Published in final edited form as:

Eur J Surg Oncol. 2020 January ; 46(1): 98–104. doi:10.1016/j.ejso.2019.07.023.

Acute primary testicular failure due to radiotherapy increases risk of severe postoperative adverse events in rectal cancer patients.

John Tapper, MD MSc^{*}, Stefan Arver, MD PhD[†], Torbjörn Holm, MD PhD^{*}, Matteo Bottai, ScD[§], Mikael Machado, MD PhD[°], Ravi Jasuja, PhD^{a,b}, Anna Martling, MD PhD^{*}, Christian Buchli, MD PhD^{*}

^{*}Department of Molecular Medicine and Surgery, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden.

[†]Department of Medicine/Huddinge Karolinska Institutet and ANOVA, Karolinska University Hospital, Stockholm, Sweden

[°]Surgical Clinic, Sergelkliniken, Stockholm, Sweden.

[§]Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

^aFunction Promoting Therapies, Waltham, MA.

^bResearch Program in Men's Health: Aging and Metabolism, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Abstract

Aim: The aim of this study is to analyze postoperative adverse events (AE) in relation to acute primary testicular failure after radiotherapy (RT) for rectal cancer.

Method: This relation was assessed in 104 men, included in a previous prospective cohort study of men treated with surgical resection of the rectum for rectal cancer stage I-III. Postoperative AE were graded according to Clavien-Dindo (2004). Grade 3 or more was set as cut-off for severe postoperative AE. The impact of primary testicular failure on postoperative AE was related to the cumulative mean testicular dose (TD) and the change in Testosterone (T) and Luteinizing hormone (LH) sampled at baseline and after RT.

Results: Twenty-six study participants (25%) had severe postoperative AE. Baseline characteristics and endocrine testicular function did not differ significantly between groups with

Corresponding Author: John Tapper, MD MSc, Department of Molecular Medicine and Surgery, Karolinska Institutet. Solna D2:05, Stockholm 17176, Sweden Tel: +(46) 851770000; Fax: +(46) 8331587. john.tapper@ki.se.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclaimers: None.

Conflict of Interest
No

(AE+) and without severe postoperative AE (AE-). After RT, the LH/T-ratio was higher in AE+, 0.603 (0.2–2.5) vs 0.452 (0.127–5.926) ($p=0.035$). The longitudinal regression analysis showed that preoperative change in T (OR 0.844, 95% CI 0.720 – 0.990, $p=0.034$), LH/T-ratio (OR 2.020, 95% CI 1.010 – 4.039, $p=0.047$) and low T ($<8\text{nmol/L}$, OR 2.605, 95 CI 0.951 – 7.139, $p=0.063$) were related to severe postoperative AE.

Conclusion: Preoperative decline in T due to primary testicular failure induced by preoperative RT could be a risk factor regarding short-term outcome of surgery in men with rectal cancer.

1. Introduction

Short-term outcomes after treatment for rectal cancer differ between men and women [1–3]. Risk of mortality in men after anterior resection is up to three times higher than in women [4]. The risk for anastomotic leakage after colorectal resection is markedly increased in men compared to women, with odds ratios ranging between 1.48 to 3.08, and the postoperative mortality risk is further increased by anastomotic leakage [1, 2, 5–10]. Men have twice the risk of prolonged postoperative ileus, and surgical site infections have been shown to affect men more often than women [11–14]. After colorectal cancer surgery, women have less risk of in-hospital mortality, 30-day readmission and have shorter length of hospital stay [15]. The potential causes for this disparity between sexes are not fully elucidated. Anatomical differences between sexes have been suggested to increase the level of difficulty in surgery of men, and hence increase the risk of postoperative complications. However, male sex is a strong independent factor and by itself doubles the risk for intrabdominal anastomotic leaks, regardless of tumor level and also in colon cancer, and increases the risk of wound disruption by more than 50 percent [9, 10, 16, 17].

Preoperative radiotherapy (RT) increases the risk for postoperative adverse events (AE) [6, 18]. In the Stockholm III trial, the proportion of AE was highest in the group treated with 25 Gy and immediate surgery, 53%, versus 41% in the group treated with 25 Gy and delayed surgery for 4–8 weeks [19]. This raises the question if elapsed time between RT and surgery matters. In men, preoperative RT for rectal cancer results in primary testicular failure, characterized by an acute decrease in testosterone (T), resulting in a regulatory increase in luteinizing hormone (LH) as directed by the hypothalamic–pituitary–gonadal axis [20–22]. These previous data indicate that the elapsed time between RT and surgery is important regarding the state of recovery of endocrine testicular function. Testosterone is an important anabolic hormone in men and low levels are related to impaired wound healing and loss of lean mass in both healthy and injured men [23]. The addition of radiation-induced primary testicular failure to major surgery may be associated with adverse perioperative outcomes, as the decrease of T may influence healing after surgery for rectal cancer. This could be one mechanism explaining the differences in postoperative outcomes between men and women.

Accordingly, the aim of this study is to analyze postoperative AE in relation to primary testicular failure after RT for rectal cancer.

2. Material and Method

2.1 Study design and setting

This analysis of postoperative AE is restricted to men treated with surgical resection of the rectum for rectal cancer stage I-III, and is based on data from a previous prospective cohort study, analyzing the effect of RT on testicular function. Results from that cohort study showed that RT results in primary testicular failure related to the testicular radiation dose. Earlier publications have provided a detailed report on methods [20, 24]. The study was approved by the Regional Ethical Review Board (Dnr 2009/1860 –31/2) and registered under the Clinical Trial ID at www.clinicaltrials.gov. In the present study, the relationship between predictors for acute primary testicular failure, i.e. testicular radiation dose and preoperative changes in sex hormones, and postoperative adverse events graded according to Clavien-Dindo, was examined [25].

2.2 Participants

This study is based on participants from the previously described prospective cohort study [20]. 104 men had surgery for rectal cancer, stage I-III, and were included in analysis (Figure 1). The prescribed doses were 25 Gy, 50 Gy or 50.4 Gy. Men treated with 50.4 Gy had concomitant chemotherapy. Surgery after 25 Gy was performed directly or delayed 4 or more weeks, and full-dose preoperative chemotherapy according to the RAPIDO trial was possible [26]. White blood cell (WBC) counts and levels of C-reactive protein (CRP) and albumin (Alb) were analyzed at the Departments of Clinical Chemistry of the respective hospital.

2.3 Predictors of acute primary testicular failure

Testicular exposure to radiation was quantified by the cumulative mean testicular dose (TD), derived from treatment planning CT, relative TD was calculated by TD divided by prescribed dose times 100 [24]. The change in testicular endocrine function was assessed by measurement of circulating sex hormone levels, based on fasting morning blood sample at baseline, and after completed RT. Serum testosterone (T), luteinizing hormone (LH) and sex hormone binding globulin (SHBG) were analyzed using commercial assays [27, 28]. Free T levels were calculated [29]. The state of the hypothalamic–pituitary–gonadal axis was assessed by the LH-T ratio. Serum T levels below 8 nmol/L were regarded as biochemical hypogonadism.

2.4 Postoperative outcomes

Adverse events during the first 30 days postoperatively were recorded and graded according to Clavien-Dindo [25]. Grade three or more was regarded as severe, defined as AEs that resulted in surgical, endoscopic or radiological intervention (grade 3), IC/ICU management (grade 4) or death (grade 5). The highest graded severe postoperative AE for each study participant was used. Co-morbidities, American Society of Anesthesiologists (ASA) Physical Status score, disease- and treatment-related data were derived from medical reports.

2.5 Statistical analysis

Statistical analyses were performed with Stata version 14 (StataCorp LP, College Station, TX). Categorical data were reported as frequency (percentage) and continuous data as median (range). Wilcoxon rank-sum or Fisher exact tests were used for cross-sectional group comparisons and Wilcoxon's signed-Rank test or McNamer's test for longitudinal comparisons. Longitudinal regression models based on generalized estimating equation (GEE) were applied to evaluate the effect of preoperative change in endocrine testicular function, TD, patient-, disease- and treatment-related factors on severe postoperative AE. The robust variance estimator was used for calculations of standard error. All models were adjusted for elapsed time between start of RT and surgery to account for the T decline within days and the consecutive physiological LH increase described previously [20]. Final models were adjusted for age, BMI and ASA-score to account for the impact of age, obesity and comorbidity on the hypothalamic-pituitary-gonadal axis according to survey data from the general population [30]. Smoking, tumor stage, distance from the anal verge and type of surgery did not change the point estimates by more than 10% and were omitted in the adjusted analysis.

3. Results

3.1 Participants

Twenty-six of 104 participants had severe postoperative AE, resulting in a cumulative incidence of 25%. Patient-, disease- and treatment-related characteristics for both groups (AE+ and AE-) are displayed in Table 1. Baseline characteristics were comparable, except for hospital stay, which was longer for AE+ with 16 (4–46) days vs. AE- with 9 (4–31) days ($p < 0.001$). The median TD was 0.461 (0–14.193) Gy in AE+ and 0.660 (0–14.369) Gy in AE- ($p = 0.571$).

3.2 Endocrine testicular function

The levels of T and LH were similar at baseline and the proportion of low T was 19% in AE+ and 14% in AE- ($p = 0.539$), as shown in Table 2. After RT, median T levels decreased from 11.5 nmol/L to 8.7 nmol/L in AE+ and from 11 nmol/L to 9.6 nmol/L in AE-. The cross-sectional comparison of preoperative hormone levels showed a significant difference in LH/T-ratio with 0.603 (0.2–2.5) for AE+ vs 0.452 (0.127–5.926) for AE- ($p = 0.035$). At the day of admission and at the first day after surgery, CRP, WBC and Alb were similar between both groups.

3.3 Postoperative adverse events

In total 39 severe postoperative AE were recorded among the 26 study participants. One died from aspiration (grade 5: 1.0%), four had life-threatening complications requiring intensive care (grade 4: 3.8%), and 21 participants required surgical, endoscopic or radiological intervention with (grade 3b: 16.3%) or without (grade 3a: 3.8%) general anesthesia. Types of severe postoperative AE are specified in appendix A.

3.4 Longitudinal regression analysis

The preoperative change in endocrine testicular function was not related significantly to severe postoperative AE in the univariate analysis, but change in T indicated an inverse association with AE (OR: 0.878, 95% CI 0.759 – 1.015, $p=0.078$) (Table 3).

After adjustment for age, ASA-score and BMI, the preoperative change in T was inversely related to severe postoperative AE, OR 0.844 (95% CI 0.720 – 0.990, $p=0.034$), which equals an OR of 1.18 for severe postoperative AE per 1 nmol/l preoperative decrease in T. LH/T-ratio was also related to severe postoperative AE, OR 2.020 (95% CI 1.010 – 4.039, $p=0.047$). Figure 2 illustrates the relationship between change in serum T and predicted probability of having a severe postoperative AE, where an individual study participant can change in either direction. The TD and the relative TD were not associated with severe postoperative AE. The remaining covariates, analyzed in this study, were not related to severe postoperative AE (appendix B).

4. Discussion

This study on 104 men treated for rectal cancer demonstrates that the risk of severe postoperative adverse events is related to radiation-induced primary testicular failure, displayed by preoperative decrease in T levels and increase in LH/T-ratio.

We have previously demonstrated that RT in men treated for rectal cancer leads to a dose-dependent primary testicular failure, attributed to radiation-induced Leydig cell dysfunction [20]. Interestingly, this study clearly indicates that the decline in T due to primary testicular failure after RT is associated with severe postoperative AE. Other predictors/signs of primary testicular failure, the testicular exposure to radiation and the consecutive increase in LH, were not found to be associated with severe postoperative AE by themselves. Collectively, these data suggest that the perioperative T level is an important factor regarding susceptibility for severe postoperative AE. The parent study data includes different types of RT and varying time to surgery. Therefore, it is not possible to distinguish if impaired T production is due to immediate radiation-induced Leydig cell damage or due to pathological response to hypothalamic-pituitary-gonadal axis stimulation. The radiation dose was similar between groups, which may point towards an individual vulnerability to radiation and is reinforced by the significantly elevated preoperative LH/T-ratio in AE+. The confounding effect of age, ASA and BMI on the investigated association between primary testicular failure and postoperative AE is expected as these factors are known to affect sex hormone levels and the hypothalamic-pituitary-gonadal axis [30].

The literature on the impact of endocrine testicular function on perioperative morbidity, while observed in diverse clinical/preclinical settings, seem limited in rectal cancer patients. Low T in patients undergoing abdominal surgery was a risk factor for postoperative complications in both sexes, and postoperative AE resulted in delayed recovery of T levels after surgery [31]. Androgens have also been related to increased morbidity after trauma, with possible exception for thermal injuries [32]. In critical illness, the hypothalamic-pituitary-gonadal axis is suppressed, with decreased T and increased estradiol levels [33, 34]. Estradiol has been described as a “marker of injury severity and a predictor of death in

the critically injured patient”, with elevated levels in non-survivors of both sexes in an intensive care unit setting [34]. In men, about 80% of the circulating estradiol comes from testosterone, converted by the intracellular enzyme aromatase [35]. Circulating testosterone and estradiol levels have been shown to be positively correlated [36]. Primary testicular failure deprives the male body from its main anabolic hormone, tipping the scale toward a more catabolic state. It may further restrict the substrate, testosterone, for aromatase in these patients and result in decreased estradiol. However, the mechanisms behind the protective effect of circulating T regarding postoperative severe adverse events in men treated with abdominal surgery have not been investigated in detail. In rat models, androgens act inhibitory on intestine perfusion and endothelial function, which may be reflected in reduced healing of intestinal anastomoses. [37]. Mucosal wound healing is decreased with higher testosterone in younger men while estrogen is beneficial for cutaneous wound healing [38, 39]. The potential adverse effect of T on anastomosis healing is in contrast to the beneficial effects described above. The present study is too small and includes all types of severe adverse events which precludes further inference on specific T actions.

The results of this are based on a study population with heterogeneity regarding type of RT and surgery for rectal cancer. However, the included study participants were not restricted on age, comorbidity, tumor distance from anal verge, TNM status or preoperative levels of sex hormones. There was a high proportion of APE, due to referrals to the tertiary centers. Setting the bar of severe postoperative events at Clavien-Dindo grade 3+, minimizes the risk of missed information as the severity of those events forces inclusion in the study participants’ medical records. Sex hormone levels were assessed according to standardized guidelines to decrease the risk of information bias. The longitudinal regression analysis did not show association with known risk factors for severe postoperative AE, such as age and high ASA-score, which could be interpreted as type two errors as the study was not powered to do so [2, 4]. The sample size was still large enough to detect the associations between T and LH/T-ratio and severe postoperative AE. Internal validity of this study is deemed adequate. External validity is affected by the study participants in general having more advanced, and lower situated, rectal cancer than in the comparable population, yielding a relatively higher TD resulting in a more severe primary testicular failure.

5. Conclusions

The present study elucidates that a preoperative decline in T, following preoperative RT, is a risk factor for severe postoperative AE in men undergoing treatment for rectal cancer. This could be a mechanism explaining part of gender differences in postoperative morbidity and mortality after surgery for rectal cancer.

Acknowledgements:

The Regional Agreement on Medical Training and Clinical Research (ALF) between the Stockholm Community Council and Karolinska Institutet, The Stockholm Cancer Society and the Swedish Cancer Society provided financial support. Madelene Ahlberg provided valuable support in collecting data.

Research support: The Regional Agreement on Medical Training and Clinical Research (ALF) between the Stockholm Community Council and Karolinska Institutet. The Stockholm Cancer Society and the Swedish Cancer

Society provided financial support. National Institutes of Health grant R43 AG045011-01A1, R44 AG045011-02 (RJ).

Appendix

Appendix A.

First recorded severe adverse event, Clavien-Dindo 3+

Grade	Event
3a	Anastomotic stricture
3a	Deep infection (fascia, muscle)
3a	Urinary leak
3a	Intraabdominal/pelvic infection
3b	Stoma late prolapse
3b	Stoma early bowel perforation
3b	Intraabdominal/pelvic infection
3b	Ischemia leg
3b	Stoma late prolapse
3b	Wound dehiscence
3b	Foreign body extraction
3b	Femur fracture
3b	Stoma early retraction
3b	Stoma late stenosis
3b	Incisional hernia
3b	Small bowel obstruction
3b	Small bowel obstruction
3b	Anastomotic leak
3b	Incisional hernia
3b	Intraabdominal/pelvic infection
3b	Anastomotic leak
4a	Respiratory failure
4a	Respiratory failure
4a	Postoperative bleeding
4b	Wound dehiscence
5	Aspiration

Appendix B.

Longitudinal regression analysis of possible confounders and predictors for severe postoperative adverse events. All models adjusted for time elapsed between start of RT and surgery.

	Odds Ratio for Clavien-Dindo 3+	95% Confidence interval	p
Age (yr)	1.007	0.998 – 1.015	0.738
Body Mass Index (kg/m2)	1.048	0.948 – 1.159	0.357

	Odds Ratio for Clavien-Dindo 3+	95% Confidence interval	p
ASA-score			
I	ref.		
II	1.448	0.478 – 4.383	0.512
III	0.623	0.138 – 2.817	0.539
Smoking status	1.239	0.399 – 3.850	0.711
Radiological tumor stage			
1–3a/b	ref.		
3c/d - 4	0.541	0.201 – 1.454	0.223
Tumor distance from anal verge (cm)	0.972	0.875 – 1.080	0.599
Surgery 4+ weeks after radiotherapy	ref.		
Surgery close after radiotherapy	1.539	0.647 – 3.661	0.329
Postoperative laboratory markers			
Preoperative C-reactive protein level, mg/L			
10	ref.		
>10	1.372	0.496 – 3.797	0.542
White blood cell count, Units $\times 10^9/L$			
8.8	ref.		
>8.8	1.874	0.530 – 6.629	0.330
Albumin, g/L			
34	ref.		
<34	2.244	0.898 – 5.609	0.084
Type of resection			
Anterior resection	ref.		
Abdominoperineal excision	1.343	0.567 – 3.182	0.502

6. Literature

1. Pommergaard HC, et al. Preoperative risk factors for anastomotic leakage after resection for colorectal cancer: a systematic review and meta-analysis. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2014;16:662–71. [PubMed: 24655784]
2. McDermott FD, et al. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *The British journal of surgery* 2015;102:462–79. [PubMed: 25703524]
3. Registry SCC. Inga allvarliga komplikationer efter operation av ändtarmscancer. Andel patienter utan allvarliga komplikationer efter operation av ändtarmscancer. editor^, editors” City: The Swedish Association of Local Authorities and Regions, SALAR. 2019-02-06.,
4. Matthiessen P, et al. Population-based study of risk factors for postoperative death after anterior resection of the rectum. *The British journal of surgery* 2006;93:498–503. [PubMed: 16491473]
5. Bertelsen CA, et al. Anastomotic leakage after anterior resection for rectal cancer: risk factors. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2010;12:37–43.

6. Sparreboom CL, et al. Different Risk Factors for Early and Late Colorectal Anastomotic Leakage in a Nationwide Audit. *Diseases of the colon and rectum* 2018;61:1258–66. [PubMed: 30239395]
7. Kang CY, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. *JAMA Surg* 2013;148:65–71. [PubMed: 22986932]
8. Zhou C, et al. Male gender is associated with an increased risk of anastomotic leak in rectal cancer patients after total mesorectal excision. *Gastroenterology report* 2018;6:137–43. [PubMed: 29780603]
9. Law WI, et al. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. *American journal of surgery* 2000;179:92–6. [PubMed: 10773140]
10. Nikolian VC, et al. Anastomotic leak after colorectal resection: A population-based study of risk factors and hospital variation. *Surgery* 2017;161:1619–27. [PubMed: 28238345]
11. Sutton E, et al. Risk factors for superficial surgical site infection after elective rectal cancer resection: a multivariate analysis of 8880 patients from the American College of Surgeons National Surgical Quality Improvement Program database. *The Journal of surgical research* 2017;207:205–14. [PubMed: 27979478]
12. Gomila A, et al. Risk factors and outcomes of organ-space surgical site infections after elective colon and rectal surgery. *Antimicrobial resistance and infection control* 2017;6:40. [PubMed: 28439408]
13. Segal CG, et al. An evaluation of differences in risk factors for individual types of surgical site infections after colon surgery. *Surgery* 2014;156:1253–60. [PubMed: 25178993]
14. Hain E, et al. Risk factors for prolonged postoperative ileus after laparoscopic sphincter-saving total mesorectal excision for rectal cancer: an analysis of 428 consecutive patients 2018;32:337–44.
15. Pucciarelli S, et al. In-hospital mortality, 30-day readmission, and length of hospital stay after surgery for primary colorectal cancer: A national population-based study. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2017;43:1312–23.
16. Carlson MA. Acute wound failure. *The Surgical clinics of North America* 1997;77:607–36. [PubMed: 9194883]
17. Frasson M, et al. Risk Factors for Anastomotic Leak After Colon Resection for Cancer: Multivariate Analysis and Nomogram From a Multicentric, Prospective, National Study With 3193 Patients. *Ann Surg* 2015;262:321–30. [PubMed: 25361221]
18. Cedermark B, et al. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. *Stockholm Colorectal Cancer Study Group. Cancer* 1995;75:2269–75. [PubMed: 7712435]
19. Erlandsson J, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *The lancet oncology* 2017;18:336–46. [PubMed: 28190762]
20. Buchli C, et al. Risk of Acute Testicular Failure After Preoperative Radiotherapy for Rectal Cancer: A Prospective Cohort Study. *Ann Surg* 2018;267:326–31. [PubMed: 27849668]
21. Bruheim K, et al. Radiotherapy for rectal cancer is associated with reduced serum testosterone and increased FSH and LH. *International journal of radiation oncology, biology, physics* 2008;70:722–7.
22. Dueland S, et al. Radiation therapy induced changes in male sex hormone levels in rectal cancer patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2003;68:249–53. [PubMed: 13129632]
23. Demling RH. The role of anabolic hormones for wound healing in catabolic states. *Journal of burns and wounds* 2005;4:e2-e. [PubMed: 16921407]
24. Buchli C, et al. Assessment of testicular dose during preoperative radiotherapy for rectal cancer. *Acta Oncol* 2016;55:496–501. [PubMed: 26362484]
25. Dindo D, et al. Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. *Annals of Surgery* 2004;240:205–13. [PubMed: 15273542]

26. Nilsson PJ, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer--the RAPIDO trial. *BMC cancer* 2013;13:279. [PubMed: 23742033]
27. Lehtihet M, et al. S-testosterone decrease after a mixed meal in healthy men independent of SHBG and gonadotrophin levels. *Andrologia* 2012;44:405–10. [PubMed: 22524522]
28. Bhasin S, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism* 2010;95:2536–59. [PubMed: 20525905]
29. Zakharov MN, et al. A multi-step, dynamic allosteric model of testosterone's binding to sex hormone binding globulin. *Molecular and cellular endocrinology* 2015;399:190–200. [PubMed: 25240469]
30. Wu FC, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *The Journal of clinical endocrinology and metabolism* 2008;93:2737–45. [PubMed: 18270261]
31. Sah BK, et al. Does testosterone prevent early postoperative complications after gastrointestinal surgery? *World journal of gastroenterology* : WJG 2009;15:5604–9. [PubMed: 19938202]
32. Al-Tarrah K, et al. The influence of sex steroid hormones on the response to trauma and burn injury. *Burns Trauma* 2017;5:29. [PubMed: 28920065]
33. Spratt DI, et al. Reproductive axis suppression in acute illness is related to disease severity. *The Journal of clinical endocrinology and metabolism* 1993;76:1548–54. [PubMed: 8501163]
34. Dossett LA, et al. High levels of endogenous estrogens are associated with death in the critically injured adult. *The Journal of trauma* 2008;64:580–5. [PubMed: 18332796]
35. Longcope C, et al. Conversion of blood androgens to estrogens in normal adult men and women. *The Journal of Clinical Investigation* 1969;48:2191–201. [PubMed: 5355335]
36. Dhindsa S, et al. Low estradiol concentrations in men with subnormal testosterone concentrations and type 2 diabetes. *Diabetes care* 2011;34:1854–9. [PubMed: 21715518]
37. Ba ZF, et al. Gender differences in small intestinal endothelial function: inhibitory role of androgens. *American journal of physiology Gastrointestinal and liver physiology* 2004;286:G452–7. [PubMed: 14563675]
38. Engeland CG, et al. Sex hormones and mucosal wound healing. *Brain Behavior and Immunity* 2009;23:629–35.
39. Gilliver SC, et al. The hormonal regulation of cutaneous wound healing. *Clinics in Dermatology* 2007;25:56–62. [PubMed: 17276202]

Figure 1.
Study participant flow chart.

Figure 2. Predicted risk of severe postoperative adverse events graded 3+ according to Clavien-Dindo in relation to the preoperative change in serum testosterone. The curve describes the expected change in risk for severe postoperative adverse event with 95% confidence interval related to the preoperative change in serum testosterone.

Table 1.

Clinical characteristics

	Clavien 0–2	Clavien 3+	<i>p</i>
Number of participants	78	26	
Age (Years)	63.5 (36–82)	63 (32–86)	0.816 [†]
BMI (kg/m ²)	24.8 (16.1–35.3)	26.2 (20.8–40.6)	0.145 [†]
ASA-score			
I	17 (22)	4 (15.5)	
II	41 (52.5)	18 (69)	0.372 [*]
III	20 (25.5)	4 (15.5)	
No. of comorbidities			
0	30 (38.5)	10 (38.5)	
1	18 (23)	9 (34.5)	0.446 [*]
2	30 (38.5)	7 (27)	
Current smoker			
No	68 (87)	22 (85)	0.746 [*]
Yes	10 (13)	4 (15)	
Radiological tumor stage			
T2	9 (11)	6 (23)	
T3 a/b	35 (45)	11 (42)	0.539 [*]
T3 c/d	10 (13)	3 (12)	
T4	24 (31)	6 (23)	
Radiological lymph node status			
N0	29 (37)	13 (50)	0.573 [*]
N+	49 (63)	13 (50)	
Tumor distance from anal verge (cm)	8 (1–15)	7 (1–14)	0.595 [†]
Neoadjuvant treatment			
None	10 (12.8)	3 (11.5)	0.258 [*]
25 Gy, direct surgery	30 (38.5)	11 (42.3)	
25 Gy, delayed surgery	8 (10.2)	7 (26.9)	
25 Gy, chemotherapy and delayed surgery	10 (12.8)	1 (3.9)	
50 Gy	2 (2.6)	0 (0)	
50.4 Gy and concomitant chemotherapy	18 (23.1)	4 (15.4)	
Cumulative mean testicular dose, TD (Gy)	0.660 (0–14.369)	0.461 (0–14.193)	0.571 [†]
Relative TD (TD/Total dose *100)	2.301 (0–57.477)	1.513 (0–56.773)	0.571 [†]
Time between radiotherapy and surgery (days)	34 (1 – 192)	41 (3 – 188)	0.755 [†]
Type of resection			
Anterior resection	54 (69)	15 (58)	0.340 [*]
Abdominoperineal excision	24 (31)	11 (42)	
Surgical operation time (minutes)	304 (163–605)	332 (141–857)	0.504 [*]

	Clavien 0–2	Clavien 3+	<i>p</i>
Blood loss during surgery (mL)	600 (25–2800)	500 (150–16600)	0.783 [*]
Length of hospital stay (days)	9 (4–31)	16 (4–46)	0.000 [†]

Notes: Continuous variable reported as median (range), Categorical data reported as frequency (percentage)

^{*}=Fishe's exact test

[†]=Wilcoxon rank-sum test, ASA = American Society of Anesthesiologists, Gy = Gray.

Table 2.

Hormones and laboratory markers.

	Clavien 0–2	Clavien 3+	<i>p</i>
Baseline hormones			
Testosterone (nmol/L)	11 (4.2–22)	11.5 (4–17)	0.949 [†]
Free testosterone (pmol/L)	318.0 (89.7 – 665.7)	311.7 (100.5–496.3)	0.828 [†]
Luteinizing Hormone (IU/L)	4 (1.6–13)	4.7 (2–16)	0.127 [†]
LH/T-ratio	0.342 (0.11–2.097)	0.460 (0.182–2.5)	0.118 [†]
Proportion with Testosterone < 8 nmol/L	11 (14)	5 (19)	0.539 [*]
Preoperative hormones			
Testosterone (nmol/L)	9.6 (0.8–22)	8.7 (2.4 – 17)	0.286 [†]
Free testosterone (nmol/L)	0.266 (0.017–0.666)	0.254 (0.046–0.534)	0.276 [†]
Luteinizing Hormone (IU/L)	4.6 (1.6–16)	5.3 (2.1–16)	0.107 [†]
LH/T-ratio	0.452 (0.127–5.926)	0.603 (0.2–2.5)	0.035 [†]
Proportion with Testosterone < 8 nmol/L	22 (28)	10 (38)	0.337 [*]
Laboratory markers			
Preoperative			
C-reactive protein	3 (1–38)	4 (1–50)	0.243 [†]
White cell blood count	5.45 (3.1–11.8)	5.6 (3.7 – 11)	0.190 [†]
Albumin	38 (28–45)	38 (30 – 43)	0.905 [†]
Postoperative, day 1 after surgery			
C-reactive protein, mg/L	85 (22–196)	100 (45–219)	0.341 [†]
White cell blood count, Units × 10 ⁹ /L	7.8 (3.7 – 11.4)	8.5 (4.5 – 23.8)	0.432 [†]
Albumin, g/L	26.5 (22–35)	26.5 (22–30)	0.918 [†]

Notes: Continuous variable reported as median (range), Categorical data reported as frequency (percentage)

[†] = Wilcoxon rank-sum test

^{*} = Fische s exact test.

Table 3.

Longitudinal regression analysis of primary testicular failure after preoperative radiotherapy for rectal cancer on severe postoperative adverse events. All models are adjusted for elapsed time between start of RT and surgery.

Markers or predictors or for testicular damage.	Surgical complications, Clavien-Dindo grade 3+		
Mean change in preoperative hormones and TD	Odds Ratio for Severe AE	95% Confidence interval	p
Serum Testosterone (nmol/L)	0.878	0.759 – 1.015	0.078
Free Testosterone (pmol/L)	0.997	0.992 – 1.002	0.201
LH (IU/L)	1.067	0.917 – 1.241	0.402
LH-T ratio	1.442	0.717 – 2.899	0.304
Testosterone < 8nmol/L	1.921	0.701 – 5.259	0.204
Cumulative mean testicular radiation dose (Gy)	1.121	0.936 – 1.342	0.216•
Relative TD (Percent)	1.039	0.984 – 1.097	0.172
Mean change in preoperative hormones and TD (additionally adjusted for age, ASA & BMI)			
Serum Testosterone (nmol/L)	0.844	0.720 – 0.990	0.034
Free Testosterone (pmol/L)	0.995	0.989 – 1.001	0.077
LH (IU/L)	1.134	0.967 – 1.329	0.122
LH-T ratio	2.020	1.010 – 4.039	0.047
Testosterone < 8nmol/L	2.605	0.951 – 7.139	0.063
Cumulative mean testicular radiation dose (Gy)	1.116	0.903 – 1.380	0.310
Relative TD (Percent)	1.037	0.975 – 1.102	0.245

Notes TD = Cumulative mean testicular radiation dose. AE = postoperative adverse events graded Clavien-Dindo 3 or more. ASA = The American Society of Anesthesiologists physical status classification. BMI = Body Mass Index.