



BRIGHAM AND
WOMEN'S HOSPITAL



Translational Frontiers: Innovation in Fibroid Treatment in the 21st Century

Elizabeth A. Stewart, M.D.

Clinical Director, Center for Uterine Fibroids

Associate Professor, Harvard Medical School



HARVARD
MEDICAL SCHOOL

Teaching Affiliate

Goals for Today's Talk:

- To ask important questions
- Assess what we need
- Explore informative examples
- Set agenda items for the future



HARVARD
MEDICAL SCHOOL
Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

Current approaches to Uterine Fibroids

- Surgical excision
- Steroid hormone manipulation
- Thermoablative coagulation
- Angiographic-induced ischemia



Current approaches to Atherosclerotic Heart Disease

- Surgical excision (Bypass)
- Therapeutic Angiography
- Transplantation
- Medical Therapies
- Risk Reduction



Current approaches to Fibroids: 1960's Medical Mindset

- “Wait until you have a heart attack and then we’ll worry about doing something.”
- “Cancer is cancer. Everyone ends up dying.”

Only when hysterectomy is your treatment, does one size-fit all.



HARVARD
MEDICAL SCHOOL

Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

What is missing for myomas?

- Predictors of risk
- Early intervention
- Prevention
- Genotype/phenotype relationships

We need a “Framingham Fibroid Project”.



HARVARD
MEDICAL SCHOOL

Tracking Associates



BRIGHAM AND
WOMEN'S HOSPITAL

Why was there not a Framingham Fibroid Study?

- Morbidity key issue, not mortality
- Changes in childbearing patterns
- Economic importance of women
- Hysterectomy as effective contraception
- Sexism and Racism



HARVARD
MEDICAL SCHOOL
Tracking Ancestry



BRIGHAM AND
WOMEN'S HOSPITAL

What is the most cost effective therapy for uterine leiomyomas?

- Hysterectomy
- Are there other values?



HARVARD
MEDICAL SCHOOL
Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

What is the most cost effective therapy for erectile dysfunction?

- Current pharmacologic therapies?
- Penile implants?
- Adjustment of expectations?



HARVARD
MEDICAL SCHOOL

Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

Economic importance of fibroids

- Hysterectomy (\$1.2 billion annually)
- Other surgeries and UAE
- OCPs and Progestin therapies
- Sanitary products including diapers
- Lost work productivity
- Alternative and complimentary therapies
- Quality of Life



HARVARD
MEDICAL SCHOOL
Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

FDA-approved treatment for Uterine Leiomyomas

- Lupron®
- Embospheres®
- Contour SE™
- Exablate 2000®



HARVARD
MEDICAL SCHOOL
Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

Devices for endometrial ablation

- Resectoscope
- Balloon ablation (Thermachoice®,
Cavaterm®)
- (Cryoablation) (Her Option®)
- Circulating Water (Hydro
ThermAblator®)
- 3D-Bipolar Mesh (Novasure®)



HARVARD
MEDICAL SCHOOL

Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

Limited choices

- Larger range of sizes than other diseases:
- **More versatile treatments or earlier treatment?**
- Women not actively seeking current therapies are termed “asymptomatic”.

I propose that women have adapted to burden of disease, or view available treatments as worse than the disease.



HARVARD
MEDICAL SCHOOL

Teaching America



BRIGHAM AND
WOMEN'S HOSPITAL

Special issues for future myoma treatments?

- High risk of myoma recurrence: both visible on imaging and requiring intervention
- Risk of uterine rupture in future pregnancies: averting disaster for mothers and babies



HARVARD
MEDICAL SCHOOL

Tracking Advances



BRIGHAM AND
WOMEN'S HOSPITAL

Innovation pathway #1: Fibroid therapies piggybacked off existing indications

- GnRH agonists: Prostate Cancer
- UAE: Post-partum hemorrhage and tumor embolization



HARVARD
MEDICAL SCHOOL

Tracking Advances



BRIGHAM AND
WOMEN'S HOSPITAL

Hypothesis: Insulin-like Growth Factors and the growth hormone system are abnormal in the fibroid uterus.

Therefore, drugs which act on this system (somatostatin analogues) may decrease fibroid symptoms.

Lanreotide: 3 month treatment

- 24% reduction in uterine volume at 3 months
- 17% reduction at 6 months; no rapid rebound
- Not marketed in US: orphan drug status

DeLeo et al: Fertil Steril 75: 632-3 2001

Hypothesis: The angiogenic growth factor bFGF is a mediator of leiomyoma-related menorrhagia

*Stewart and Nowak: 1996 : Hum Reprod Update
2:295-306.*

bFGF mRNA and protein are overexpressed in leiomyomas compared to normal myometrium

Mangrulkar et al: 1995: Biol Reprod 53:636-46

The bFGF type 1 receptor is abnormally expressed in the endometrium of the myomatous uterus

Anania et al: 1997; Molec Hum Reprod 3:385-91

Interferon- α decreases bFGF-
stimulated leiomyoma cell
proliferation *in vitro*

*Lee et al: 1998: Am J Reprod Immunol 40:19-
25.*

Interferon and Leiomyomas

Leiomyoma Volume

Pre-treatment 202 cm³

Interferon Treatment

5 months post-treatment 29 cm³

7 months post-treatment 22 cm³

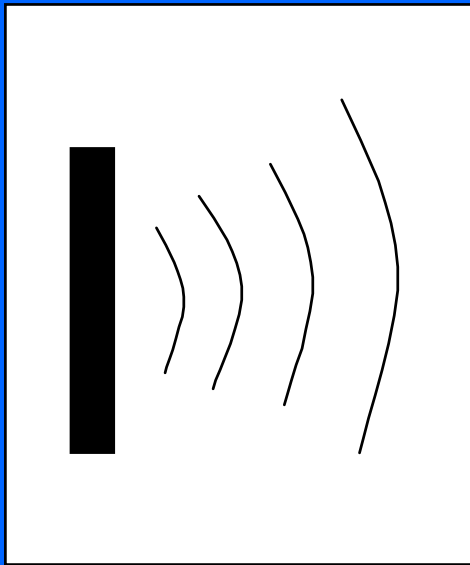
17 months post-treatment 21 cm³

Minakuchi et al. Lancet 1999: 353(2127-8)

Pioneering Novel Therapeutic Approaches

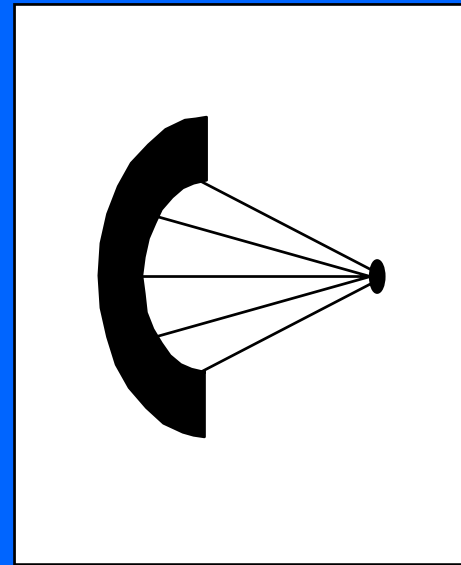
Focused Ultrasound

Plane waves from flat surface



Diagnostic
Ultrasound

Concave surface brings waves to focus



Therapeutic
Ultrasound
FUS or HIFU

Limitation of Thermoablative Therapy

No way to gauge adequacy of treatment:

- Not enough and efficacy limited
- Too much and safety compromised

MRI provides real-time thermal monitoring and precise anatomic visualization

MRI: T₁, T₂ and 4 T's

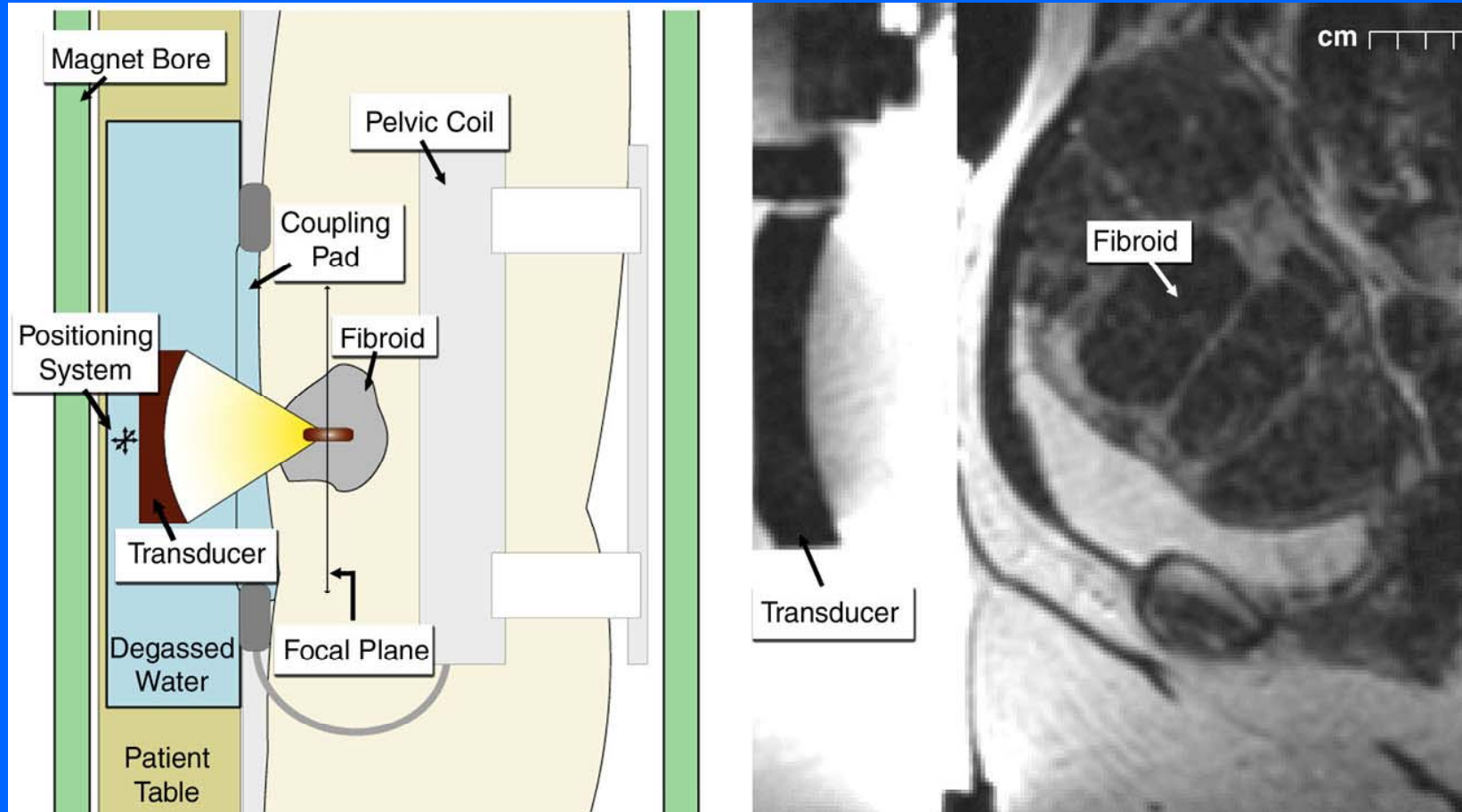
Targeting

Temperature mapping

Test sonication

Therapy Verification
with gadolinium

MRI-guided Focused Ultrasound



Tempany et al: Radiology 2003; 226: 897-905



HARVARD
MEDICAL SCHOOL

Training Tomorrow



BRIGHAM AND
WOMEN'S HOSPITAL

Feasibility study: Treating women before hysterectomy

- Objective assessment of treatment
- Close follow-up for complete assessment
- Minimization of risk to subjects
- Basis for understanding the biology

Stewart et al: Am J Ob Gyn 189: 48-54,2003

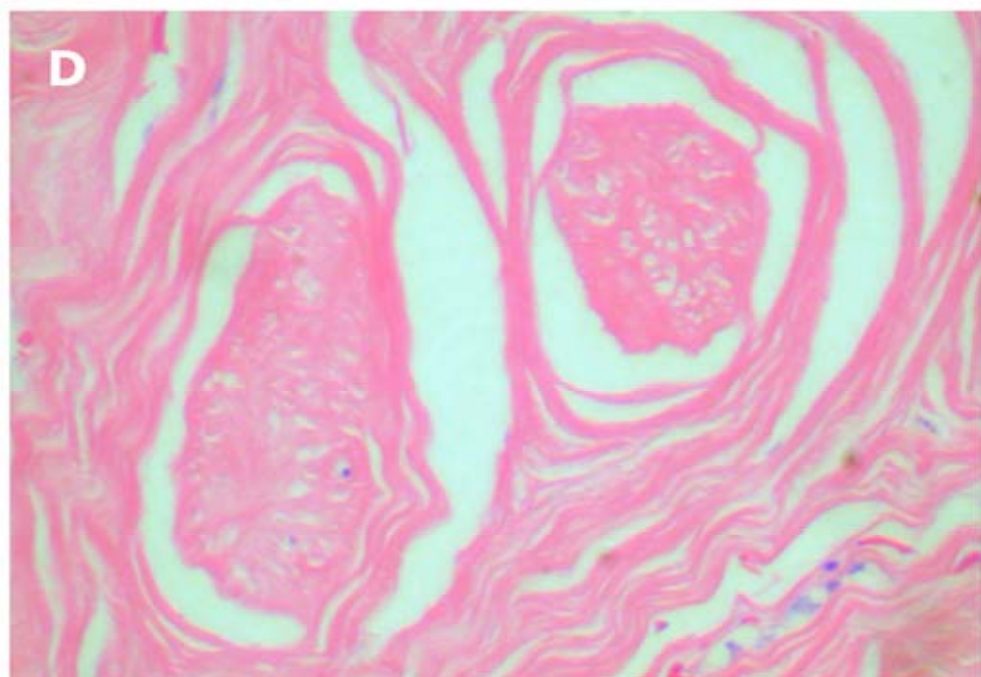
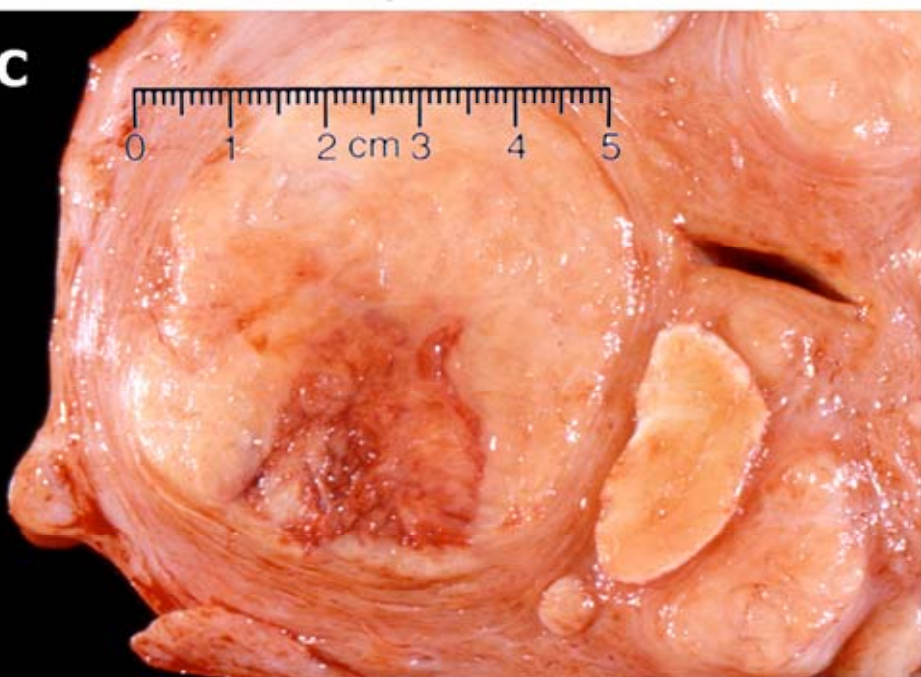
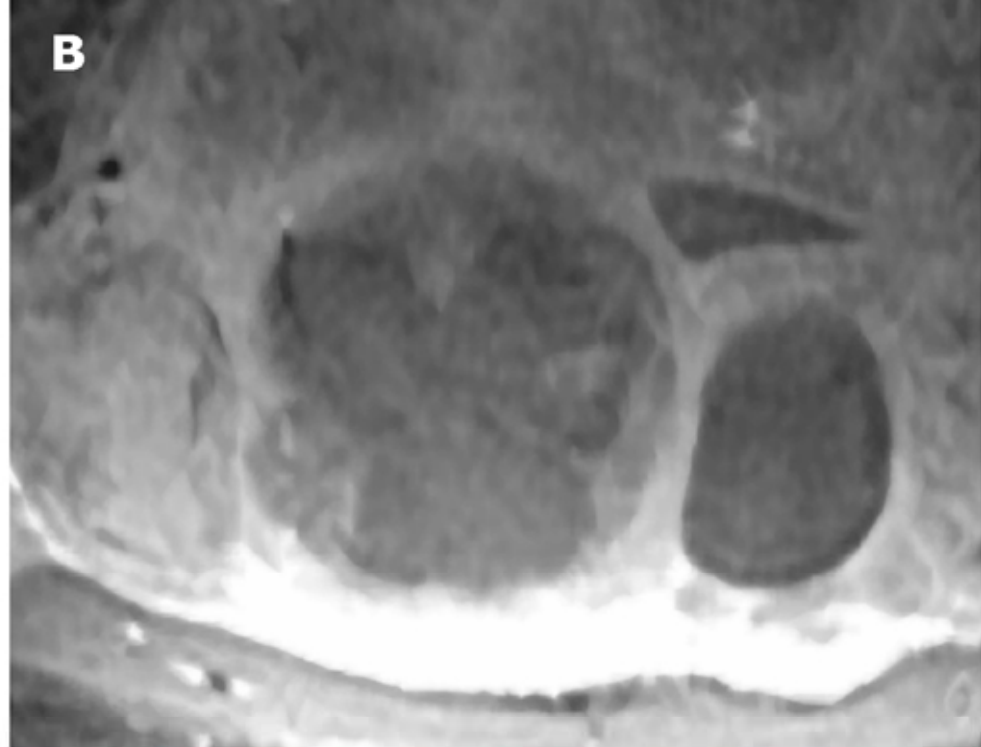
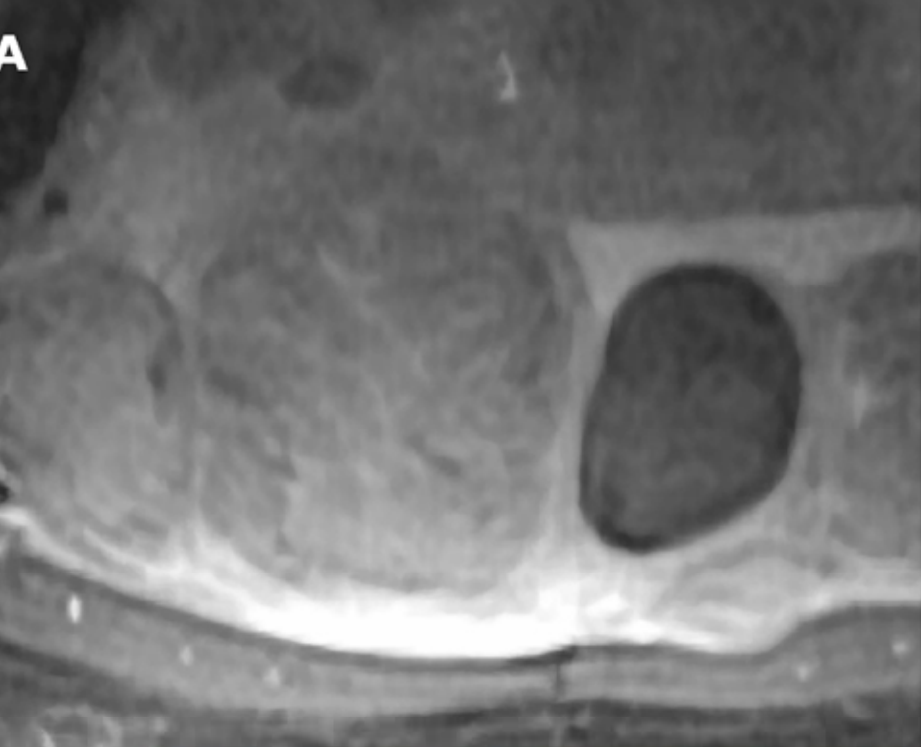


HARVARD
MEDICAL SCHOOL

Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL



Pain: Not what you see with UAE

	<u>Pre-</u>	<u>Intra-</u>	<u>Post-</u>
Pain	0.3	1.1 *	0.5
Discomfort	0.2	0.8 *	0.5 +

Scale: None (0) to Severe (3)

*p<0.0001 +p<0.0004

10% of women taking pain meds at 72 hours

Stewart et al: Am J Ob Gyn 189: 48-54,2003



HARVARD
MEDICAL SCHOOL

Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

Adverse Events: Excellent Safety Profile

- 4 % minor skin burns
- 4 % increased bleeding following FUS
- 1 % hospitalization for nausea
- 1 % non-targeted sonication (uterine serosa)

Stewart et al: Am J Ob Gyn 189: 48-54,2003

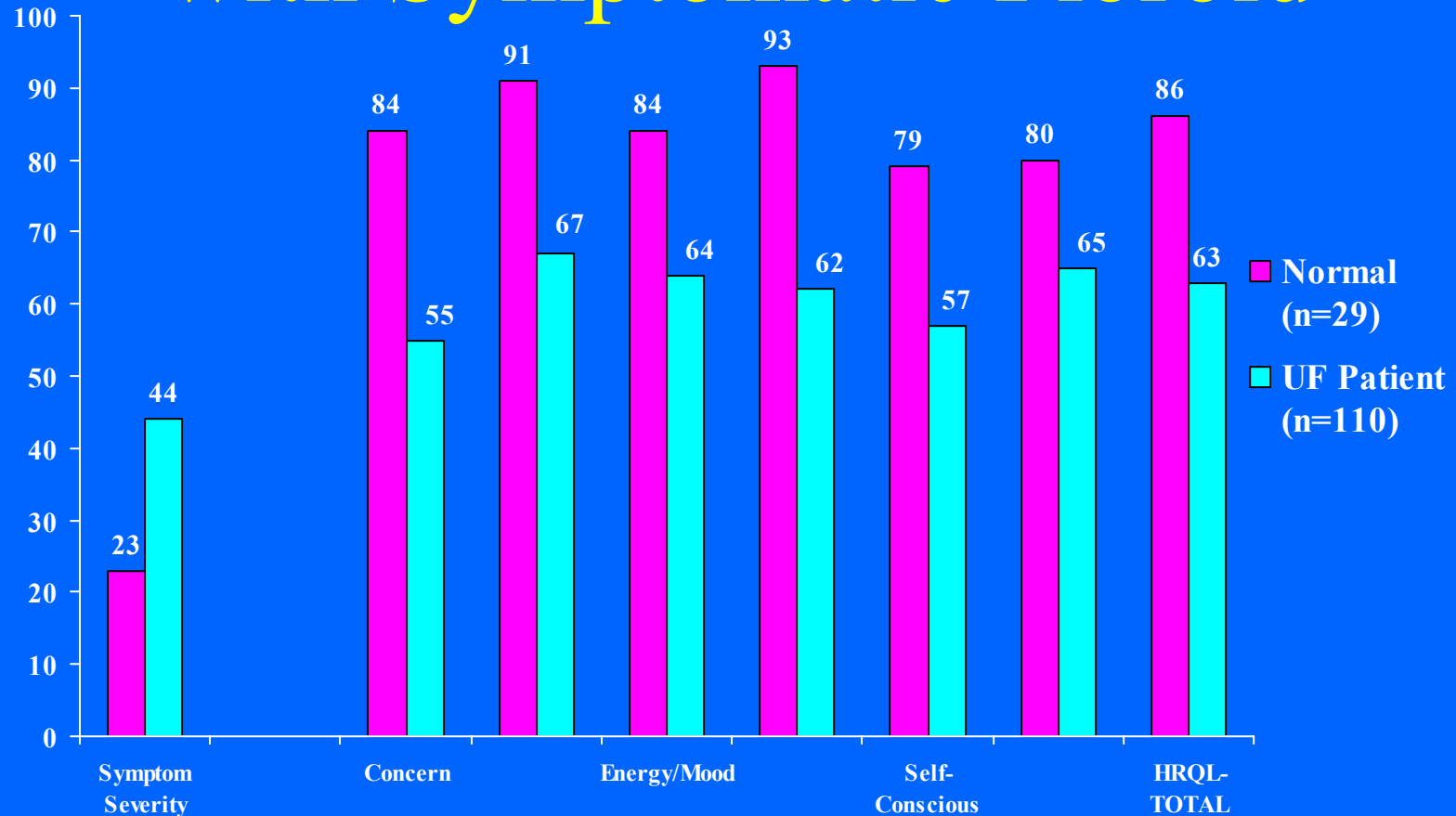


HARVARD
MEDICAL SCHOOL
Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

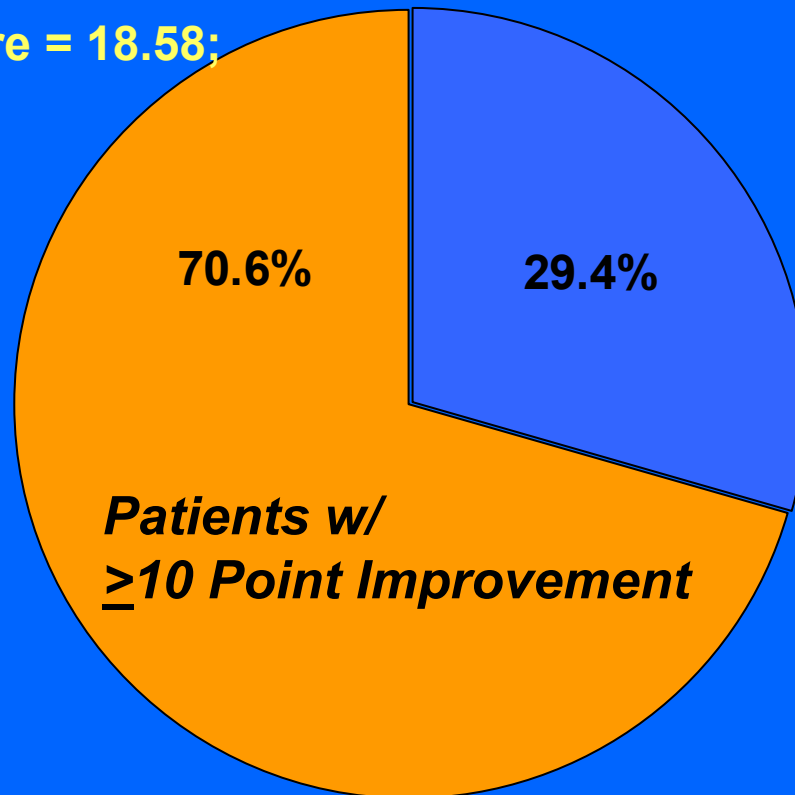
UFS-QOL: Differentiates women with Symptomatic Fibroid



James B. Spies M.D., Karin Coyne PhD, et.al. "The UFS-QOL, a new Disease-specific Symptom and Health-related Quality of Life Questionnaire for Leiomyomata. *Obstet Gynecol* 2002 Feb;99(2):290-300

Primary Efficacy Endpoint: 6 Month SSS demonstrates improvement

ITT N = 109: Chi-square = 18.58;
p < 0.0001



Hindley et al: Am J Radiology: 183: 1713-9, 2004

Excellent Safety Profile

No: Deaths

Emergent surgical procedures

Life threatening events

**Most serious event: Sacral neuropathy
resolving by 12 months**

Hindley et al: Am J Radiology: 183: 1713-9, 2004

Goals for Commercial Treatment

- Confirmation of safety with wider use
- Characterizing optimal candidate
- Optimizing treatment regimen(s)
- Randomized comparison to other therapies
- Maximize durability of response
- Assessing role for women who desire future fertility

FDA Labeling for ExAblate®

2000: A Fibroid Specific Therapy

- Premenopausal women
- Symptomatic fibroids
- No desire for future fertility



HARVARD
MEDICAL SCHOOL

Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL

Potential Advantages of a Fibroid-specific therapy

- Fewer complications such as postembolization syndrome or adhesions**
- Correlation of specific symptoms with specific myomas**
- Potential benefit for women desiring pregnancy**

Uterine rupture

- Testing of innovative therapies on post-reproductive women until safety and efficacy established
- Long-term follow-up of treatment series to define pregnancy outcomes



What do we need?

- Outcomes research on current therapies
- Prediction of risk and outcomes: epidemiology and genetics
- Minimally invasive therapy for existing disease
- Medical therapy to prevent disease and recurrence risk



What do we need?

- Better assessment tools
- Industry recognition of economics
- Interdisciplinary collaboration
- NIH Study section favorable to benign gynecology and clinical trials
- Advocacy



HARVARD
MEDICAL SCHOOL
Teaching Associates



BRIGHAM AND
WOMEN'S HOSPITAL



Center for Uterine Fibroids



Brigham and Women's Hospital
Departments of Obstetrics / Gynecology and Pathology
623 Thorn Building
20 Shattuck Street
Boston, Massachusetts 02115
1-800-722-5520 (x80081)

Please note that our extension has changed!

The mission of the Center for Uterine Fibroids is:

- To define the causes of fibroid-related symptoms by investigating the hormonal, genetic, and molecular processes of fibroid growth and development