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Pelvic floor functional outcomes after total abdominal versus total laparoscopic hysterectomy for endometrial cancer

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PII: S0002-9378(17)32807-7

DOI: 10.1016/j.ajog.2017.12.233

Reference: YMOB 12021

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 27 October 2017

Revised Date: 15 December 2017

Accepted Date: 27 December 2017

Please cite this article as: Higgs P, Janda M, Asher R, Gebski V, Forder P, Obermair A, Pelvic floor functional outcomes after total abdominal versus total laparoscopic hysterectomy for endometrial cancer, *American Journal of Obstetrics and Gynecology* (2018), doi: 10.1016/j.ajog.2017.12.233.

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Title: Pelvic floor functional outcomes after total abdominal versus total laparoscopic hysterectomy for endometrial cancer

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Disclosure Statement

OA reported receiving travel grants from the O. R. Company; being the founder and managing director of SurgicalPerformance Pty Ltd; and being a consultant for Covidien. No other disclosures were reported.

Funding

Funding Cancer Council Queensland, Cancer Council New South Wales, Cancer Council Victoria, Cancer Council Western Australia; NHMRC project grant 456110; Cancer Australia project grants 631523 and 1098905; The Women and Infants Research Foundation, Western Australia; Royal Brisbane and Women's Hospital Foundation; Wesley Research Institute; Gallipoli Research Foundation; Gynetech; TYCO Healthcare, Australia; Johnson and Johnson Medical, Australia; Hunter New England Centre for Gynaecological Cancer; Genesis Oncology Trust; Smart Health Research Grant/QLD Health, Cherish Foundation. The sponsors had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Trial registration

clinicaltrials.gov Identifier: NCT00096408; Australian New Zealand Clinical Trials Registry: CTRN12606000261516

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Word counts

Abstract: 259

Main text: 2651

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Condensation: Women undergoing hysterectomy for endometrial cancer can expect that the surgery will improve their pelvic floor function at least in the short term.

Short title: Pelvic floor function after hysterectomy

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Abstract:

Background: Pelvic floor functioning is an important concern for women requiring a hysterectomy for endometrial cancer. The incidence of pelvic floor symptoms has not been reported in women who have undergone a hysterectomy for early-stage endometrial cancer.

Objectives: To evaluate pelvic floor function in women who have had surgical treatment for early stage endometrial cancer as part of the multinational Laparoscopic Approach to Cancer of the Endometrium (LACE) trial and to compare patients' outcomes who had total abdominal total versus total laparoscopic hysterectomy.

Study Design: Multinational, phase 3, randomized non-inferiority trial comparing disease-free survival of patients who had total abdominal hysterectomy versus total laparoscopic hysterectomy. This substudy analyses the results from a self-administered validated questionnaire on pelvic floor symptoms (Pelvic Floor Distress Inventory (PFDI)) administered pre-operatively, and at follow-up visits 6, 18, 30, 42, and 54 months post-operatively.

Results: Overall, 381 patients with endometrial cancer were included in the analysis (total abdominal hysterectomy n=195; total laparoscopic hysterectomy n=186). At 6-months post-surgery both groups experienced an improvement in Pelvic Floor Distress Inventory scores compared to presurgical pelvic floor wellbeing (total abdominal hysterectomy: mean change -11.17, 95% CI: -17.11 to -5.24; total laparoscopic hysterectomy mean change -10.25, 95% CI: -16.31 to -4.19). The magnitude of change from baseline in pelvic floor symptoms did not differ between both treatment groups up to 54 months post-surgery.

Conclusion: These findings suggest that pelvic floor function in terms of urinary, bowel and prolapse symptoms are unlikely to deteriorate following abdominal or laparoscopic

hysterectomy and are reassuring for women undergoing hysterectomy for early stage endometrial cancer.

Keywords: endometrial cancer, minimally invasive hysterectomy, pelvic floor, quality of life

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Introduction

Endometrial cancer represents a significant health issue for women across the world. An estimated 300,000 women were diagnosed with endometrial cancer in 2012 and its incidence is still rising.[1] Advanced age, and an oversupply of endogenous or exogenous oestrogen are the most common and well established risk factors for endometrial cancer. Patients often have comorbidities such as obesity, diabetes mellitus and hypertension.[2-5] Treatment of endometrial cancer is primarily surgical and open, abdominal surgery should generally be avoided because its association with increased treatment-related morbidity at comparable survival outcomes.[6-8]

Urinary incontinence, pelvic organ prolapse and bowel dysfunction are common conditions following childbirth and the incidence of symptoms increases with age, the number of vaginal deliveries and obesity.[9, 10] These conditions significantly impact on women's quality of life, have considerable financial implications and contribute to health care utilization, personal and health care costs.[11, 12] Previous studies on urinary function in gynecological cancer patients have shown a decline in function following cancer treatment.[13-15] However, these studies analyzed pelvic floor outcomes of very diverse groups of patients who had treatment for cervical and endometrial cancer, who required simple or radical hysterectomies and even included patients who received definitive pelvic radiotherapy. It was concluded that women with early-stage endometrial cancer undergoing either total abdominal hysterectomy (TAH) or total laparoscopic hysterectomy (TLH) had better pelvic floor functional outcomes compared to those who required more aggressive cancer treatment.[13-16] Data on which these conclusions have been placed is limited, and confirmation in larger studies of early stage endometrial cancer patients is required to advise the ever increasing number of patients of the expectations with respect to pelvic floor function after surgery.

The aim of the present study was to evaluate pelvic floor function in a large cohort of women receiving surgical treatment for early stage endometrial cancer as part of the multinational Laparoscopic Approach to Cancer of the Endometrium (LACE) trial and to compare outcomes of patients who had TAH versus TLH.

Materials and Methods

Study design and procedures

The LACE trial was a multinational randomized, phase 3 clinical trial comparing total abdominal hysterectomy (TAH) to total laparoscopic hysterectomy (TLH) in women with apparent Stage 1 endometrial cancer (EC). All patients also had a bilateral salpingectomy and oophorectomy. A total of 760 patients were recruited through 20 gynecological cancer centres in Australia, New Zealand, and Hong Kong. Ethics approval was obtained from each hospital's Human Research and Ethics Committees. The lead Human Research Ethics (HRE) Committee was the Royal Brisbane & Women's Hospital HRE Committee (approval number: EC00172 - 20 September 2004). Written informed consent was obtained from patients prior to randomization. Quality of Life (QoL) outcomes[17], incidence and risk factors for adverse events[7, 18] and recurrence and survival data[6] of the LACE trial have been previously reported.

Eligibility and exclusion criteria were described in detail previously.[19] In brief; patients with histologically confirmed endometrial adenocarcinoma of any FIGO grade without evidence of extra-uterine disease by imaging (computed tomography (CT) or Magnetic Resonance Imaging (MRI) of the abdomen and pelvis and chest radiograph or chest CT) were eligible. Women with a histological cell-type other than endometrioid on curettage, clinically advanced disease (stage II – IV using FIGO 2009 criteria for stage or bulky lymph nodes on imaging), or uterine size greater than 10 weeks of gestation were ineligible.

Patient-related assessments were collected prior to surgery, at week 1, and months 1, 3, and 6, post-surgery. All patients were followed up at 12 months post-surgery and then annually for survival outcomes. Patients without events were censored at the date of data lock (3rd March 2016) or date of last contact for patients lost to follow up. Randomization procedures were also described in detail previously.[6]

The surgical procedures and their steps have been described in detail earlier.[19] For the TLH an anatomically curved silicone tube with a proximal airtight cap that prevents loss of pneumoperitoneum, enables instrument access and facilitates the safe removal of specimens transvaginally was used (McCartney Tube™, The O.R. Company, Melbourne, Australia). TAH was performed through a vertical midline or lower transverse incision.

Histopathological findings were used to determine the need for adjuvant treatment according to local institutional clinical practice guidelines, and typically were discussed in multidisciplinary meetings. The delivery and management of radiation therapy or chemotherapy was carried out according to local institutional clinical practice guidelines. Data on dosimetry or chemotherapy dosing was recorded.

All clinical Adverse Events (AEs) encountered during the clinical study were documented. The intensity of AEs was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTC-AE v3.0). The incidence of, and risk factors for, AEs was reported previously.[7, 18]

For quality assurance of the surgical intervention, a rigorous accreditation process was followed as described in detail previously.[19] Surgeons were required to (i) be certified gynecological oncologists proficient in TAH and TLH or under the direct supervision of a certified gynecological oncologist in theatre; and (ii) had to be accredited by the LACE trial committee after they provided evidence of surgical proficiency.

Outcomes

While the primary outcome of the LACE trial was disease-free survival (DFS) at 4.5 years, for this substudy, the outcome of interest was pelvic floor symptoms; a pre-specified secondary outcome measured using the Pelvic Floor Distress Inventory (PFDI). The PFDI was only introduced after approximately half of the patients had already been enrolled in the study and only collected for patients enrolled in the latter (n=381) part of the trial. This sample size was sufficient to provide 80% power to detect a difference between the two groups of at least 15 points or more (one standard deviation (SD)) in the PFDI summary score. Previous work has identified that a PFDI summary score of 13.5 or more reflects a minimally important change among women with mild to moderate pelvic floor symptoms.[20]

The PFDI[21] is a 20-item questionnaire consisting of three domains; the 6-item pelvic organ prolapse distress inventory (POPDI-6), the 8-item colorectal-anal distress inventory (CRADI-8) and the 6-item urinary distress inventory (UDI-6). Item response values ranged from 0-4. Following the PFDI scoring instructions, the mean score from the items in each subscale was multiplied by 25 to provide a common range for the subscales (range 0-100), the overall PFDI score was the summation of the subscale scores (range 0-300). A higher score signifies worse pelvic floor wellbeing. The PFDI provides a standardized and reproducible assessment of symptom severity and pelvic floor wellbeing changes in women with pelvic floor disorders. It has been reported to have good test-retest reliability, internal consistency and in external validation was found to be sensitive to change.[22] Use of this psychometrically robust self-administered questionnaire is a valid way of measuring the presence, severity, and impact of a symptom or condition on a patient's activities and well-being. The PFDI was administered pre-operatively, then at follow-up visits 6, 18, 30, 42 and 54 months post-operatively.

Statistical Analysis

All statistical analyses were conducted according to the intention-to-treat (ITT) principle.

The number of completed questionnaires at each time point was summarized. Patients who had not completed the PFDI pre-operatively were excluded from analysis. Incomplete questionnaires were excluded when analysing the PFDI total score; when analysing the domains separately, those domains which were completed fully were included in the analysis even if the remainder of the questionnaire was incomplete.

Patient demographic and clinical characteristics are presented as frequency (%) if categorical and mean (SD) if continuous. Pelvic floor scores (total and sub-domains) were summarized as mean (SD) at each time point by randomization group. Plots were constructed to graphically visualize the mean scores (with corresponding 95% confidence interval) over time for the total score and each of the pelvic organ prolapse, colorectal-anal and urinary distress inventory domains. In addition, a patient was considered to have pelvic floor symptoms if they answered ‘moderate’ or ‘severe’ for at least one of the PFDI questions and the proportion of patients with pelvic floor symptoms was summarised at each time point.

At each time point, differences from baseline for each outcome were calculated and these differences analysed using the repeated measure method of generalised estimating equations (GEEs) (which account for correlated outcomes and can account for missing data, retaining all available observations in the models). Additionally, time-by-treatment interaction terms were fitted to estimate the change in scores from baseline to each time point and to determine whether these changes differed between the treatment groups. This approach takes into account the within-patient correlation that occurs in the scores, using an exchangeable correlation structure for the robust variance estimation. As pelvic floor wellbeing of patients overall was good, the analyses then specifically focussed on women who reported at least one

or more moderate to severe pelvic floor symptoms on any of the questionnaire items. The proportion of women at each timepoint was summarised. Stratified analyses then reported whether women had pelvic floor issues already before surgery or developed new pelvic floor issues after surgery, and whether these resolved or remained at subsequent timepoints. The proportion of women with pelvic floor symptoms was also assessed depending on whether or not adjuvant therapy was received.

All analyses were conducted in SAS version 9.3 (SAS Institute, Inc, Cary, NC) and STATA version 14.1 (Statacorp, Texas) with significance testing at at the 5% level (two-sided) . No statistical adjustments to the analysis were made for multiple testing or to account for missing data.

Results

Of the 760 patients randomized into the LACE trial, 381 patients completed the PFDI questionnaire pre-operatively and at least one follow-up PFDI questionnaire. Of these, 195 patients were in the total abdominal hysterectomy (TAH) group with 186 patients in the total laparoscopic hysterectomy (TLH) group (Figure 1).

Baseline characteristics were similar between randomization groups (Table 1). Demographic and clinical characteristics were representative of the overall LACE population (Supplementary Table 1).

Pre-operatively, of the 381 participating patients, 322 (85%) patients provided a complete PFDI response with all three subscales answered . By 54 months post-op, participation had dropped to 207 (54%) due to death and/or disease progression (n=41, 24%), 88 (51%) patients had not been followed up to the 54-month timepoint and the remaining 45 (26%) did not complete their questionnaire at the 54-month time point. For the individual scales, the

pelvic organ prolapse domain had the highest completion rate (92-97% over time) while the colorectal-anal distress subscale had the lowest rate (89-94%) (Supplementary Table2).

Summary of PFDI scores over time

Figures 2A-D show the mean scores (with 95% CI around the mean) for PFDI and domains at the pre-specified time points, according to treatment group. Within both treatment groups, there was an initial improvement in pelvic floor function 6-months post-surgery primarily due to pelvic organ prolapse, and urinary distress domains. Patients in the TLH group consistently had a lower pelvic floor functioning score indicating better wellbeing, which was most pronounced in the urinary distress domain, but the difference between the TAH and TLH group scores was not statistically significant.

Change in PFDI scores over time

The results from the GEE models assessing the difference in change from baseline between the TLH and TAH groups are presented as a forest plot in Figure 3 (and supplementary Table 4). For all the models, the interaction between treatment and time was not statistically significant, suggesting that the change in PFDI over time did not differ between the randomization groups. At 6-months post-surgery both treatment groups experienced an improvement in total PFDI score (TAH: mean change -11.17, 95% CI: -17.11 to -5.24; TLH mean change -10.25, 95% CI: -16.31 to -4.19). However, there was no evidence of a significant difference between the treatment groups over time in terms of change from baseline PFDI scores with confidence intervals all overlapping the zero (Figure 3).

Patients in both the TAH and TLH groups showed an improvement from baseline in the pelvic organ prolapse domain at each time point; however there was no evidence to support a difference between the two treatment groups in change in the pelvic organ prolapse symptoms (interaction p-value = 0.79). Similarly, both treatment groups showed an

improvement at 6 months post-surgery in the urinary distress domain (TAH change -4.60, 95% CI: -7.47 to – 1.79; TLH mean change -4.19, 95% CI: -7.12 to -1.26; Figure 3). There were no significant changes in the colorectal-anal distress domain over time or between treatment groups.

Although the proportion of patients with at least one moderate to severe pelvic floor problem was higher in the TAH group overall, and in the pelvic organ prolapse and urinary distress domains across most postsurgical time points, the difference in the proportions of women in the TAH or TLH groups who reported at least one symptom was small (about 3-5%) (Table 2). The stratified summary of patients shows that 30% in both groups had no moderate to severe symptoms at baseline and throughout the study observation period, 43% of patients in the TAH and 48% of patients in the TLH group had one or more moderate to severe symptom at baseline, and 24% of patients in the TAH group, and 19% in the TLH group developed one or more moderate to severe new symptoms after baseline. Of those women reporting either existing or new symptoms about half resolved and half persisted in both treatment groups (Table 3). There was no difference in persisting or new pelvic floor symptoms between women who did or did not receive adjuvant therapy (Supplementary Table 3).

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Comment

This study provides some answers to questions commonly asked by patients who require surgery for endometrial cancer about how their symptoms of urinary incontinence, pelvic organ prolapse and bowel dysfunction may progress. Women in both groups improved initially and their scores then slowly declined while maintaining some beneficial gains compared to their pre-surgical pelvic floor wellbeing. The data also reported here show that there was no difference between TLH and TAH with respect to pelvic floor symptoms for up to 54 months post-surgery. These findings will reassure for women undergoing hysterectomy for endometrial cancer, either by TAH or TLH.

The data provided here have been obtained through a prospective, randomised trial using a validated questionnaire that was completed by patients prior to surgery and up to 54 months post-surgery at multiple time points. Recently, the results of three randomised controlled clinical trials were published suggesting that TLH is superior to TAH in regards to short-term outcomes and equivalent with respect to survival outcomes.[6, 8, 23] The data reported here provides additional empirical evidence by demonstrating that women who receive TLH will have similar outcomes compared to women treated by TAH with respect to pelvic floor functioning.

Our findings extend previous studies by directly comparing two approaches to total hysterectomy in a homogenous group of patients with early endometrial cancer. Previous studies on the pelvic floor function after hysterectomy have mainly enrolled women with benign indications, or concentrated on the differences in outcomes between total and subtotal hysterectomy. A Cochrane review comparing those two techniques found no difference in regards to urinary incontinence, bowel function or sexual function.[24] However, comparing pre- and post- hysterectomy scores, there was an overall improvement in symptoms of

urinary incontinence post-hysterectomy noted in that review for both total and subtotal hysterectomy. The only previous study assessing bowel function found no difference pre- or post-operatively between the different routes of hysterectomy, and no changes over time.[25] Sexual function was also not found to be different between the different hysterectomy techniques, with a trend towards improvement post-operatively.[24] Subsequently, another Cochrane review specifically examining the impact of route of hysterectomy for benign conditions noted an absence of high-quality data on urinary, bowel, sexual function and quality of life and suggested the collection of long-term data for all of these patient reported outcomes.[26]

The importance of using data from prospective studies when examining pelvic floor function and quality of life has been acknowledged by clinicians and women alike. Previously, the perception of deterioration of pelvic floor function has been related to women dating the onset of their symptoms to a significant life event (e.g. a hysterectomy).[27] However, this concern has been not be confirmed by prospective studies on hysterectomy for benign conditions.[24, 25] Women in the present study had, on average, good pelvic floor functioning, and the average score did not change significantly after surgery in either group. The present study now provides evidence for women who require a hysterectomy for early-stage endometrial cancer, and who have one or more moderate to severe symptom before surgery, that at least half can expect a resolution of those symptoms.

Previous studies on women who require hysterectomy for cervical or endometrial cancer have found an increase in urinary and bowel dysfunction secondary to radical hysterectomy and adjuvant pelvic radiation therapy being associated with more severe urinary and bowel symptoms, and impact on quality of life.[13-15] In contrast, most patients on the LACE trial had a Piver Type 1 hysterectomy and pelvic floor function, in terms of urinary, bowel and prolapse symptoms, did not deteriorate. This could point to the possibility that pelvic floor

symptoms experienced by women after gynecological cancer in previous studies may arise as a cause of nerve damage inflicted by radical hysterectomy with or without postoperative radiation treatment, rather than a standard Piver Type 1 hysterectomy.[28-30]

In conclusion, this study adds to the understanding of pelvic floor function for women following hysterectomy, particularly after an endometrial cancer diagnosis, with reassurance that their function is unlikely to deteriorate after surgery with Piver Type I hysterectomy for endometrial cancer. Our study addresses some of previously raised research questions and provides answers for clinicians and women on what they can expected following either open or laparoscopic hysterectomy for stage 1 endometrial cancer. This should aid in the counselling process prior to hysterectomy via open or laparoscopic routes.

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Table 1: Sociodemographic and clinical characteristics summarised by randomised treatment group

	TAH (N=195)	TLH (N=186)
Age in years, mean (SD)	62.6 (10.9)	63.0 (9.5)
BMI Category		
Normal (<25kg/m^2)	26 (13)	21 (11)
Overweight (25-29.99 kg/m^2)	42 (22)	47 (25)
Obesity class I (30-34.99 kg/m^2)	41 (21)	34 (18)
Obesity class II (35-39.99 kg/m^2)	35 (18)	39 (21)
Obesity class III (≥40 kg/m^2)	44 (23)	41 (22)
Missing	7 (4)	4 (2)
Education		
Completed 12 years of school or less	126 (65)	115 (62)
Completed > 12 years of school	64 (33)	69 (37)
Missing	5 (3)	2 (1)
Employment		
Employed full-time	21 (11)	32 (17)
Employed part-time or casual	33 (17)	21 (11)
Retired	75 (38)	77 (41)
Other	61 (31)	54 (29)
Missing	5 (3)	2 (1)
Marital status		
Partnered	121 (62)	112 (60)
Not partnered	69 (35)	72 (39)
Missing	5 (3)	2 (1)
Private health insurance		

	TAH (N=195)	TLH (N=186)
No	142 (73)	130 (70)
Yes	48 (25)	54 (29)
Missing	5 (3)	2 (1)
Household Income		
AU$40,000+	49 (25)	46 (25)
Less than AU$40,000	118 (61)	118 (63)
Missing	5 (3)	2 (1)
Birth country		
Australia	121 (62)	113 (61)
Other	69 (35)	71 (38)
Not answered	23 (12)	20 (11)
Missing	5 (3)	2 (1)
ECOG status		
0	168 (86)	168 (90)
1	27 (14)	18 (10)
PFDI† at Baseline (/300)*		
N	194	186
Mean(SD)	44.5 (44.6)	38.2 (38.7)
PFDI† at Baseline (/300) (completed)		
N	165	157
Mean(SD)	40.2 (42.4))	38.2 (38.7)
Pelvic Floor issues††		
N (%)	83 (43)	90 (48)

Abbreviations: TAH=Total Abdominal Hysterectomy; TLH=Total Laparoscopic Hysterectomy, PFDI Pelvic Floor Distress inventory

* Estimate includes incomplete questionnaires

†PFDI score calculated as 25*(score/number of questions answered)

†† defined as reporting at least one or more symptom of moderate or severe extent

n (%) presented unless otherwise indicated

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Table 2: The number (%) of patients with pelvic floor problems defined as at least one symptom of moderate of severe severity for any item within the total score combining the three subscales and each scale individually

PFDI Scale		**Pre-op (n = 381)**	**6 months post-op (n = 320)**	**18 month FU (n = 291)**	**30 month FU (n = 274)**	**42 month FU (n = 227)**	**54 month FU (n = 207)**
PFDI (Total):	TAH	56 (29%)	34 (21%)	32 (21%)	31 (22%)	25 (22%)	24 (24%)
	TLH	43 (23%)	21 (13%)	31 (22%)	21 (16%)	13 (12%)	12 (11%)
POPDI-6	TAH	9 (5%)	4 (2%)	7 (5%)	0	2 (2%)	2 (2%)
(only)	TLH	14 (8%)	4 (3%)	0	2 (1%)	5 (4%)	2 (2%)
CRADI-8	TAH	7 (4%)	9 (5%)	9 (6%)	9 (6%)	7 (6%)	1 (1%)
(only)	TLH	13 (7%)	7 (4%)	10 (7%)	11 (8%)	9 (8%)	9 (8%)
UDI-6	TAH	11 (6%)	8 (5%)	11 (7%)	7 (5%)	7 (6%)	10 (10%)
(only)	TLH	20 (11%)	10 (6%)	9 (6%)	11 (8%)	14 (13%)	8 (8%)

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Table 3: Proportion of participants who experienced at least one moderate to severe symptom grouped by stable, resolved or unresolved symptom burden over the course of the study

Outcome of PFDI symptoms		*Total Abdominal Hysterectomy (n=195)*	*Total Laparoscopic Hysterectomy (n=186)*
No symptoms throughout the observation period:		59 (30%)	56 (30%)
Baseline symptoms		83 (43%)	90 (48%)
	Resolved	38 (19%)	38 (20%)
	Unresolved	39 (20%)	44 (24%)
	Unknown	6 (3%)	8 (4%)
New symptoms		46 (24%)	36 (19%)
	Resolved	17 (9%)	17 (9%)
	Unresolved	29 (15%)	19 (10%)
Unknown*		7 (4%)	4 (2%)

Abbreviations: PFDI Pelvic Floor Distress inventory; **patients with no symptoms at baseline who only answered the baseline questionnaire

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Figure Captions

Figure 1: Participant Flow

Figure 2: Total PFDI and domain scores over time by treatment group (mean score with 95% CI).

Figure 3: Forest plot of the GEE estimates for the mean difference (95% CI) in pelvic floor wellbeing scores from baseline between the TAH and TLH group.

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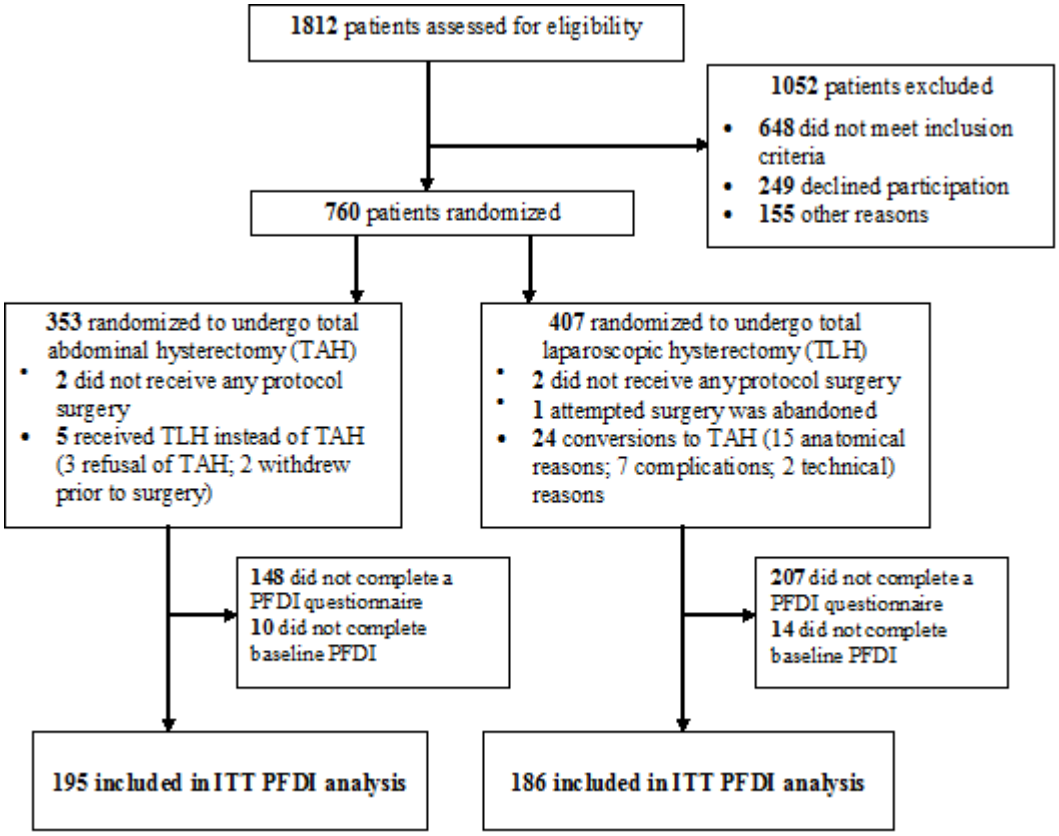

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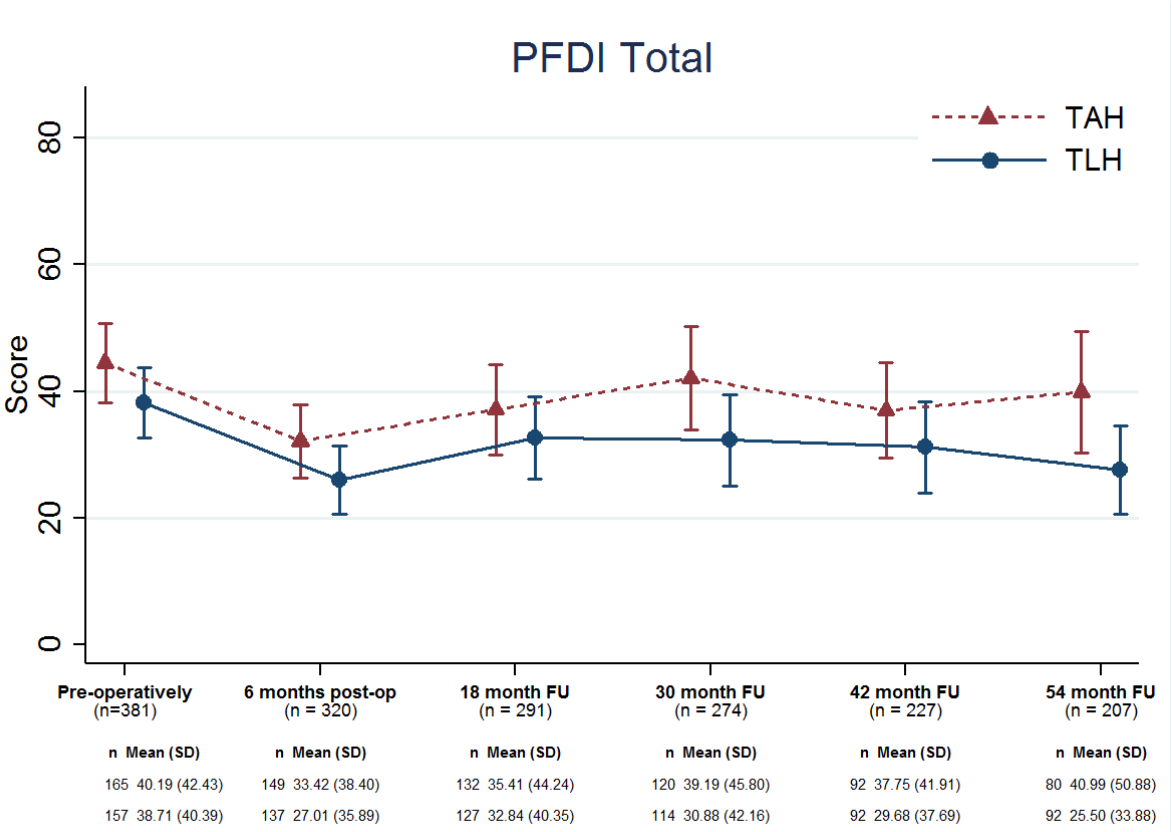

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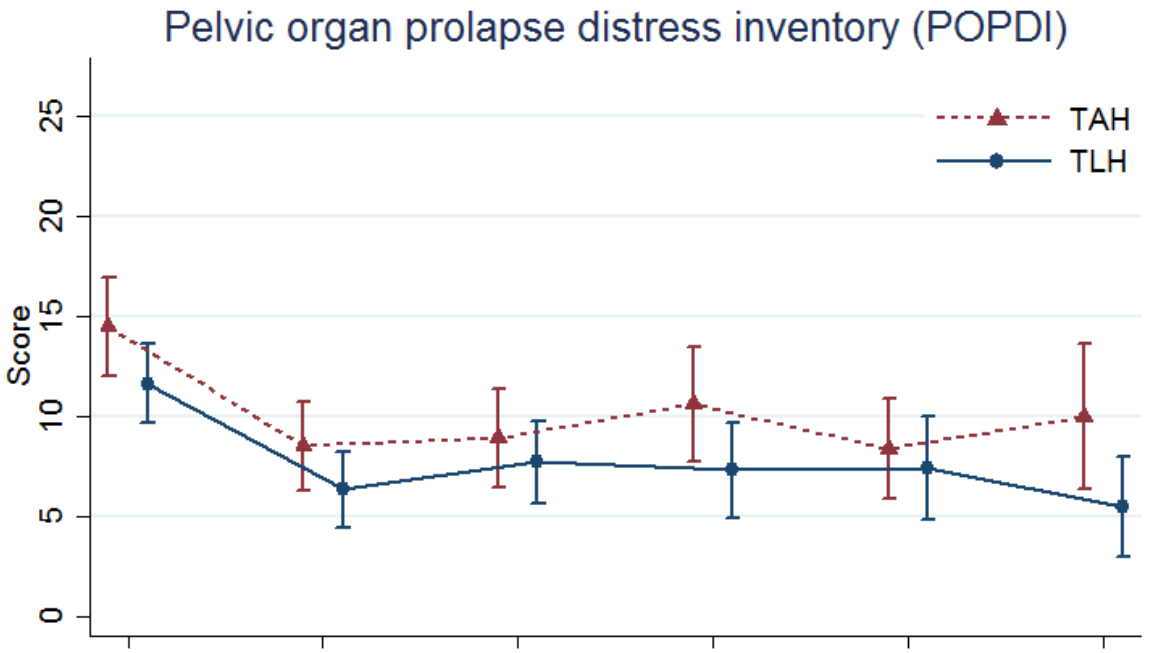

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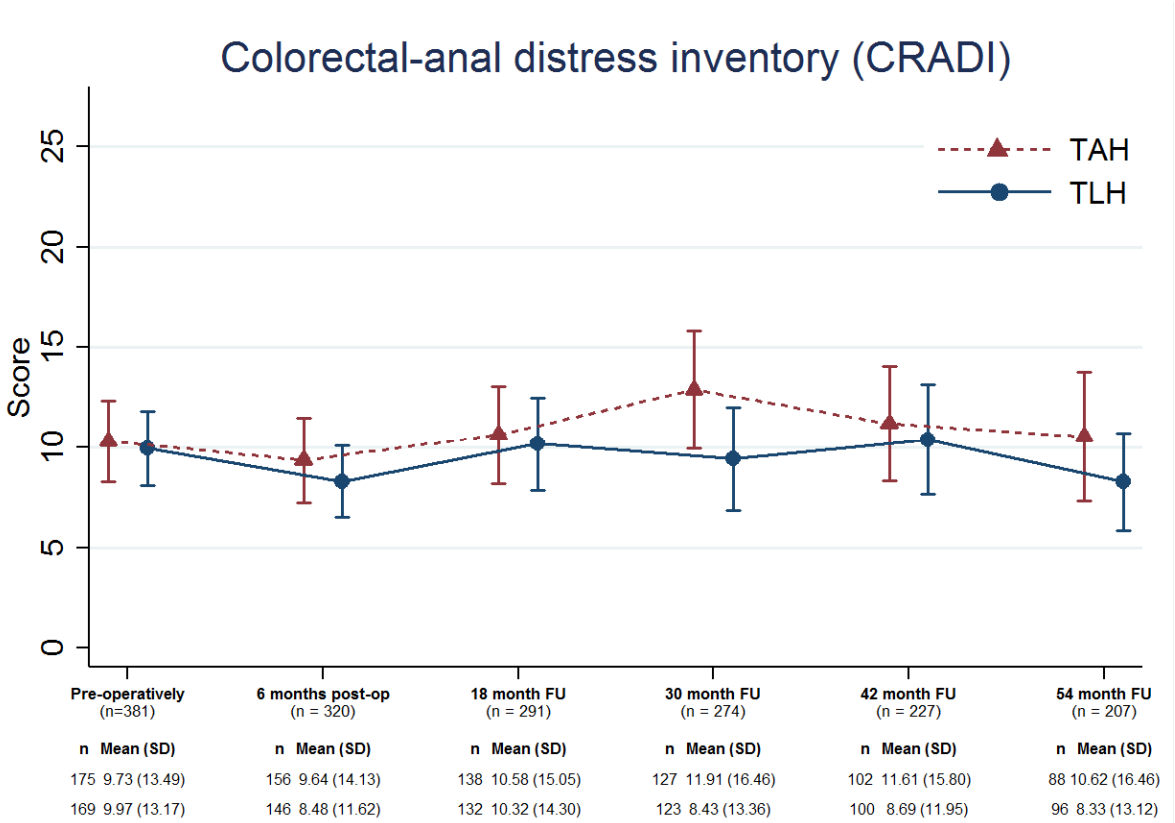

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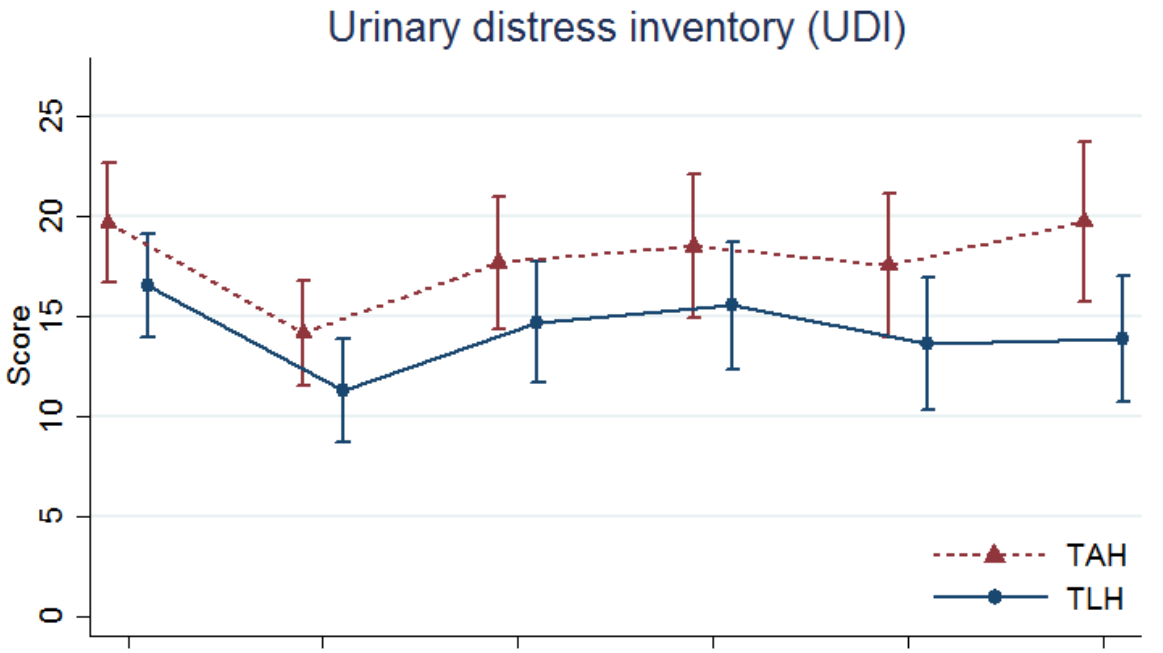

Pre-operatively (n=381)		6 months post-op (n = 320)		18 month FU (n = 291)		30 month FU (n = 274)		42 month FU (n = 227)		54 month FU (n = 207)	
n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
187	19.63 (21.50)	159	14.54 (17.23)	138	17.21 (20.29)	130	18.46 (21.05)	102	11.61 (15.80)	91	20.60 (20.73)
174	16.69 (18.29)	145	11.52 (16.60)	134	14.83 (18.64)	125	15.77 (18.82)	101	13.78 (18.02)	97	13.27 (15.14)

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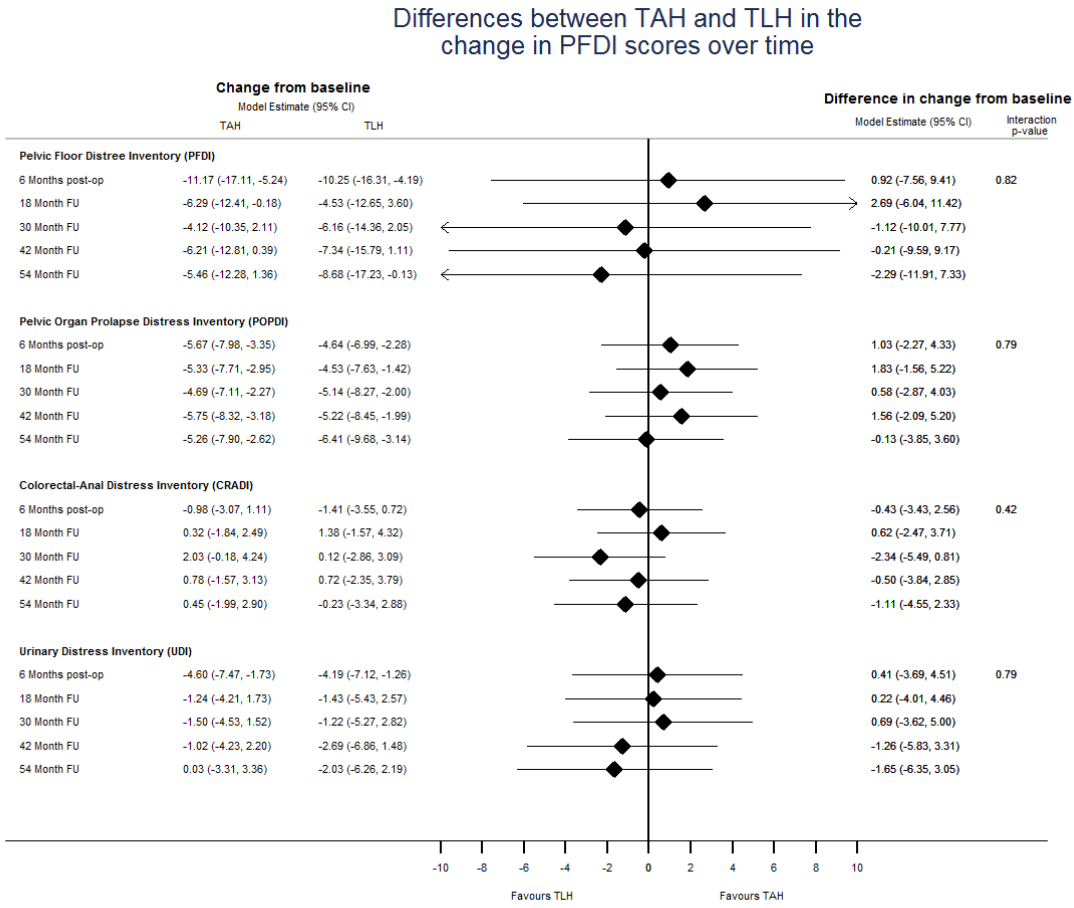

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Supp Table 1: Baseline patient characteristics summarised by treatment group

	Total Abdominal Hysterectomy (N=353)	Total Laparoscopic Hysterectomy (N=407)	Total Abdominal Hysterectomy (N=195)	Total Laparoscopic Hysterectomy (N=186)
Age in years, mean (SD)	63.1 (10.6)	63.3 (10.0)	62.6 (10.9)	63.0 (9.5)
ECOG status				
0	303 (86%)	352 (86%)	168 (86%)	168 (90%)
1	50 (14%)	55 (14%)	27 (14%)	18 (10%)
Grade of Differentiation				
Grade 1 (Well differentiated)	223 (63%)	259 (64%)	125 (64%)	115 (62%)
Grade 2 (Moderately differentiated)	107 (30%)	120 (29%)	53 (27%)	54 (29%)
Grade 3 (Poorly differentiated)	23 (7%)	28 (7%)	17 (9%)	17 (9%)
Surgical Stage				
Missing	3 (1%)	4 (1%)	1 (1%)	1 (1%)
I			1 (1%)	
IA	237 (67%)	286 (70%)	130 (67%)	131 (70%)
IB	44 (12%)	55 (14%)	20 (10%)	23 (12%)
II	45 (13%)	32 (8%)	27 (14%)	15 (8%)
IIIA	4 (1%)	11 (3%)	3 (2%)	5 (3%)
IIIB	1 (<1%)	4 (1%)	1 (1%)	2 (1%)
IIIC1	12 (3%)	11 (3%)	7 (4%)	9 (5%)
IIIC2	3 (1%)	1 (<1%)	1 (1%)	
IVA	1 (<1%)	0 (<1%)	1 (1%)	
IVB	3 (1%)	3 (1%)	3 (2%)	
Node dissection performed				
Yes	147 (42%)	246 (60%)	112 (57%)	79 (42%)
No	206 (58%)	161 (40%)	83 (43%)	107 (58%)
Adjuvant Therapy				
None	261 (74%)	336 (83%)	133 (68%)	137 (74%)
Chemotherapy or radiation (or both)	92 (26%)	71 (17%)	62 (32%)	49 (26%)
Hospital Stay				
≤2 days			3 (2%)	128 (69%)
>2 days			192 (98%)	58 (31%)

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Supp table 2: Number of questionnaires and PFDI scales completed at each visit (n=381)

	Pre-op	Post-operative follow up months				
		6	18	30	42	54
Completed questionnaires [a,b]	381 (100)	320 (84)	291 (76)	274 (72)	227 (60)	207 (54)
Completed scales [c]						
Pelvic Floor Distress Inventory (PFDI)	322 (85)	286 (89)	259 (89)	234 (85)	184 (81)	172 (83)
Pelvic organ prolapse (POPDI-6)	369 (97)	307 (96)	278 (96)	260 (95)	210 (93)	190 (92)
Colorectal-Anal (CRADI-8)	344 (90)	302 (94)	270 (93)	250 (91)	202 (89)	184 (89)
Urinary (UDI-6)	361 (95)	304 (95)	272 (93)	255 (93)	203 (89)	188 (91)

n (%) presented

[a] Includes both fully and partially completed questionnaires

[b] Pre-op number used as the denominator for the row percentages

[c] Percentages expressed a column percent for the time period count of completed questionnaires

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Supp table 3: Summary of moderate/severe PFDI symptom outcomes during the study by adjuvant treatment

Outcome of PFDI symptoms		*Adjuvant therapy* (n=111)*	*No adjuvant therapy (n=270)*
No symptoms:		35 (32%)	80 (30%)
Baseline symptoms		49 (44%)	124 (46%)
	Resolved	22 (20%)	54 (20%)
	Unresolved	25 (23%)	58 (21%)
	Unknown	2 (1%)	12 (4%)
New symptoms		27 (24%)	66 (24%)
	Resolved	12 (11%)	22 (8%)
	Unresolved	13 (12%)	35 (13%)
Unknown		2 (4%)	9 (3%)

*commencement of adjuvant therapy varied on a patient basis depending on surgical outcome and progression, therefore, PFDI outcomes may not coincide with adjuvant therapy

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Supp table 4: Results from the GEE modelling, including a time-by-randomisation group interaction term alongside main effects

	PFDI Model Estimate (95% CI)	p-value	POPDI Model Estimate (95% CI)	p-value	CRADI Model Estimate (95% CI)	p-value	UDI Model Estimate (95% CI)	p-value
TLH vs. TAH	0.92 (-7.56, 9.41)	0.83	0.41 (-3.69, 4.51)	0.84	-0.43 (-3.43, 2.56)	0.78	1.03 (-2.27, 4.33)	0.54
Visit		0.12		0.02		0.09		0.89
18 Month FU	4.88 (-0.49, 10.25)		3.36 (0.65, 6.07)		1.30 (-0.70, 3.31)		0.33 (-1.67, 2.34)	
30 Month FU	7.06 (1.49, 12.63)		3.10 (0.30, 5.90)		3.01 (0.93, 5.09)		0.98 (-1.10, 3.06)	
42 Month FU	4.96 (-1.01, 10.93)		3.59 (0.58, 6.59)		1.76 (-0.47, 3.99)		-0.08 (-2.33, 2.17)	
54 Month FU	5.71 (-0.45, 11.87)		4.63 (1.52, 7.74)		1.43 (-0.88, 3.74)		0.41 (-1.90, 2.72)	
Treatment-by-Time		0.82		0.79		0.42		0.79
18 Month FU	1.77 (-5.96, 9.49)		-0.19 (-4.08, 3.70)		1.06 (-1.83, 3.94)		0.81 (-2.08, 3.69)	
30 Month FU	-2.04 (-9.98, 5.91)		0.28 (-3.71, 4.28)		-1.91 (-4.87, 1.06)		-0.45 (-3.41, 2.52)	
42 Month FU	-1.13 (-9.60, 7.34)		-1.67 (-5.94, 2.59)		-0.06 (-3.22, 3.10)		0.53 (-2.66, 3.72)	
54 Month FU	-3.22 (-11.93, 5.49)		-2.06 (-6.45, 2.33)		-0.68 (-3.94, 2.58)		-1.15 (-4.42, 2.11)	

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Supp table 5: Results from the GEE modelling, including a time-by-randomisation group interaction term alongside main effects and adjusting for known prognostic variables

	PFDI Model Estimate (95% CI)	p-value	POPDI Model Estimate (95% CI)	p-value	CRADI Model Estimate (95% CI)	p-value	UDI Model Estimate (95% CI)	p-value
TLH vs. TAH	1.1 (-7.53, 9.72)	0.80	-0.38 (-3.39, 2.63)	0.80	0.14 (-4.04, 4.32)	0.95	1.37 (-1.95, 4.69)	0.42
Visit		0.14		0.10		0.04		0.81
18 Month FU	5.18 (-0.23, 10.6)		1.16 (-0.84, 3.16)		3.63 (0.89, 6.36)		0.53 (-1.52, 2.59)	
30 Month FU	7.02 (1.40, 12.65)		2.93 (0.86, 5.00)		2.99 (0.16, 5.83)		1.13 (-1.00, 3.26)	
42 Month FU	4.77 (-1.24, 10.78)		1.6 (-0.62, 3.82)		3.49 (0.46, 6.51)		0.01 (-2.29, 2.30)	
54 Month FU	5.05 (-1.15, 11.25)		1.39 (-0.9, 3.69)		4.11 (0.98, 7.24)		0.35 (-2.01, 2.70)	
Treatment-by-Time		0.89		0.44		0.78		0.85
18 Month FU	1.15 (-6.61, 8.92)		1.11 (-1.76, 3.97)		-0.52 (-4.43, 3.39)		0.45 (-2.49, 3.39)	
30 Month FU	-1.85 (-9.84, 6.14)		-1.73 (-4.67, 1.22)		0.42 (-3.60, 4.44)		-0.56 (-3.59, 2.46)	
42 Month FU	-1.11 (-9.62, 7.41)		0.21 (-2.93, 3.35)		-1.86 (-6.15, 2.44)		0.47 (-2.78, 3.72)	
54 Month FU	-3.25 (-12, 5.50)		-0.68 (-3.91, 2.55)		-1.89 (-6.31, 2.52)		-1.38 (-4.71, 1.95)	
Age (≥65 vs. <65)	-2.79 (-10.33, 4.74)	0.47	-1.65 (-4.21, 0.92)	0.21	-0.19 (-3.78, 3.41)	0.92	-0.84 (-3.76, 2.07)	
BMI (≥30 vs. < 30)	5.82 (-1.87, 13.52)	0.14	1.17 (-1.44, 3.79)	0.38	2.37 (-1.30, 6.04)	0.21	2.28 (-0.70, 5.26)	
ECOG (1 vs. 0)	-2.85 (-14.62, 8.91)	0.64	1.3 (-2.71, 5.30)	0.53	-2.68 (-8.30, 2.93)	0.35	-1.72 (-6.28, 2.83)	
History of malignancy	6.35 (-6.78, 19.48)	0.34	1.77 (-2.7, 6.24)	0.44	1.58 (-4.69, 7.84)	0.62	2.99 (-2.09, 8.08)	
Node dissection	-2.02 (-9.91, 5.87)	0.62	-1.72 (-4.41, 0.97)	0.21	-1.34 (-5.10, 2.43)	0.49	0.82 (-2.23, 3.88)	
Surgical stage		0.26		0.34		0.03		
2 vs. 1	-7.7 (-19.63, 4.24)		3.03 (-1.04, 7.1)		-7.58 (-13.28, -1.88)		-3.21 (-7.83, 1.40)	
3 or 4 vs. 1	-8.54 (-22.25, 5.16)		0.99 (-3.68, 5.66)		-0.24 (-6.78, 6.30)		-9.38 (-14.68, -4.08)	
Differentiation		0.99		0.92		0.78		
2 vs. 1	-0.39 (-8.92, 8.14)		0.07 (-2.84, 2.97)		1.39 (-2.69, 5.46)		-1.55 (-4.87, 1.76)	
3 vs. 1	0.58 (-11.6, 12.75)		-0.8 (-4.95, 3.35)		1.35 (-4.46, 7.16)		0.26 (-4.45, 4.97)	

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