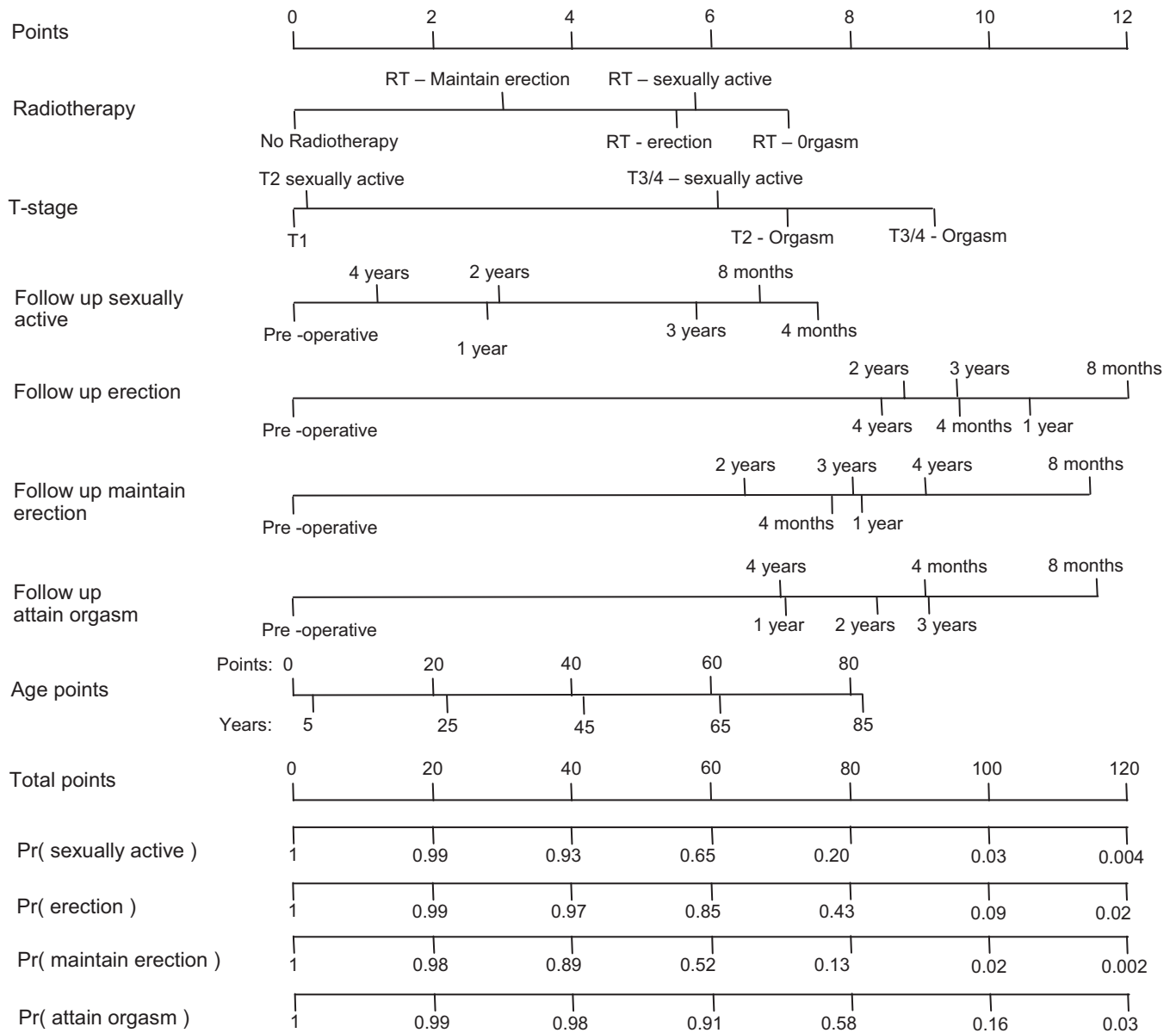
The nomogram for predicting sexual dysfunction on 4 of the 5 domains at various time intervals after proctosigmoidectomy for rectal cancer is displayed in Figure 1. Model performance was evaluated in 100 patients (validation set), which was randomly drawn from the study population, the results of which are summarized in Table 5. The discrimination was generally good at all time points (area under the receiver operator characteristic [ROC] curve of over 0.7) across all domains other than for dry orgasm, in which it was consistently inferior with an ROC curve of under 0.6. The accuracy of discrimination across each domain also varied with the time of follow up, a difference that was not statistically significant as demonstrated in Table 5. All models showed adequate calibration with no significant differences in the observed and expected outcomes. Subgroup analysis was performed by comparing the observed and model-predicted ability to attain an erection at different time points after proctosigmoidectomy with no significant differences noted (Hosmer Lemeshow test = 4.961, 5 df,  $P = 0.421$ ).

## DISCUSSION

Surgical resection of rectal cancer has been shown to have a significant impact on sexual function in men with erectile dysfunction in 5% to 65% of patients<sup>8,17–21</sup> and loss of ability to ejaculate in 12% to 69%.<sup>8,17–22</sup> The intimate anatomic relationship of the nerves responsible for sexual function<sup>23</sup> (the sympathetic hypogastric nerves controlling ejaculation and the parasympathetic sacral splanchnic nerves controlling erection) to the rectum within the confines of a

narrow male pelvis makes them vulnerable to iatrogenic surgical damage. Extended resections for advanced primary and locally recurrent rectal cancers have reported sexual dysfunction in over 50% of patients.<sup>24</sup> Total mesorectal excision (TME) with dissection outside the fascia propria of the rectum and identification and preservation of pelvic nerves has shown a reduction in impairment of sexual function. Nesbakken et al<sup>17</sup> reported one of 24 patients developing impotence leading to abstinence from sexual activity after TME. However, other authors have shown that some impairment of sexual function remains despite the refinements in surgical technique. Kim et al<sup>25</sup> documented significant decreases in all 5 domains of the International Prostate Symptom Score (erectile function, satisfaction, orgasmic function, sexual function, and overall satisfaction) after TME as compared with before surgery, although Maurer et al<sup>26</sup> demonstrated that preservation of male sexual function was significantly better after TME than after conventional rectal cancer surgery. Patients undergoing abdominoperineal resection were excluded from the current study because it was considered that factors such as perineal pain, unhealed perineal wound, and permanent stoma could not be controlled for and that this should be considered as a component of a future study.

Surgery may result in sexual dysfunction, but other factors such as patient age and adjuvant therapy may influence function,<sup>8,18</sup> and this complex interaction makes assessment of the impact of associated factors such as radiotherapy difficult. A study of male patients undergoing radiotherapy alone for bladder cancer reported a reduction in the ability of



**FIGURE 1.** Nomogram for predicting sexual dysfunction at various time intervals after proctosigmoidectomy for rectal cancer. Instructions for use: Locate the point where a patient has adjuvant radiotherapy (RT) and wants to calculate the probability of attaining an orgasm “RT orgasm.” Draw a line straight upward to the “points axis” to determine how many points toward sexual dysfunction the patient receives. Repeat the process for other axes, each time drawing straight upward to the “point axis.” The point for age is calculated directly from its own axis. Sum the points achieved for each predictor and locate this sum on the “total points axis.” Draw a line straight down to find the patient’s probability of attaining an orgasm postoperatively.

patients to attain an erection from 72% before treatment to 56% after treatment, confirming that radiotherapy alone will impact on sexual function.<sup>27</sup> A study of radiotherapy for prostate cancer reported erectile dysfunction in 45% of patients after 9 to 18 months of follow up and 77% at 4 to 5 years of follow up.<sup>28</sup> The impact of the addition of radiotherapy to patients undergoing rectal cancer resection has been reported by Bonnel et al.<sup>7</sup> Of 42 patients undergoing resection, 16 received preoperative radiotherapy and 26 surgery

alone. All 24 sexually active patients in the surgery group retained the ability to ejaculate as compared with 9 of 11 sexually active patients in the radiotherapy group ( $P < 0.09$ ). The authors concluded that the addition of preoperative radiotherapy to patients undergoing TME may impair male sexual function.

In the current study, radiotherapy appeared to have a significant adverse effect on male sexual function in patients undergoing rectal cancer resection, which is in addition to

**TABLE 5.** Model Performance for 5 End Points of Sexual Dysfunction

Sexual Function	Model Discrimination		Model Calibration		Observed-to-Expected Outcome
	Area Under ROC Curve	SE of AUROC	HL Chi-squared Test	P Value	
Sexually active	0.765	0.017	1.772	0.880	65.0%: 63.2%
Ability to have an erection	0.730	0.018	4.961	0.421	74.5%: 71.5%
Ability to maintain an erection	0.720	0.017	4.579	0.469	60.3%: 57.7%
Ability to attain orgasm	0.758	0.020	5.098	0.404	77.3%: 66.7%
Dry orgasm	0.591	0.025	0.673	0.984	17.2%: 17.0%

ROC indicates receiver operator characteristic; SE, standard error; AUROC, area under the receiver operator characteristic; HL, HL.

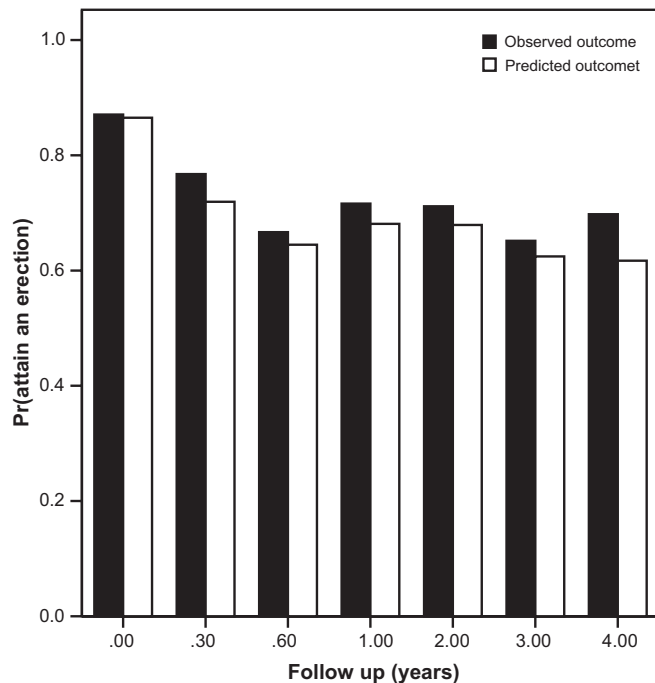
any impairment resulting from surgery alone. There was a reduction across all domains, namely the ability to get and to maintain an erection, attain orgasm, ejaculate, and the likelihood of being sexually active. Pelvic surgery has been shown to affect female sexual function,<sup>29</sup> and radiotherapy may be additional to this,<sup>30</sup> but this is an area of future research. The radiotherapy group and the surgery alone group were very similar but did differ in terms of tumor stage, tumor height, postoperative tumor size, and administration of adjuvant chemotherapy. It was to be expected that the tumors in the radiotherapy group would be of a more advanced stage because this would be the stimulus for administration of radiotherapy. The possibility of a more extended resection being required for T4 tumors, thereby increasing the potential for surgery-induced dysfunction, and the fact that there were more of these patients in the radiotherapy group was considered, but the overall number of T4 patients was small and the postoperative tumor size was actually smaller in the radiotherapy group. This is likely to be the result of tumor shrinkage secondary to the radiotherapy. The tumors in the radiotherapy group were closer to the anal verge at a mean of 6 cm as compared with 9 cm, but this difference in height was not a significant predictor of sexual dysfunction, and when adjusted for comparability for height, the difference in sexual dysfunction persisted. There was no difference in postoperative complications between the radiotherapy and surgery alone groups, and the overall 5-year survival was good at 73.6% and 75.9%, respectively.

Radiotherapy did significantly affect the ability to get an erection, maintain an erection, attain orgasm, and be sexually active, but the age of the patient and the duration of time after surgery both significantly affected the likelihood of dysfunction. Age-dependent deterioration in sexual dysfunction is well recognized,<sup>18</sup> and there was a marked deterioration between the ages of 55 and 65 years. This is similar to the findings of Havenga et al<sup>8</sup> and Mannaerts et al<sup>24</sup> and is important when individualizing potential morbidity. There was significant variability in sexual function present among the different time points of follow up, with maximal deterioration occurring at 8 months after surgery with a subsequent slow and incomplete recovery. The etiology of this is likely to be multifactorial and may relate to resolution of pelvic inflammation, recovery of nerve function, and alteration in body image over time.

The interaction of factors affecting sexual function is complex and multivariate analysis identified radiotherapy,

patient age, tumor stage, and time after surgery as all having a significant impact on each domain of sexual function. It was necessary to develop a model for impairment of sexual function for each functional domain because the impact of the influencing factors differed across the domains. Multivariate analysis was used to identify influencing factors and the extent that they impacted on sexual function both on the level of an individual patient and across the whole group of patients with selected factors being significant across both extents. Testing the individual models for each domain demonstrated good discrimination, as represented by an area under the ROC curve of over 0.7, namely that each model correctly records a higher likelihood of sexual dysfunction for each particular domain for those patients who actually have sexual dysfunction.<sup>16</sup> The accuracy of discrimination across each domain also varied with the time of follow up. The discrimination was generally good at all time points across all domains other than for dry orgasm, in which it was consistently inferior with an ROC curve of under 0.6 and thereby less accurate prediction. Graphic representation of the probability of getting an erection is represented in Figure 1 with the appearance of a good "fit" of the median regression lines. There is inevitably some variation in accuracy across individuals, but the model does appear to give a good estimation of potential erectile function, and this is confirmed by statistical testing of the model. The method of testing the model could be criticized, because it was necessary to both develop and validate the model across the same study group rather than using a split-sample validation technique, which would have been done preferentially if patient numbers had been greater<sup>15</sup>; however, the model appeared to be accurate. External validation is also required either temporally within the same institution or with an external institution.

Clinical judgment usually forms the basis for patient counseling and decision analysis but is prone to bias,<sup>31,32</sup> and clinicians usually predict the preferred outcome rather than the most likely outcome.<sup>32</sup> Diblasio et al<sup>33</sup> stated that "a nomogram should accurately predict which patients will and will not reach the end point (discrimination), generate predictions that closely approximate actual outcome (calibration), and perform consistently when applied to different data sets (validation)." The nomogram in Figure 2 shows good discrimination and calibration. Validation is very good, but because it has been internally validated, there is the possibility that this is artificially high and validation should be confirmed against external data. The nomogram allows quan-



**FIGURE 2.** Comparison of observed and model-predicted ability to attain an erection after proctosigmoidectomy for rectal cancer on a random sample of 100 patients drawn from the original study population. Hosmer Lemeshow test = 4.961, 5 df,  $P = 0.421$ .

titative prediction of the probability of sexual dysfunction for 4 sexual function domains, taking into account the individual patient characteristics of age, time after surgery, tumor stage, and the application or not of radiotherapy. Dry orgasm has not been included because the model performance was not adequate.

The question of the clinical application of this nomogram does arise because otherwise it is an exercise in complex statistical analysis and of academic interest to the treating physician rather than of personal relevance to the patient. It does have an important clinical application; however, if it allows a more complete informed patient consent and particularly if it can impact on management decisions. The primary outcomes when determining management of resectable rectal cancer are survival and local recurrence, but functional outcome is an important consideration, particularly when the potential survival benefit of an intervention is limited but the potential morbidity is not. Radiotherapy does have an important role in the management of rectal cancer and in more advanced tumors when there is concern over the potential resection margin, which is an important component of multimodality therapy.<sup>2</sup> There does need to be consideration of the balance between risk and benefit, however, with the aim of tailoring management to the individual patient.<sup>34</sup> Preoperative staging with magnetic resonance imaging may give some indication of potential benefits from radiotherapy,<sup>35</sup> but application of this model may allow a prediction of potential morbidity, at least in terms of sexual dysfunction, which may

aid both the treating physician and the patient in making an evidence-based decision on management.

The application of radiotherapy in the management of male patients undergoing surgical resection of rectal cancer does result in increased sexual dysfunction. The extent of dysfunction is influenced by the age of the patient, and although there is some recovery over time, this is incomplete. It is possible to quantify the risk of sexual dysfunction preoperatively using the proposed index, and this could assist both patients and physicians in making better informed choices on management.

## REFERENCES

- Ruo L, Guillem J. Major 20th-century advances in the management of rectal cancer. *Dis Colon Rectum*. 1999;42:563–578.
- Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomised trials. *Lancet*. 2001;358:1291–1304.
- Rouanet P, Fabre JM, Dubois JB, et al. Conservative surgery for low rectal carcinoma after high-dose radiation. Functional and oncologic results. *Ann Surg*. 1995;221:67–73.
- Dahlberg M, Glimelius B, Graf W, et al. Preoperative irradiation affects functional results after surgery for rectal cancer. *Dis Colon Rectum*. 1998;41:543–551.
- Dehni N, McNamara D, Schlegel R, et al. Clinical effects of preoperative radiation therapy on anorectal function after proctectomy and colonic J-pouch-anal anastomosis. *Dis Colon Rectum*. 2002;45:1635–1640.
- Ooi B, Tjandra J, Green M. Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: an overview. *Dis Colon Rectum*. 1999;42:402–418.
- Bonnell C, Parc Y, Pocard M, et al. Effects of preoperative radiotherapy for primary resectable rectal adenocarcinoma on male sexual and urinary function. *Dis Colon Rectum*. 2002;45:934–939.
- Havenga K, Enker W, McDermott K, et al. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. *J Am Coll Surg*. 1996;182:495–502.
- Lavery I, Lopez-Kostner F, Pelley R, et al. Treatment of colon and rectal cancer. *Surg Clin North Am*. 2000;80:535–569.
- Lopez-Kostner F, Lavery I, Hool G, et al. Total mesorectal excision is not necessary for cancers of the upper rectum. *Surgery*. 1998;124:612–618.
- Lavery I, Lopez-Kostner F, Fazio V, et al. Chances of cure are not compromised with sphincter-saving procedures for cancer of the lower third of the rectum. *Surgery*. 1997;122:779–785.
- Health Do. Hospital episode statistics, main operations 2000/01. Available at: [www.doh.gov.uk/hes/standard\\_data/available\\_tables/main\\_operations/index.html](http://www.doh.gov.uk/hes/standard_data/available_tables/main_operations/index.html).
- Rasbash J, Browne W, Goldstein H, et al., eds. *A User's Guide to MLwiN*. London:University of London; 2001.
- Efron B, Tibshiran IR. *An Introduction to the Bootstrap*. New York: Chapman and Hall; 1993.
- Hosmer D, Lemeshow S. *Applied Logistic Regression*, 2nd ed. New York: John Wiley & Sons Inc; 2000.
- Hanley J, McNeil B. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36.
- Nesbakken A, Nygaard K, Bull-Njaa T, et al. Bladder and sexual dysfunction after mesorectal excision for rectal cancer. *Br J Surg*. 2000;87:206–210.
- Danzi M, Ferulano G, Abate S, et al. Male sexual function after abdominoperineal resection for rectal cancer. *Dis Colon Rectum*. 1983; 26:665–668.
- Santangelo M, Romano G, Sassaroli C. Sexual function after resection for rectal cancer. *Am J Surg*. 1987;154:502–504.
- Baslev I, Harling H. Sexual dysfunction following operation for carcinoma of the rectum. *Dis Colon Rectum*. 1983;26:785–788.
- Williams NS, Johnston D. The quality of life after rectal excision for low rectal cancer. *Br J Surg*. 1983;70:460–462.
- Enker W. Potency, cure, and local control in the operative treatment of

- rectal cancer. *Arch Surg*. 1992;127:1396–1402.
23. Church J, Raudkivi P, Hill G. The surgical anatomy of the rectum—a review with particular relevance to the hazards of rectal mobilization. *Int J Colorectal Dis*. 1987;11–19.
  24. Mannaerts G, Schijven M, Hendriks A, et al. Urologic and sexual morbidity following multimodality treatment for locally advanced primary and locally recurrent rectal cancer. *Eur J Surg Oncol*. 2001;27:265–272.
  25. Kim N, Aahn T, Park J, et al. Assessment of sexual and voiding function after total mesorectal excision with pelvic autonomic nerve preservation in males with rectal cancer. *Dis Colon Rectum*. 2002;45:1178–1185.
  26. Maurer C, Z'graggen K, Renzulli P, et al. Total male genital function compared with conventional rectal cancer surgery—mesorectal excision preserves. *Br J Surg*. 2001;88:1501–1505.
  27. Little F, Howard G. Sexual function following radical radiotherapy for bladder cancer. *Radiother Oncol*. 1998;49:157–161.
  28. Al-Abany M, Steineck G, Agren Cronqvist A, et al. Improving the preservation of erectile function after external beam radiation therapy for prostate cancer. *Radiother Oncol*. 2000;57:201–206.
  29. Poad D, Arnold E. Sexual function after pelvic surgery in women. *Aust N Z J Obstet Gynaecol*. 1994;34:471–474.
  30. Bergmark K, Avall-Lundqvist E, Dickman P, et al. Vaginal changes and sexuality in women with a history of cervical cancer. *N Engl J Med*. 1999;340:1383–1389.
  31. Hogarth R. *Judgement and Choice*, 2nd ed. New York: John Wiley & Sons, Inc; 1987.
  32. Kattan M. Expert systems in medicine. In: Smelser N, Baltes P, eds. *International Encyclopedia of the Social Behavioral Sciences*. New York: Elsevier Science Ltd; 2001:5135–5139.
  33. Diblasio C, Kattan M. Use of nomograms to predict the risk of disease recurrence after definitive local therapy for prostate cancer. *Urology*. 2003;62(suppl 6B):9–18.
  34. Edwards D, Mortensen N. Is radiotherapy for rectal cancer indicated if surgery is optimized? *Eur J Surg Oncol*. 2001;27:442–445.
  35. Salerno G, Daniels I, Heald R, et al. Management and imaging of low rectal carcinoma. *Surg Oncol*. 2004;13:55–61.

## Discussions

DR. DAVID A. ROTHENBERGER (MINNEAPOLIS, MINNESOTA): It is a privilege to discuss this provocative paper. My congratulations to the authors. This is a difficult, complex clinical subject that is hard to investigate well. As noted in the manuscript, this subject has generated some interest in the past but not a lot of firm data.

I don't believe the study design is actually a prospective cohort study as you stated, but instead I would characterize it as a nonrandomized observational case control study. As such, it is a retrospective study with major limitations, so we should keep that in mind. Nonetheless, I think the data presented is useful in assessing impact on sexual function following radiation in male patients.

The thing that intrigued me the most about this paper was the development of a nomogram, and I would like to ask a few questions about that and some of the other aspects of your paper.

Number 1, your report is restricted to male sexual dysfunction and I would like to know whether you assessed the impact of radiation for rectal cancer on female sexual function. Parenthetically, I might note that the Dutch group from Leiden and Nijmegen have just published in the March 20, 2005 issue of *the Journal of Clinical Oncology* a pro-

spective trial of sexual dysfunction in patients who had undergone preoperative short course radiotherapy. They reported that both men and women had sexual dysfunction but that women were more negatively impacted than males.

Secondly, it appears to me that you have tried to validate the nomogram internally using the same population. I am not a statistician, but my statisticians tell me that that is a no-no and that you must validate the nomogram in patients other than those from whom you generated the data to develop the nomogram.

Thirdly, how are you going to utilize the nomogram to predict the likelihood of sexual dysfunction in males undergoing rectal cancer treatments? You suggest we should do so but I would be interested to know precisely how the Cleveland Clinic surgeons intend to utilize this predictive model.

Fourthly, you have excluded abdominoperineal resections from your analysis, and I am wondering why.

Finally, perhaps you could explain the uniform protocol that you referred to in your paper that has been adopted by the group at the Cleveland Clinic for use of neoadjuvant and adjuvant therapy and whether you are going to alter that protocol based on these findings.

DR. ALEXANDER G. HERIOT (LONDON, ENGLAND): I would like to thank Dr. Rothenberger for agreeing to review our paper and for his insightful questions. Taking them in order, your comment this is a nonrandomized case-controlled study is appropriate though all the data were collected prospectively within this study.

You asked why we didn't look at female sexual function. This is a very sensitive area to look at. We did actually obtain data on female sexual function and found that our response rates from female patients were lower. The Dutch group is to be commended on being able to obtain this data from the patients. Obviously it may be different in Europe but it is interesting to note that they reported similar results.

You commented on the statistical aspects in terms of validation. As I mentioned at the end of the talk we internally validated the model by randomly resecting 50% of the patient population and testing its accuracy using 10,000 bootstrap samples. When tested the accuracy of the model was adequate, however we do need to evaluate the model externally by testing it with other institutions.

You asked how this model may be applied clinically. I think the main use would be to individualize treatment to patients. You are trying to fully inform patients when you see them in the office. And this does give us the opportunity to give patients more information on the potential benefits and the risks of radiotherapy and of surgery on their sexual function.

We did exclude abdominoperineal resection patients. Though we considered using them, we felt that the possibility of uncontrollable factors such as perineal pain, unhealed

perineal wound and permanent colostomy, could confuse the data and make the outcomes less clear. This is 1 of the patient groups that we should be looking at in the future.

There is no uniform protocol for use of adjuvant therapy at the Cleveland Clinic. Therapy is decided on an individual basis. There are broad guidelines however. Patients with a tumor of under 10 centimeters from the anal verge undergo proctectomy with total mesorectal excision. Tumors above 10 centimeters from the anal verge undergo proctectomy with a distal margin of 5 centimeters. Radiotherapy is applied selectively, with the majority of patients with tumor below 10 centimeters who have tumors of a T stage of T3 or greater or which are node positive, most of which are imaged by endoanal ultrasound, will generally receive radiotherapy. Radiotherapy to tumors higher than 10 centimeters is done on a selective basis with very bulky tumors with which we have some preoperative surgical concerns regarding resection margins receive radiotherapy in an attempt to downsize the tumor.

I think the data we have from our study is unlikely to alter the management in the majority of our cases because the oncologic outcome remains the primary outcome. However, in selected patients where there is some debate over the potential benefits from radiotherapy versus potential side effects, it will allow us to make more informed decisions for the optimal management for that patient.

DR. WARREN E. ENKER (NEW YORK, NEW YORK): I didn't get from either the abstract or the presentation whether this was a questionnaire or an interview trial. Both have notorious problems in terms of interpretation. What Dr. Havenga from the Netherlands found when he did his study was that interviewing male patients was extremely difficult. That male patients tended to boast about their performance when speaking to a male and, in the case of decreased performance, they simply didn't want to talk to a female, either a nurse or a physician assistant, if it was an interview process. So the attempt to elicit information has many pitfalls whether it is questionnaire or interview.

Secondly, distal tumors, those which are closer to requiring either a temporary or a permanent stoma and those which require dissection in the very low pelvis, have an increased incidence of sexual dysfunction. And I wonder whether or not those factors were analyzed as part of your multivariate analysis. Dr. Takahashi has pointed out that rectal anastomoses below 4 centimeters from the anal verge are associated in their hands with increased sexual dysfunction despite the practice of autonomic nerve preservation in Japan.

Finally, I am not sure whether I understood it from your presentation or not, but in looking at the ability to sustain an erection, were you able to get any sense or data whether you were dealing with neurogenic or vasculogenic impotence?

DR. ALEXANDER G. HERIOT (LONDON, ENGLAND): Thanks for your questions. They show great insight obviously from personal experience of these patients.

On your first question on whether the patients were assessed by questionnaire or by interview technique, all the patients were assessed by a postal questionnaire. If the patients did not complete or return the questionnaire, they were telephoned and interviewed.

On your second question on the potential increase in sexual dysfunction in more distal tumors, in this study where we were only looking at patients undergoing restorative resection, we found that tumor height did not have an impact on the sexual dysfunction. I agree that distal tumors have greater potential risk of damage to the nervi erigentes, in particular anterior tumors, but we certainly haven't shown that in this study with this limited number of patients. The presence of a stoma did not have an impact on this group of patients but again, with an expanded study we may find it does.

Your final question was on the ability of the patient to sustain an erection, whether it was neurogenic or vasculogenic. With the data we had, we didn't get a feel on which of the two was more likely. It would be perhaps interesting to look at these patients and try as a separate study with the use of drugs such as sildenafil to see if we get an idea which was more likely the causative factor of their impotence.

DR. NICHOLAS J. PETRELLI (NEWARK, DELAWARE): I also enjoyed this presentation and would agree with my 2 colleagues' previous comments. However, I think a model like this is necessary. Because, as you know, the paradigm shift in this country is towards preoperative not only radiation but preoperative chemoradiation, combined modality, and with the newer drugs such as oxaliplatin and capecitabine and many of the targeted agents which are radiation sensitizers, I think we are going to see an increase in the problem of sexual dysfunction.

DR. ALEXANDER G. HERIOT (LONDON, ENGLAND): I quite agree with that question. We are aiming to generate a decision tree model for evidence-based practice. If you are trying to individualize your management for each particular patient, the more information you can get the better.