Phase III Randomized Trial of Laparoscopic or Robotic Radical Hysterectomy vs. Abdominal Radical Hysterectomy in Patients with Early-Stage Cervical Cancer: LACC Trial

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Bringing Together the Best in Women's Cancer Care

Disclosure

No Conflicts of Interest

Background

- Laparoscopic radical hysterectomy shows reduction in blood loss, postoperative complications, and hospital stay compared to open approach. No significant difference in 5-year DFS and OS. (N=1,539)

  Wang Y, Deng L, Xu H, Zhang Y, Liang Z. BMC Cancer 2015

- Robotic radical hysterectomy is associated with less blood loss, lower transfusion rates, lower wound related complications, and shorter hospital stay compared to open radical hysterectomy. (N=4,013)

  Shazly S, Murad M, Dowdy S, Gostout B, Famuyida A. Gyn Oncol 2016

- Disease recurrence and survival not different between robotic radical hysterectomy and open radical hysterectomy. (N=491)

  Sert BM, Boggess JF, Ahmad S, Jackson AL, Stavitzski NM, Dahl AA, Holloway RW EJSO 2016

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

Types of Resection and Appropriateness for Treatment of Cervical Cancer

- Treatment of cervical cancer is stratified by stage as delineated in the Guidelines.
- Microinvasive disease, defined as FIGO stage IA-1 with no lymphovascular space invasion (LVSI), has less than a 1% chance of lymphatic metastasis and may be managed conservatively with cone biopsy for preservation of fertility (with negative margins) or with simple hysterectomy when preservation of fertility is not desired or relevant. The intent of a cone biopsy is to remove the ectocervix and endocervical canal *en bloc* using a scalpel. This provides the pathologist with an intact, non-fragmented specimen without electrosurgical artifact, which facilitates margin status evaluation. If a loop electrosurgical excision procedure (LEEP) is chosen for treatment, the specimen should not be fragmented, and care must be undertaken to minimize electrosurgical artifact at the margins. The shape and depth of the cone biopsy may be tailored to the size, type, and location of the neoplastic lesion. For example, if there is concern for invasive adenocarcinoma versus adenocarcinoma *in situ* in the cervical canal, the cone biopsy would be designed as a narrow, long cone extending to the internal

- Radical hysterectomy with bilateral pelvic lymph node dissection (with or without SLN mapping) is the preferred treatment for FIGO stage IA-2, IB, and IIA lesions when fertility preservation is not desired. Radical hysterectomy results in resection of much wider margins compared with a simple hysterectomy, including removal of parts of the cardinal and uterosacral ligaments and the upper 1–2 cm of the vagina; in addition, pelvic and sometimes para-aortic nodes are removed. Radical hysterectomy procedures may be performed either via laparotomy or laparoscopy, and the laparoscopy approach may be either with conventional or robotic techniques. The Querleu & Morrow classification system[1] is a modern surgical classification that describes degree of resection and nerve preservation in 3-dimensional planes of resection.[2] Procedural details for the most commonly used types of hysterectomy are described in Table 1 (see CERV-B 5 of 7).

- The radical vaginal trachelectomy with laparoscopic lymphadenectomy procedure (with or without SLN mapping) offers a fertility-sparing option for carefully selected individuals with stage IA-2 or stage IB-1 lesions of 2 cm diameter or less. The cervix, upper vagina, and supporting ligaments are removed as with a type B radical hysterectomy, but the uterine corpus is preserved. In the more than 300 subsequent pregnancies currently reported, there is a 10% likelihood of second trimester loss, but 72% of patients carry their gestation to 37 weeks or more.[3] The abdominal radical trachelectomy has emerged as a reasonable fertility-sparing strategy. It provides larger resection of parametria than the vaginal approach,[4] is suitable for select stage IB1 cases, and has been utilized in lesions up to 4 cm in diameter. The operation mimics a type C radical hysterectomy.*[,1,2,5-8]

*For a description of a type C radical hysterectomy, see Table 1 (CERV-B 5 of 7).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

Primary Objective
LACC Trial

Compare **disease-free survival at 4.5 years** amongst patients who underwent a total **laparoscopic or robotic radical hysterectomy (TLRH/TRRH)** vs. a **total abdominal radical hysterectomy (TARH)** for early stage cervical cancer.

Secondary Objectives
LACC Trial

- Compare patterns of **recurrence** between arms
- Compare treatment-associated **morbidity** (6 months from surgery)
- Compare the **cost effectiveness** of TLRH/TRRH vs. TARH
- Assess **pelvic floor function**
- Compare **overall survival** between arms
- Determine the **feasibility of sentinel lymph node mapping**
- **Quality of Life (QoL)** between arms

Study Design

- International, multicenter, randomized, phase III trial to test for non-inferiority of TLRH/TRRH vs. standard care (TARH)

- Therefore, the **primary intent** to demonstrate that minimally invasive surgery was within 7.2% of the DFS rate of the standard care (TARH) arm

- Test for non-inferiority was based upon a 97.5% one-sided confidence interval. Based on exponential survival times, for a 4.5-year follow-up, a total of **740 patients (370 per arm)** was determined to have at least 90% power for non-inferiority.

Inclusion Criteria

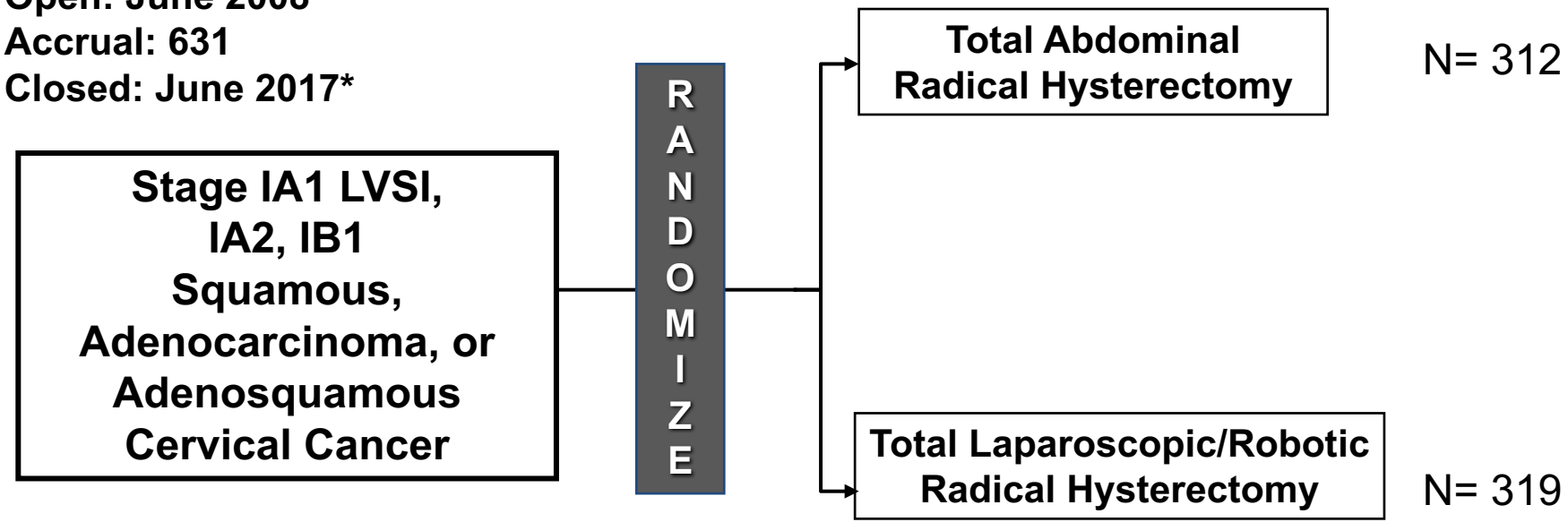
- Confirmed primary **squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma** of the uterine cervix
- FIGO **stage IA1 (with LVSI), IA2, or IB1**
- Type II or III radical hysterectomy (Piver-Rutledge Classification)
- Performance status of **ECOG 0-1**
- Age **18 years or older**
- Signed an approved Informed Consent

Inclusion Criteria
Participating Sites

- Submission of **10 cases** of TLRH/TRRH to Trial Management Committee
  - Age
  - BMI
  - Stage
  - OR time
  - EBL
  - LOS
  - Intraop and postop complications (<30 days)
  - Transfusion rates
- Total of **2 un-edited videos** of TLRH/TRRH
- Independent Review 2 members of Trial Management Committee

Study Schema

Open: June 2008
Accrual: 631
Closed: June 2017*



*Recommendation of DSMC

Baseline Characteristics

Characteristic	TARH	TLRH/TRRH
Eligible patients	312	319
Mean age in years (SD)	46.0 (10.6)	46.1 (11.0)
Mean BMI in kg/m^2 (SD)	26.2 (5.3)	27.2 (5.6)
Histology*		
Adenocarcinoma	80 (26%)	87 (27%)
SCC	210 (67%)	214 (67%)
Adenosquamous	6 (2%)	9 (3%)
Stage of disease		
IA1	5 (2%)	5 (2%)
IA2	20 (6%)	21 (7%)
IB1	287 (92%)	293 (92%)

*25 patients reported histology as one of these three types, but did not specify the type

Surgery by Randomized Treatment

	TARH	TLRH/TRRH
Randomized patients	312	319
• TARH	274 (88%)	2 (1%)
• TLRH/TRRH	8 (3%)	289 (91%)
• Withdrawn prior to surgery	19 (6%)	12 (4%)
• Surgery abandoned	11 (4%)	16 (5%)
Surgery performed as randomized	274 (88%)	289 (91%)
Method of TLRH/TRRH	N=8	N=289
• Laparoscopic	7 (88%)	244 (84%)
• Robotic	1 (13%)	45 (16%)
MIS converted to Laparotomy	1 (0%)	10 (3%)

Postoperative Histopathology

Histopathology		TARH 282	TLRH/TRRH 291	P-value
Histology	Squamous	146 (50%)	152 (52%)	0.99
	Adenocarcinoma	58 (21%)	59 (20%)	
	Adenosquamous	12 (4%)	12 (4%)	
	No residual disease	59 (21%)	60 (21%)	
	Other	7 (2%)	8 (3%)	
Grade	1	29 (10%)	34 (11%)	0.96
	2	113 (40%)	115 (40%)	
	3	61 (22%)	61 (21%)	
	Unknown	79 (28%)	81 (28%)	
Invasion	Superficial	61 (22%)	85 (29%)	0.03
	Middle	73 (26%)	50 (17%)	
	Deep	56 (20%)	64 (22%)	
	Unknown	92 (33%)	92 (32%)	

Postoperative Histopathology

Histopathology		TARH 282	TLRH/TRRH 291	P-value
Tumor size	<2cm	89 (32%)	95 (33%)	0.82
	≥2cm	101 (36%)	97 (33%)	
	Unknown	92 (33%)	99 (34%)	
LVSI	Negative	186 (66%)	196 (67%)	0.26
	Positive	81 (29%)	70 (24%)	
	Unknown	15 (5%)	25 (9%)	
Parametria	Negative	251 (89%)	254 (87%)	
	Positive	11 (4%)	19 (7%)	0.35
	Unknown	20 (7%)	18 (6%)	
Vaginal margins	Negative	248 (88%)	258 (89%)	
	Positive	6 (2%)	5 (2%)	0.40
	Unknown	28 (10%)	28 (10%)	

Histopathology

		TARH	TLRH/TRRH	P-value
Histopathology		282	291	
Median Lymph nodes (Q1 – Q3)		21 (16-30)	20 (15-26)	0.01
Positive nodes*	None	243 (86%)	253 (87%)	0.70
	Yes	37 (13%)	35 (12%)	
Surgery				
Mean OR time-hours (SD)		196 (62)	222 (71)	<0.001
Median LOS-days (range)		5 (0-69)	3 (0-72)	<0.001

*5 missing values

Adjuvant Treatment by Randomized Treatment

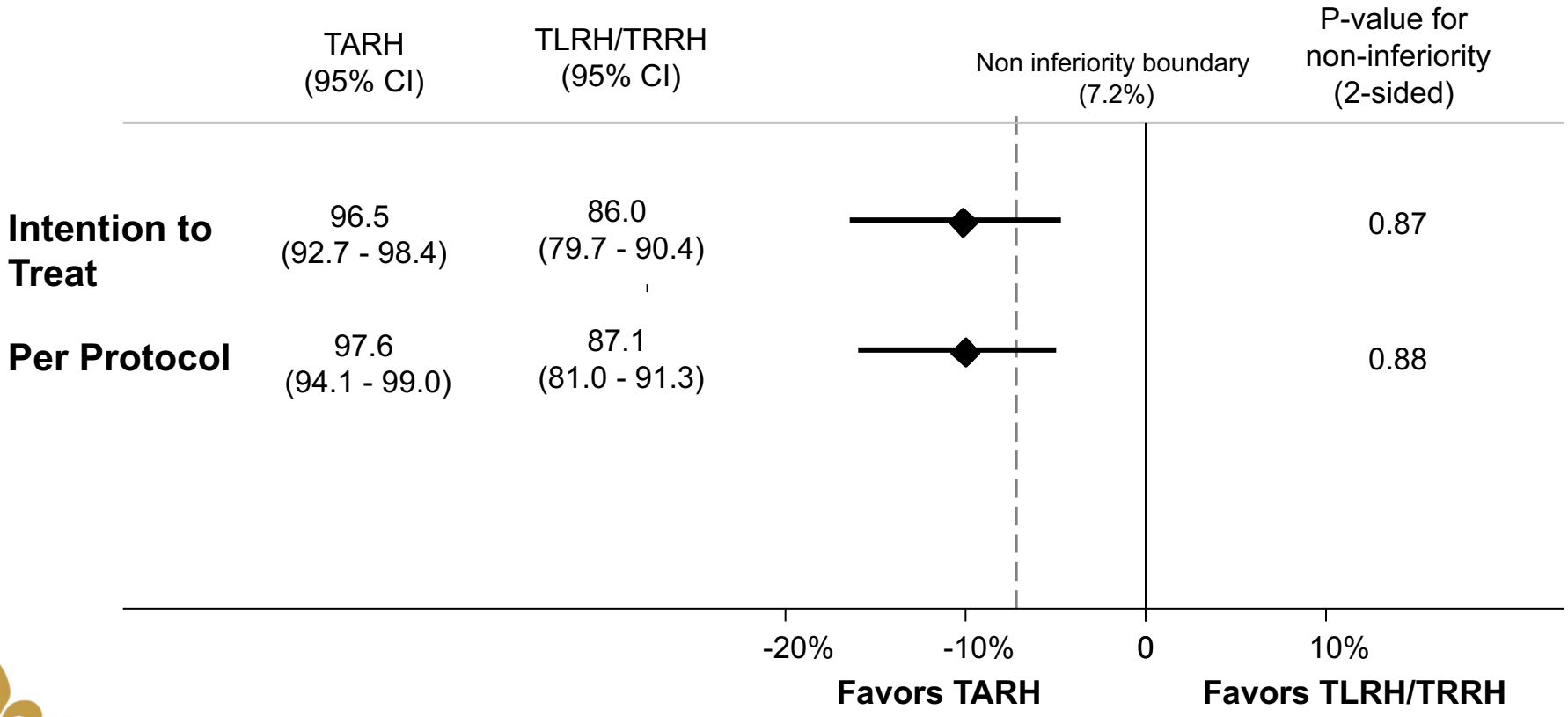
	TARH	TLRH/TRRH	P-value
Eligible patients	312	319	
Total patients treated with either chemo or radiotherapy	86 (28%)	92 (29%)	0.72
Total patients treated with at least one cycle of chemotherapy	66 (21%)	72 (23%)	0.67
Total patients treated with at least one dose of radiotherapy	73 (23%)	81 (25%)	0.56

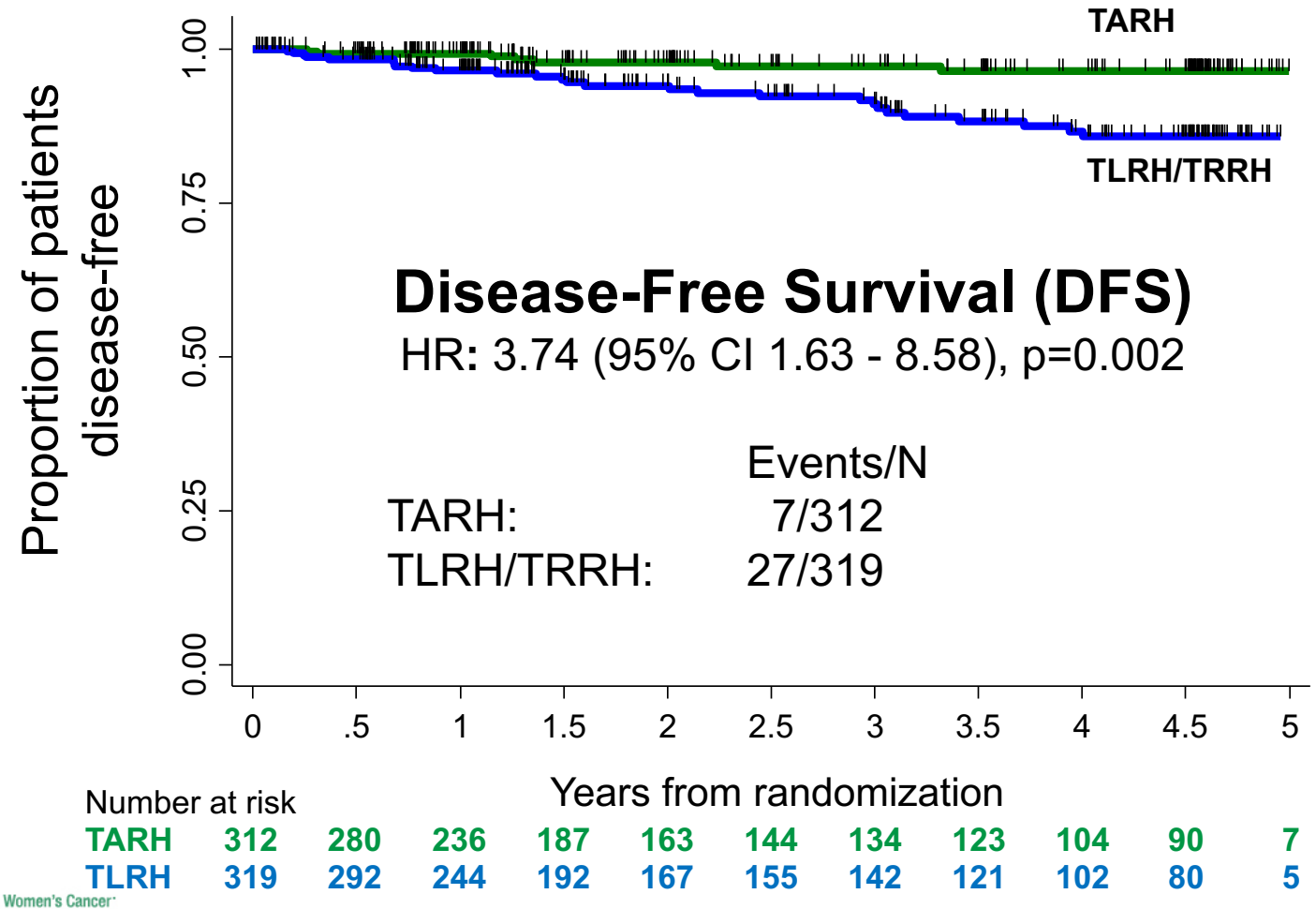
Data Completeness

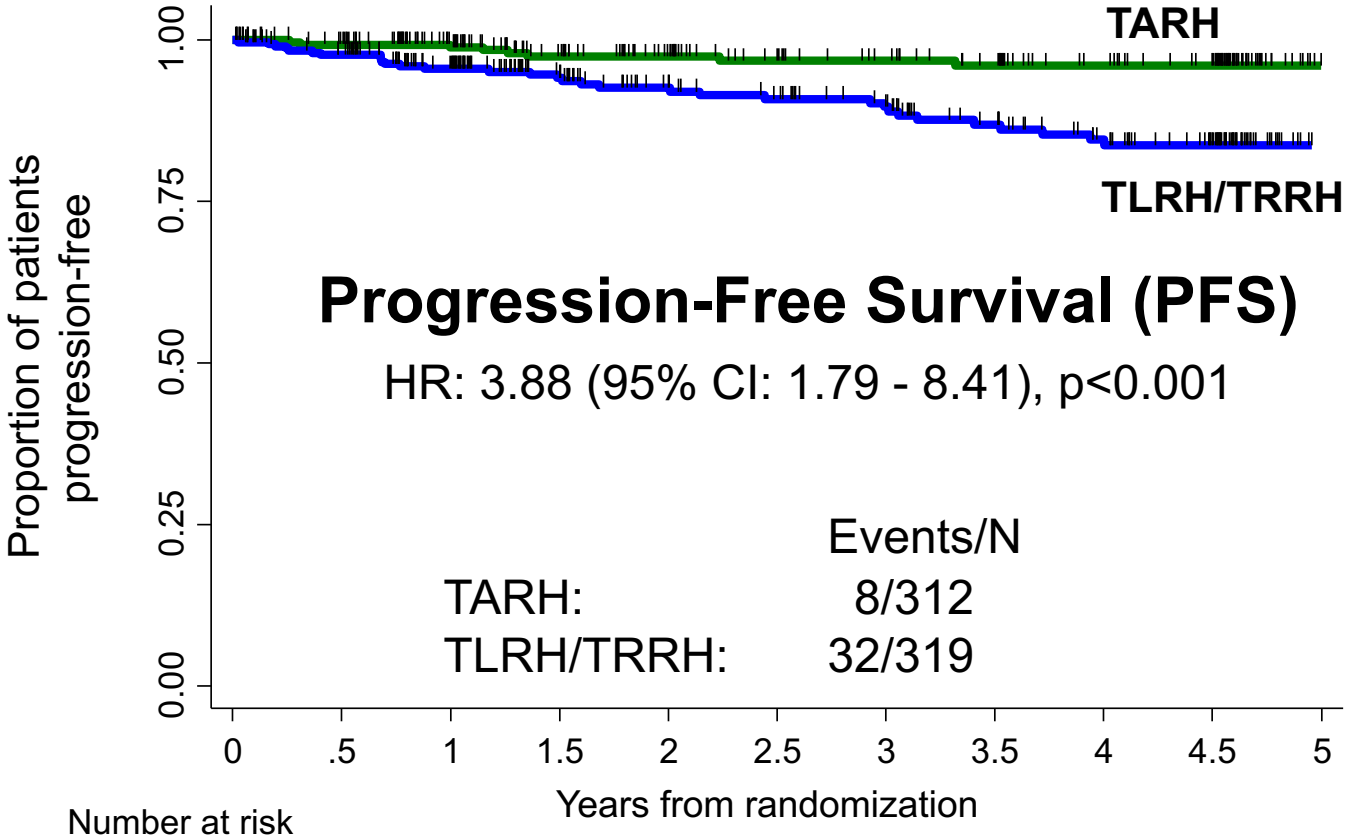
Primary outcome (DFS)	
Median Follow-up time (min- max)	2.5 years (0.0 - 6.3)
Completeness* at 4.5 years (%)	219/558 (39.2%)
Information available at 4.5 years (%)	59.7%
Overall survival	
Median Follow-up time (min- max)	2.5 years (0.0 - 6.3)
Completeness* at 4.5 years (%)	208/558 (37.3%)
Information available at 4.5 years (%)	54.3%

*Completeness is proportion of patients with the event of interest, or with follow-up to 4.5 years, out of the total patients that we can achieve data at 4.5 years (excluding withdrawals and LTFU)

Primary Outcome: DFS at 4.5 years




TARH
TLRH/TRRH
Proportion of patients disease-free
1.00
0.75
0.50
0.25
0.00
Disease-Free Survival (DFS)
HR: 3.74 (95% CI 1.63 - 8.58), p=0.002
Events/N
TARH: 7/312
TLRH/TRRH: 27/319
0
.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Years from randomization
Number at risk
TARH 312 280 236 187 163 144 134 123 104 90 7
TLRH 319 292 244 192 167 155 142 121 102 80 5



Number at risk

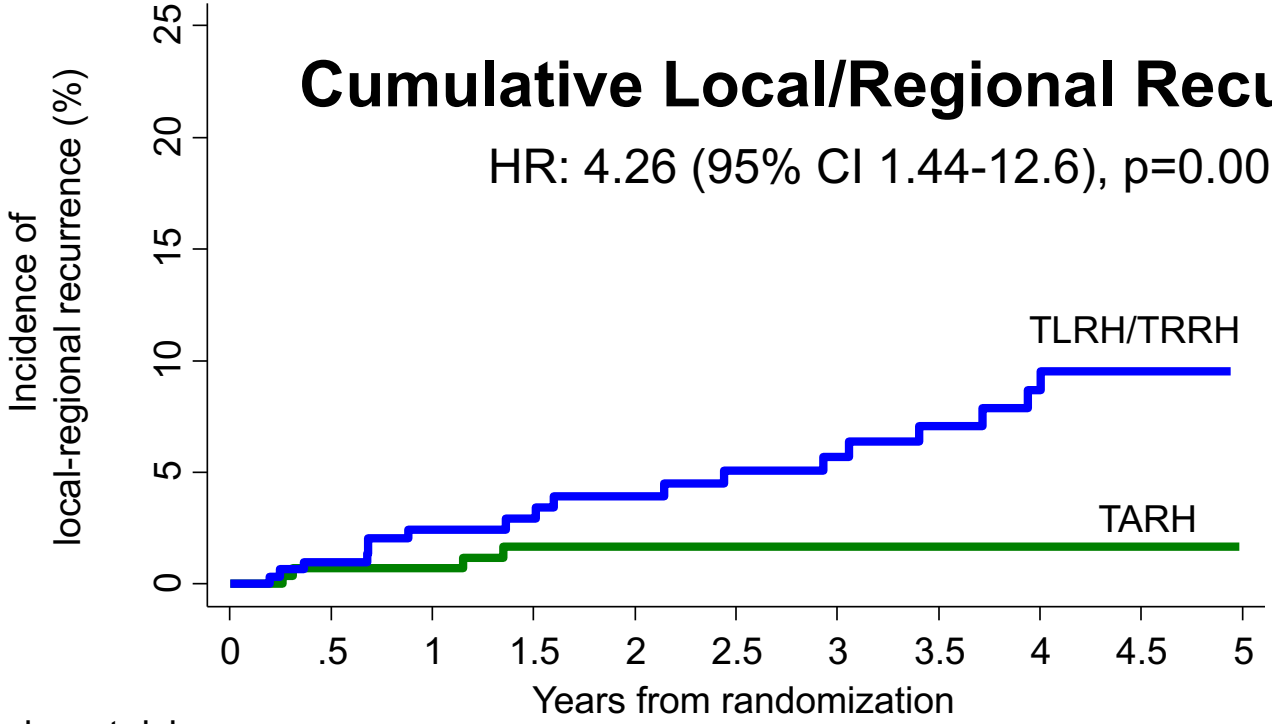
TARH	312	280	235	186	162	144	134	123	104	90	7
TLRH	319	292	244	192	167	155	142	121	101	80	5

Site of First Recurrence

	TARH	TLRH/TRRH
Total recurrences	7 (2.2%) N=312	24 (7.5%) N=319
Site of recurrence		
Vault	3 (43%)	4 (17%)
Pelvis	0 (0%)	7 (29%)
Abdomen	0 (0%)	1 (4%)
Distant	1 (14%)	2 (8%)
Multiple	2 (29%)	7 (29%)
Other	1 (14%)	3 (13%)

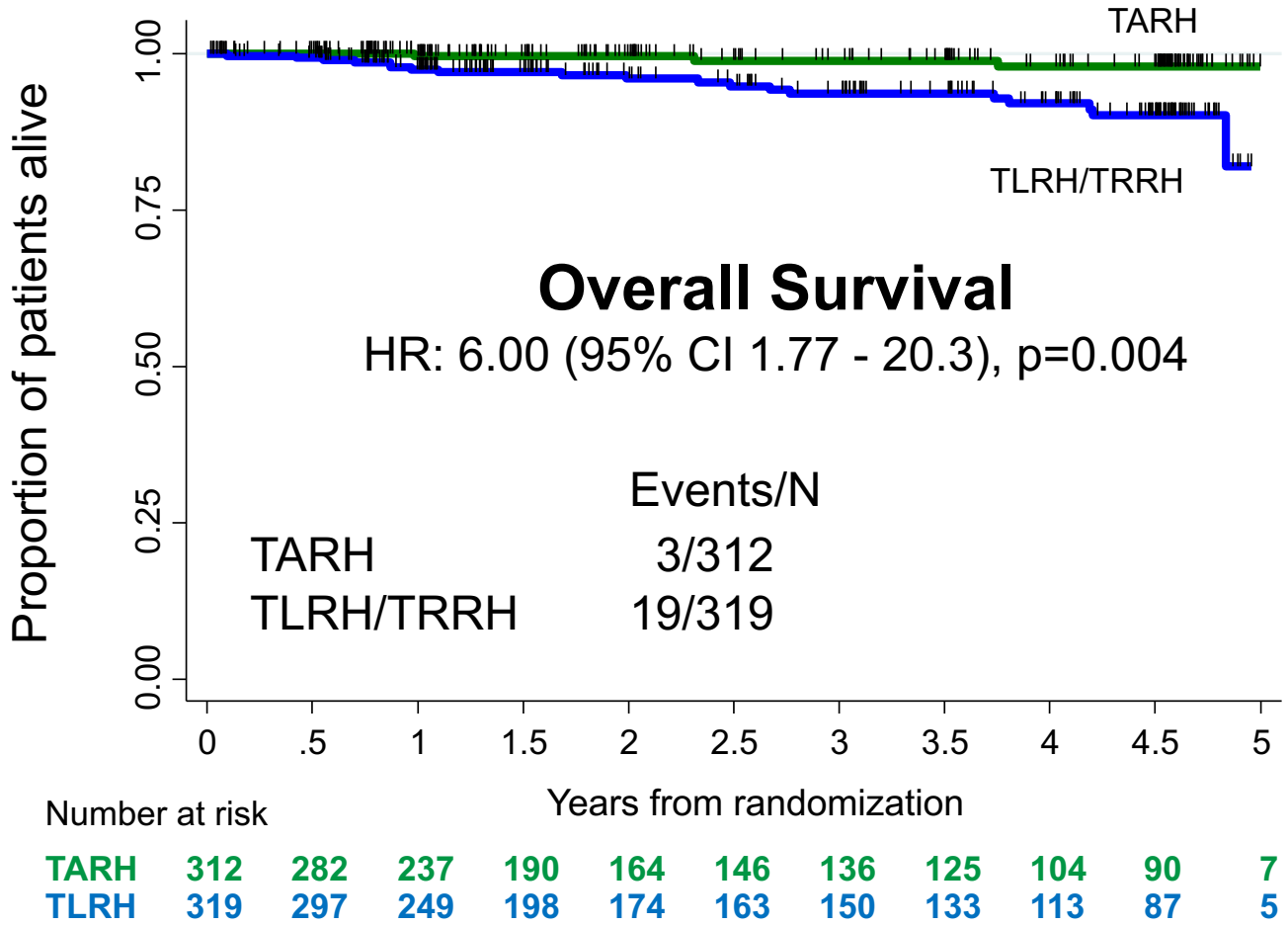
Cumulative Local/Regional Recurrence

HR: 4.26 (95% CI 1.44-12.6), p=0.009



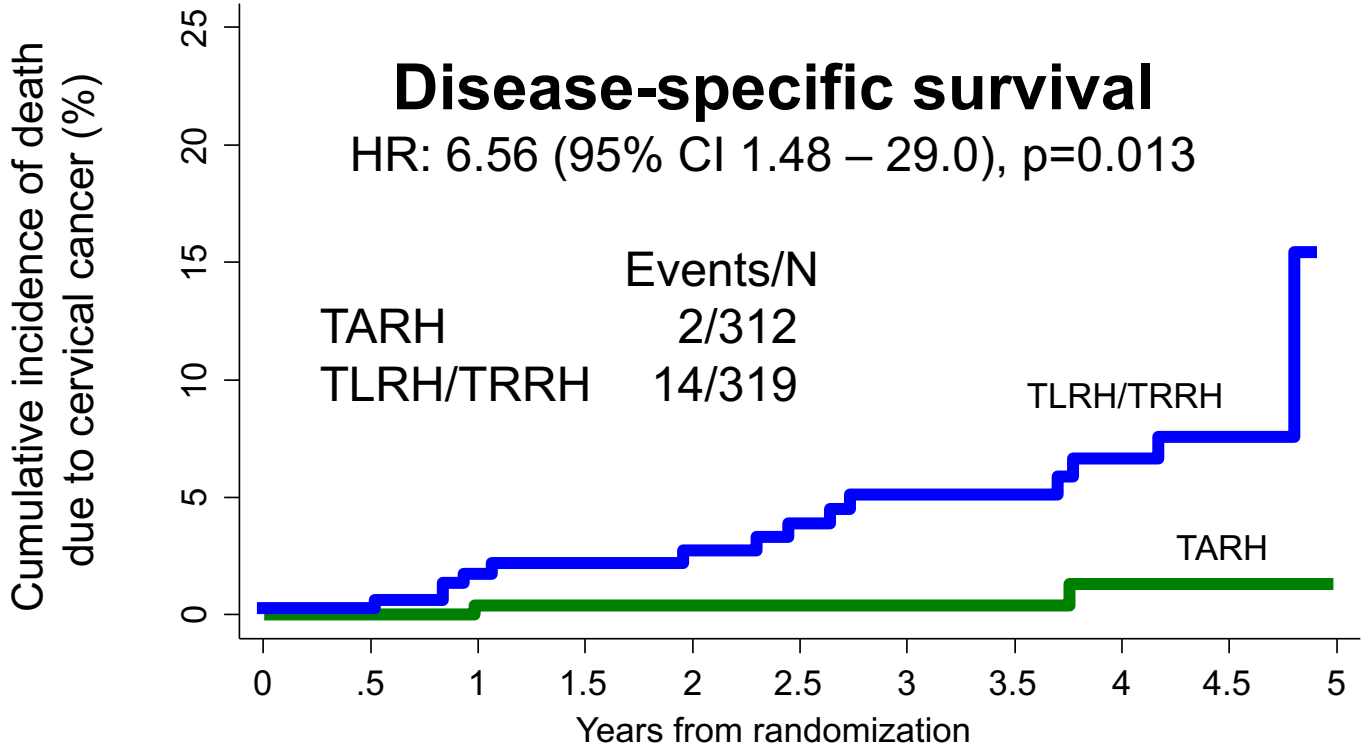
Number at risk

TARH	312	280	236	187	163	144	134	123	104	90	7
TLRH	319	292	244	192	167	155	142	121	102	80	5


TARH
TLRH/TRRH
Proportion of patients alive
1.00
0.75
0.50
0.25
0.00
Overall Survival
HR: 6.00 (95% CI 1.77 - 20.3), p=0.004
Events/N
TARH 3/312
TLRH/TRRH 19/319
0 .5 1 1.5 2 2.5 3 3.5 4 4.5 5
Years from randomization
Number at risk
TARH 312 282 237 190 164 146 136 125 104 90 7
TLRH 319 297 249 198 174 163 150 133 113 87 5

Causes of Death

Causes of death	TARH	TLRH/TRRH
Total deaths	3	19
• Due to cervical cancer	2 (1%)	14 (4%)
• Unrelated morbidity	0 (0%)	4 (1%)
• Unknown	1 (0%)	1 (0%)



Number at risk

TARH	312	282	237	190	164	146	136	125	104	90	7
TLRH	319	297	249	198	174	163	150	133	113	87	5

Conclusions

- **Disease-free survival at 4.5 years for minimally invasive radical hysterectomy was inferior compared to the open approach**

- **Minimally invasive radical hysterectomy was associated with higher rates of loco/regional recurrences**

- **Results of the LACC Trial should be discussed with patients scheduled to undergo radical hysterectomy**

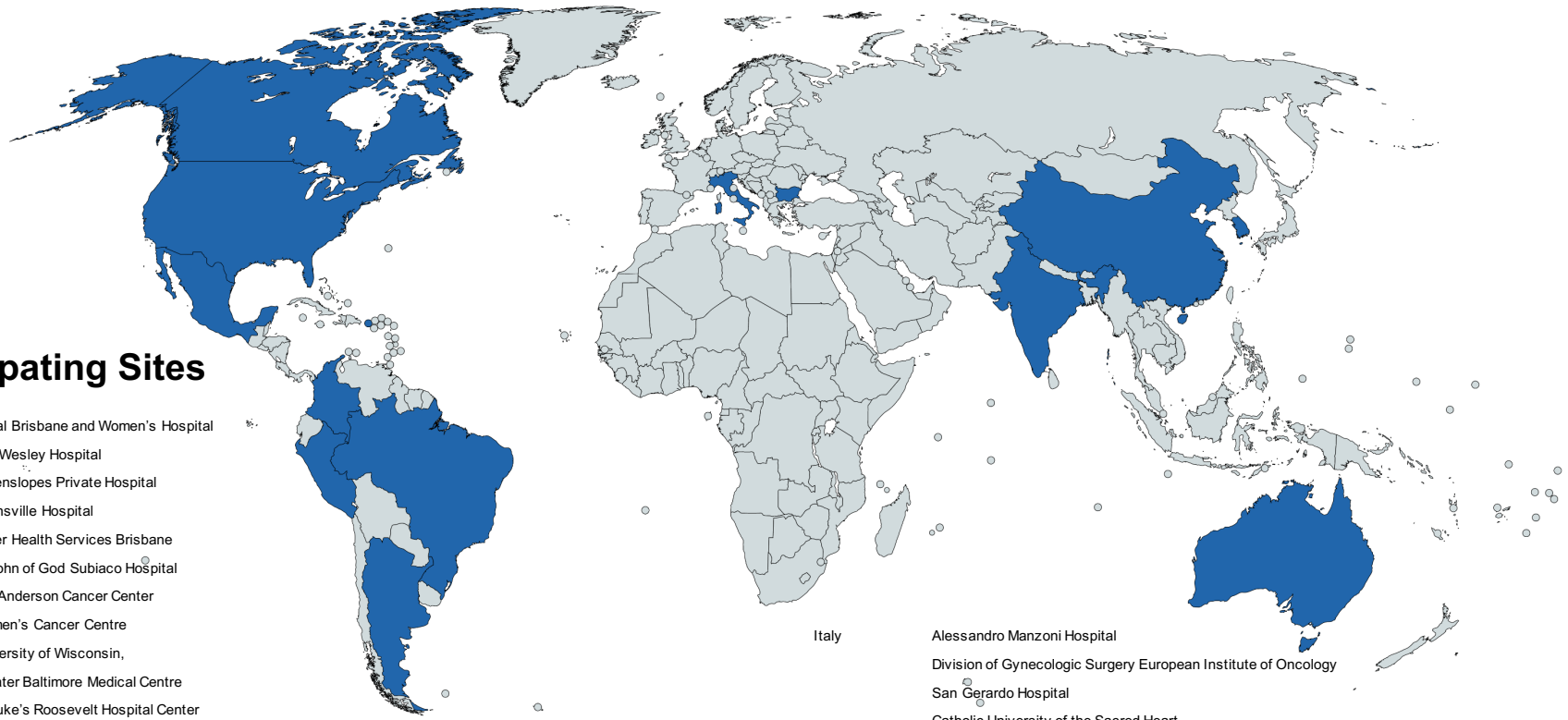
LACC Trial

- **Strengths**
  - -Largest prospective randomized trial
  - -Multicenter & international collaboration
  - -Surgeon proficiency requirements
  - -Powered to evaluate oncologic outcomes
  - -Recurrence Adjudication Committee
- **Limitations**
  - -Early termination
  - -Lack of central pathology review
  - -Data maturity

Acknowledgments

Data Safety Monitoring Committee

Robert Edwards, MD (Chair)
Ralph Freedman, MD
E. Neely Atkinson
Jeffrey Fowler, MD
Paola Gehrig, MD
Wendel Nauman, MD
Alexander Olawaiye, MD
Jennifer Davis



Participating Sites

Australia	Royal Brisbane and Women's Hospital
	The Wesley Hospital
	Greenslopes Private Hospital
	Townsville Hospital
	Mater Health Services Brisbane
	St John of God Subiaco Hospital
USA	MD Anderson Cancer Center
	Women's Cancer Centre
	University of Wisconsin,
	Greater Baltimore Medical Centre
	St Luke's Roosevelt Hospital Center
	Lyndon B. Johnson Hospital,
	The Peggy and Charles Stephenson Oklahoma Cancer Center
Puerto Rico	Gyneco-Oncológico Hospital HIMA-Oncologico
Canada	Princess Margaret Hospital
Mexico	Instituto Nacional de Cancerología
Colombia	Institito De Cancerologia Clinica Las Americas
Peru	Instituto Nacional de Enfermedades Neoplasicas
Brazil	Erastus Gaertner Hospital
	Albert Einstein Hospital
	Barretos Cancer Hospital,
	Instituto Brasileiro de Controle do Cancer
Argentina	Misericordia Hospital
Italy	Alessandro Manzoni Hospital
	Division of Gynecologic Surgery European Institute of Oncology
	San Gerardo Hospital
	Catholic University of the Sacred Heart
Bulgaria	University Hospital – Pleven
Korea	Korea Cancer Hospital
	ASAN Medical Center
	Seoul National University Hospital
China	The First Affiliated Hospital of Sun Yat-Sen University
	Zhejiang Cancer Hospital
	The first affiliated hospital of Wenzhou Medical College
India	Rajiv Gandhi Cancer Institute and Research Centre