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Morcellation:

To or not to - that is the question

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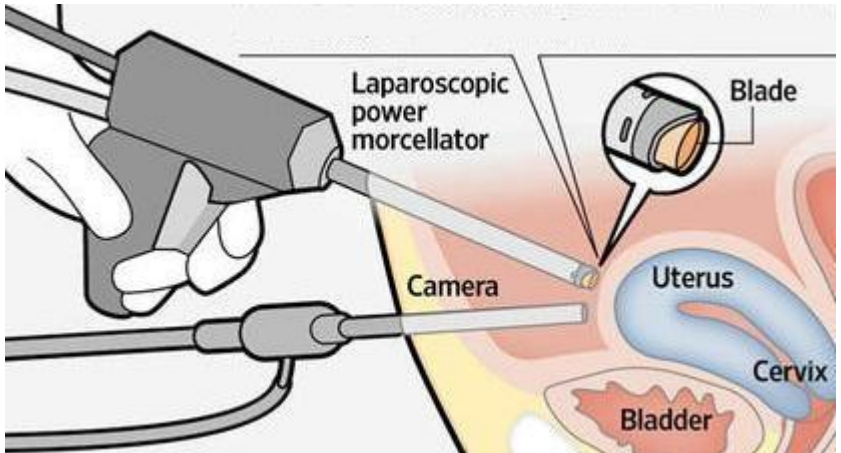

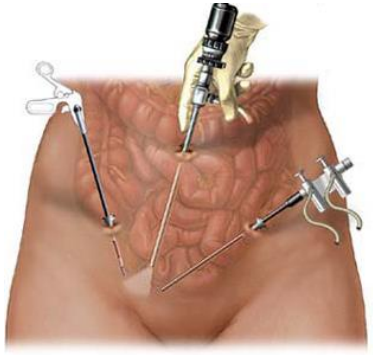

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- Fibroids:
  - non-cancerous growths made up of muscle and fibrous tissue that develop in or around uterus.
- Laparoscopy:
  - specialized technique for performing surgery using several 0.5-1cm incisions
  - Initially eVALuate study showed higher complications with laparoscopic hysterectomy
  - Subsequently: lower blood loss, decreased pain, reduced LOS, faster recovery, less DVT, lower mortality

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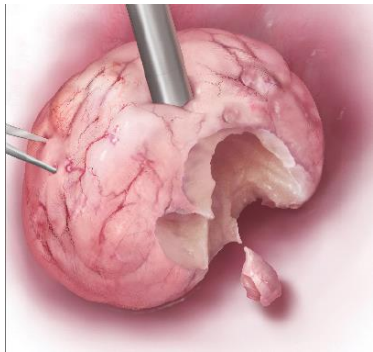
- Morcellation:
  - the fragmentation of tissue to facilitate removal of the specimen through small incisions in minimally invasive surgery
  - First approved by FDA in 1995
  - Concerns:
    - Dissemination of tissue
    - Disruption of tissue for pathology evaluation
    - Surgical complications



So why the debate?

… because of risk of fragmentation and disseminating a leiomyosarcoma into the pelvic cavity

So how did it start?

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Amy Reed, 40, mother of 6

Anaesthetist at Beth Israel

Married to Hooman Noorchashm, a cardiothoracic surgeon at Brigham and Women's.

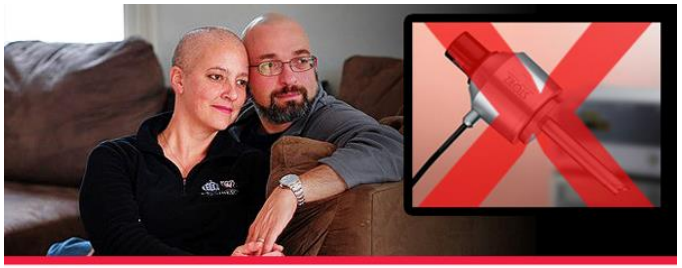
Underwent TLH with morcellation of large fibroids in 10/2013.

'They blasted it all over': Morcellation procedure can spread undiagnosed cancer

Controversial morcellation procedure to remove fibroids can spread undiagnosed cancer

JULY 30, 2014 · BY DIANE MAPES / FRED HUTCH NEWS SERVICE

Started a petition, calling for a moratorium on morcellation



TWO DOCTORS SPEARHEAD A LIFE-SAVING CAMPAIGN AGAINST POWER MORCELLATORS

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change.org

Petition by
Hooman Noorchashm
Philadelphia, United States

To:
Barack Obama, President of the United States
Jeanne Conry, President, American Congress of Obstetricians and Gynecologists
Hal Lawrence, Executive VP and CEO, American Congress of Obstetricians and Gynecologists

Place an immediate moratorium on intracorporeal uterine morcellation during minimally invasive hysterectomy, on all gynecological tissue morcellation devices and any devices used to morcellate the uterus intracorporeally in the United States and Abroad. It is your high duty to first, do no harm.

Sincerely,
[Your name]

The SGO weighs in December, 2013

"…the Society of Gynecologic Oncology (SGO) asserts that it is generally **contraindicated in the presence of documented or highly suspected malignancy**"

"The SGO recognizes that currently there is no reliable method to differentiate benign from malignant leiomyomas…Furthermore, **these diseases offer an extremely poor prognosis, even when specimens are removed intact**."

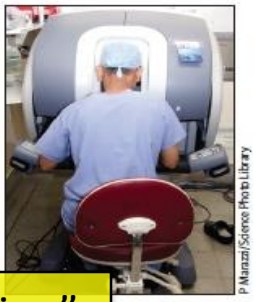
Patient safety must be a priority in all aspects of care

In December, 2013, the Society of Gynecologic Oncology (SGO) released a position statement regarding intracorporeal morcellation, a technique by which tissues excised during minimally invasive surgery are cut up to facilitate removal through small excisions, which might increase the risk of disseminating tumour cells. The statement follows the case of a Harvard anaesthetist who had a hysterectomy involving intracorporeal morcellation at Brigham and Women's Hospital, Boston, MA, USA, to found to have leiomyosarcoma, the patient is now being treated for stage IV disease. Subsequent to this case and another similar incident at the same hospital, the chair of obstetrics and gynaecology issued a note to medical staff warning that morcellation of an occult tumour may occur in between one in 400 and one in 1000 women who have this procedure—a risk at least ten times higher than previously assumed. The department head also cautioned staff that destruction of tissue could make it difficult for pathologists to determine the size of a tumour and extent of tissue invasion. The recommendation of the

and often only regulated when evidence of harm accumulates. This situation is unacceptable.

Patients have no choice but to trust the good judgement of their surgeons, and in return treating physicians should consider the best treatment for their patients based on available evidence. It is not practical to subject every new surgical procedure to the same trial processes as new drugs, but nevertheless structured follow-up and full reporting of adverse events should be side of caution where hazards are reported, as has been the case with intracorporeal morcellation—the risk of disseminating malignant cells by morcellation has been shown numerous times over the past couple of decades. Furthermore, power morcellation, which effectively minces the tissue, probably carries an inherently higher biological risk than manual morcellation. It is difficult to understand why the SGO has taken such a soft line.

Professional bodies and regulators should be proactive in ensuring that safety data is adequately reviewed before making recommendations for new



P Marazzi/Science Photo Library

For the Society of Gynecological Oncology's position statement see https://www.sgo.org/newsroom/position-statements-2/morcellation/

"It is difficult to understand why the SGO has taken such a soft line"

The Lancet Oncology, February 2014

…especially Barbara Goff (President of the SGO)

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SGO not soft on morcellation: risks and benefits must be weighed

As President of the Society of Gynecologic Oncology (SGO), I am writing in response to your leader in the February, 2014, issue of *The Lancet Oncology*, in

We have no definitive scientific evidence for whether one procedure is safer than another. Although you say that "the attitude prevails that new and expensive equipment must be an advance", we have to make calculated decisions on a daily basis as to whether we choose to adopt new technologies. We certainly agree that all medical devices should be adequately assessed for safety before they become adopted by providers.

"In the vast majority of cases, hysterectomy is done because of the presence of benign uterine fibroids. In these circumstances, intracorporial morcellation has benefited hundreds of thousands of women. It is especially beneficial for obese women. **It would be a disservice to deny these women this option**."

The Lancet Oncology, April 2014

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- Feb 2014, Lancet Editorial : "…a 1 in 400 risk of morcellating an occult tumour is unacceptable"

- March 2014, morcellation at BWH was banned, except for in bag morcellation

- April 2014, the FDA *discouraged* the use of laparoscopic power morcellation during hysterectomy or myomectomy for uterine fibroids. Morcellation not banned but physicians encouraged to seek alternatives

ACOG weighs in…May, 2014

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Power Morcellation and Occult Malignancy in Gynecologic Surgery

*A Special Report**

May 2014

- Approx 600,000 hysterectomies, 40% for fibroids
- "There is **no sufficiently large population-based series** to provide an accurate rate of preoperatively undiagnosed uterine sarcoma in patients undergoing hysterectomy."
- "ACOG encourages the FDA to call for the establishment of such a registry.

…and the AAGL, May, 2014

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AAGL *Advancing Minimally Invasive Gynecology Worldwide*

Morcellation During Uterine Tissue Extraction

- "…despite our incomplete understanding of these issues, **MIS employing morcellation remains safe when performed by experienced, high-volume surgeons** in select patients who have undergone an appropriate preoperative evaluation."

- Studies analyzed by the FDA:
  Not stratified by risk factors for sarcoma (esp. age)

- Need to consider implications of alternatives

Industry responds

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- Johnson & Johnson (Gynecare) decides not to further support morcellex until further notice on April 28th
- Later in July 2014 announced they were pulling the product off the market
- Morcellex accounted for approximately 70-80% of sales in a $60M market annually in the US
- Other companies carefully evaluating the situation
- Several companies working on the concept of bag
- morcellation

Why is industry responding in this way?

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The other shoe drops: the FDA responds…

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"Based on an FDA analysis of currently available data, it is estimated that a **1 in 350** women undergoing hysterectomy or myomectomy for the treatment of fibroids is found to have an unsuspected uterine sarcoma"

"…because there is no reliable method for predicting whether a woman with fibroids may have a uterine sarcoma**, the FDA discourages the use of laparoscopic power morcellation** during hysterectomy or myomectomy for uterine fibroids."

Black Box Warning

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- On November 24th the FDA issued an Immediately in Effect (IIE) guidance recommending;
  - Black box warning included in product labeling stating that uterine tissue may contain unsuspected cancer and the **use of power morcellators during fibroid surgery may spread cancer and decrease the long-term survival of patients**

- Contraindication of the use of power morcellators for removal of uterine tissue containing suspected fibroids in post and peri-menopausal women

But…

Most societies and government agencies advocate its use including

- British and European gynaecological societies including ESGO, BSGE
- ACOG
- AAGL
- Health Canada

Questions to be answered?

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- What is the risk of occult leiomyosarcoma?
- What is the risk of dissemination of leiomyosarcoma with morcellation?
- What are the options?

Questions to be answered?

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- **What is the risk of occult leiomyosarcoma?**
- What is the risk of dissemination of leiomyosarcoma with morcellation?
- What are the options?

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What is the risk of LMS?

- Estimated incidence of LMS in hysterectomies for presumed leiomyomata -1:300 to 1:2000

Uterine leiomyosarcoma in series of patients operated for presumed leiomyoma.

Author	Number of patients	Type of surgery	Number of LMS	Frequency of LMS
Parker et al. [5]	1332	Hysterectomy or myomectomy	1	0.08%
Leung et al. [6]	1297	Hysterectomy	3	0.23%
Leibsohn et al. [7]	1429	Hysterectomy	7	0.49%

- EBM requires the best available evidence to make clinical decisions
- So what is the best such evidence regarding rate of LMS

Comparative Effectiveness Review
Number 195

Management of Uterine Fibroids

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Table 2. Literature search strategy: morcellation and risk of cancer dissemination

	PubMed (3/13/15) Query	Results
#1	morcellation	445
#2	morcellat* AND uterine	256
#3	morcellat*	562
#4	("Electrosurgery/adverse effects"[Mesh]) OR "Uterine Myomectomy/adverse effects"[MeSH] OR morcellat*	1,251
#5	("Electrosurgery/adverse effects"[Mesh] AND uterine) OR "Uterine Myomectomy/adverse effects"[MeSH] OR morcellat*	742

AHRQ Agency for Healthcare Research and Quality | Effective Health Care Program

Key Questions

Key Question 1. What is the comparative effectiveness (benefits and harms) of treatments for uterine fibroids, including comparisons among these interventions?

Key Question 2. Does treatment effectiveness differ by patient or fibroid characteristics (e.g., age; race/ethnicity; symptoms; menopausal status; imaging characteristics; vascular supply to fibroids; or number, size, type, location, or total volume of fibroids)?

Key Question 3. What is the risk of encountering a leiomyosarcoma for masses believed to be uterine fibroids at the time of myomectomy or hysterectomy?

Key Question 4. Does survival after leiomyosarcoma differ by patient or fibroid characteristics (e.g., age; race/ethnicity; symptoms; menopausal status; imaging characteristics; vascular supply to fibroids; or number, size, type, location, or total volume of fibroids) or by surgical approach to morcellation?

- 160 studies including 136,195 women
- 40,000 of the women(29%) were from prospective studies

	Prospective	Retrospective
Myomectomy	56.7%	31.9%
Hysterectomy	35.8%	48.9%
Both	6%	19.2%

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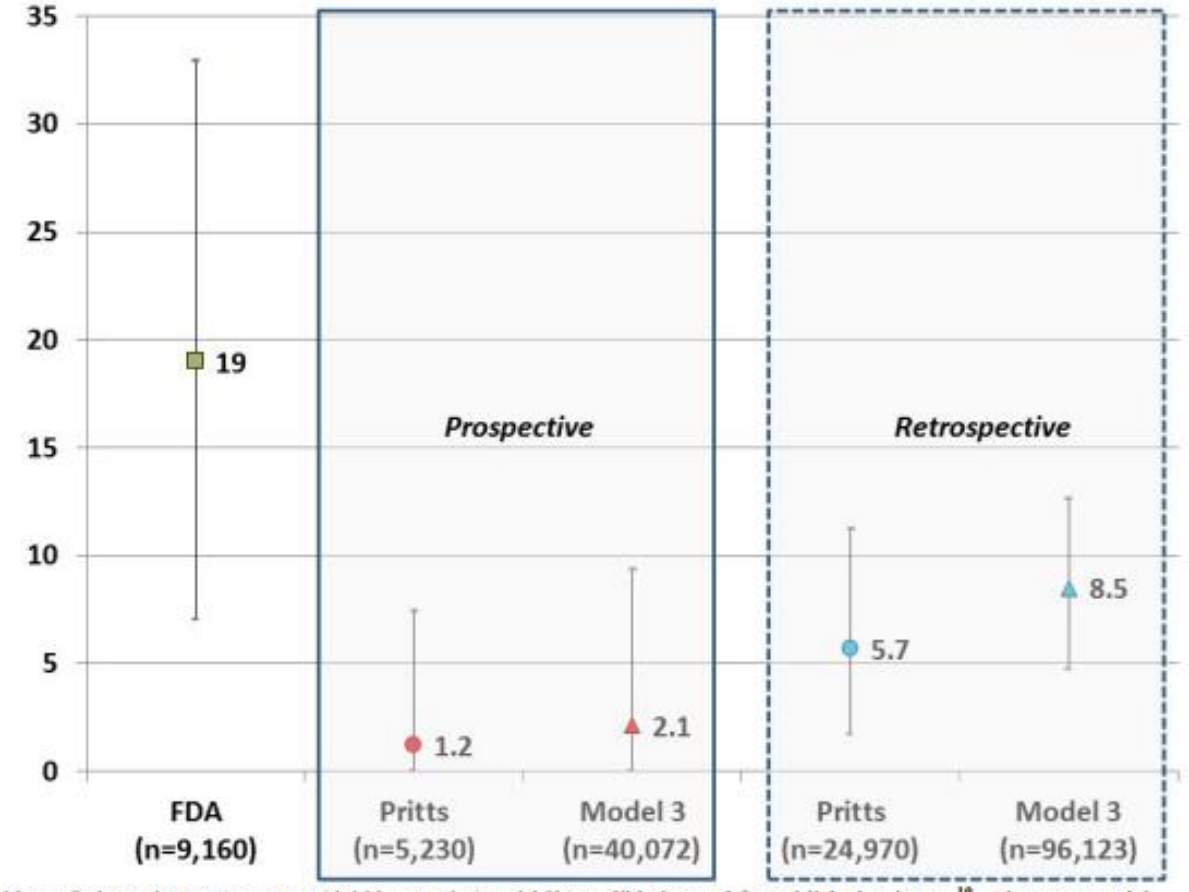
Figure 5. Risk of leiomyosarcoma at surgery for presumed fibroids



Notes: Point estimates (cases per 10,000 surgeries) and 95% credible interval for published estimates[10] and current model. Grouped by prospective (solid box) vs. retrospective (dashed box) study design. N= number of women included in each analysis. FDA indicates estimates from earlier Food and Drug Administration summary document.[24,40]

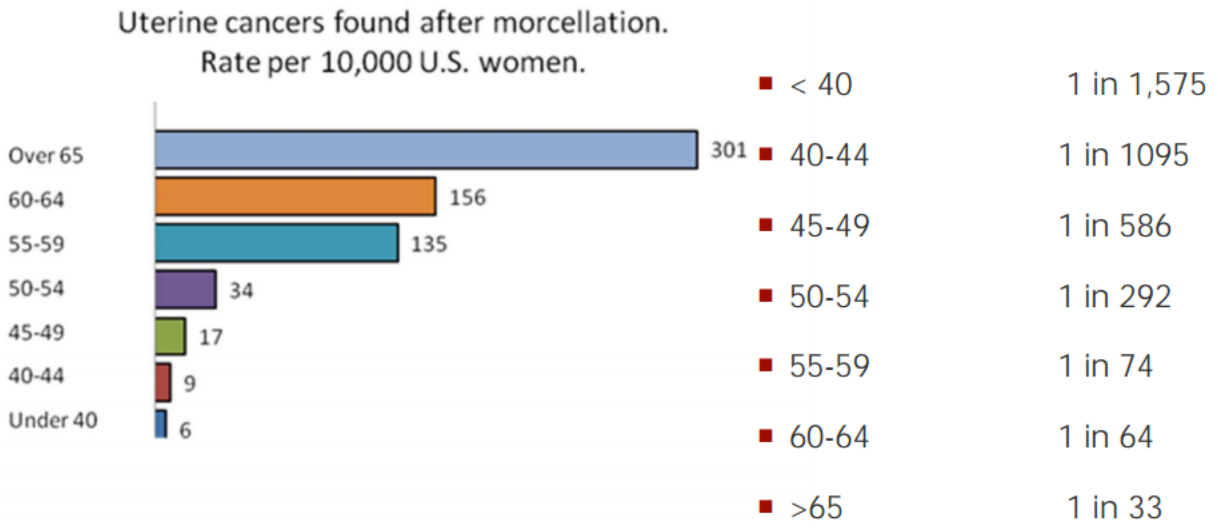
CONCLUSION:
2 in 10,000

Based on 68 prospective studies based in favour of detection, it is estimated that 2 women who have surgery for fibroids in every 10,000 have a LMS (range < to 9)

Risk factors for LMS

- Increasing age: lowest in <35 and highest in >65
- Afro-caribean 1:1400 vs 1:2500
- Tamoxifen use >5years
- History of radiation

Of the 99 cases of uterine cancer, 67 were ≥ 50 years old and an additional 17 were ≥ 45 years old.
There was no distinction made between uterine cancers.



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Questions to be answered?

- How is the risk of occult leiomyosarcoma?
  - Very low: 2 in 10,000

Questions to be answered?

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- What is the risk of occult leiomyosarcoma?
- **What is the risk of dissemination of leiomyosarcoma with morcellation?**
- What are the options?

Leiomyosarcoma: Staging and why tissue spread matters

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SEER report, 2007

Stage	Location	5-year survival
Stage I	Confined to the uterus	60%
Stage II	Confined to the pelvis	35%
Stage III	Invasion of serosa,spread to pelvic organs, positive cytology, local nodes	28%
Stage IV	Bladder, rectum, or distant metastases	15%

- Even early stage LMS have poor outcome: for stage 1-2 LMS removed INTACT
  - 70% recurrence in first 2.5yrs
  - Median survival 52 months
- LMS has high mortality regardless of surgical approach
- Women undergoing surgery for presumed fibroids are unstaged at surgery because LMS is undiagnosed

- The limited data of systemic reviews **suggests** that morcellation may affect LMS outcome but this has **not been proven** because
  - Confidence intervals overlap
  - Even in those with LMS with intact removal of uterus there is a substantial mortality risk
- Best available analysis AHRQ study: ”whilst estimates appear to favour manual or no morcellation, no statistically significant difference could be discerned”

Questions to be answered?

- What is the risk of dissemination of leiomyosarcoma with morcellation?
  - Evidence suggests that there is an increased risk but it is NOT proven. Need more data

Questions to be answered?

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- What is the risk of occult leiomyosarcoma?
- What is the risk of dissemination of leiomyosarcoma with morcellation?
- **What are the options?**

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If not laparoscopic then what?

- It is important that in addition to the potential spread of unsuspected LMS, when comparing a laparoscopic approach with an abdominal approach for a hysterectomy, its is important to consider the morbidity associated with the procedure itself

- The FDA focused more on harm of morcellation use than on harm to women deprived of it

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Table 3. Comparison of Outcomes of Abdominal Hysterectomy Without Morcellation With Laparoscopic Hysterectomy With Morcellation

Outcome	Estimated Net Difference*
Venous thromboembolism	+2%
Small bowel obstruction	+2.8%
Adhesions	+18.2% (transverse incision)
Surgical site infection	+4.8%
Length of hospital stay	+2 days
Return to work	+13.6 days
Postoperative pain	+48%
Patient satisfaction	−50.4 points†
Estimated blood loss	+45 cc
Uterine sarcomas morcellated	−0.28%
Local recurrence	−47.8%
Median time to recurrence	+28.8 months
5-year recurrence-free survival	+25%
Overall survival at 5 years	+27%

- LH: shorter LOS, less pain, less blood loss. Reduced incisional hernia, wound infection and VTE
- AH: avoids risks of morcellation
- So **decision analysis models** designed to assist physicians in deciding on surgical approach in managing fibroid uterus

Decision analysis: LH with morcellation vs AH for presumed fibroids

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- Decision tree model comparing outcomes of LH and AH
- Simulated a cohort of 100,000 undergoing LH or AH for fibroids
- Primary outcomes: LMS and hysterectomy related deaths over a 5 yrs period following surgery
- Examined frequency of transfusions, wound infection, VTE, incisional hernia, cuff dehiscence, overall mortality and complications due to occult LMS
- Also incorporated the effect of age

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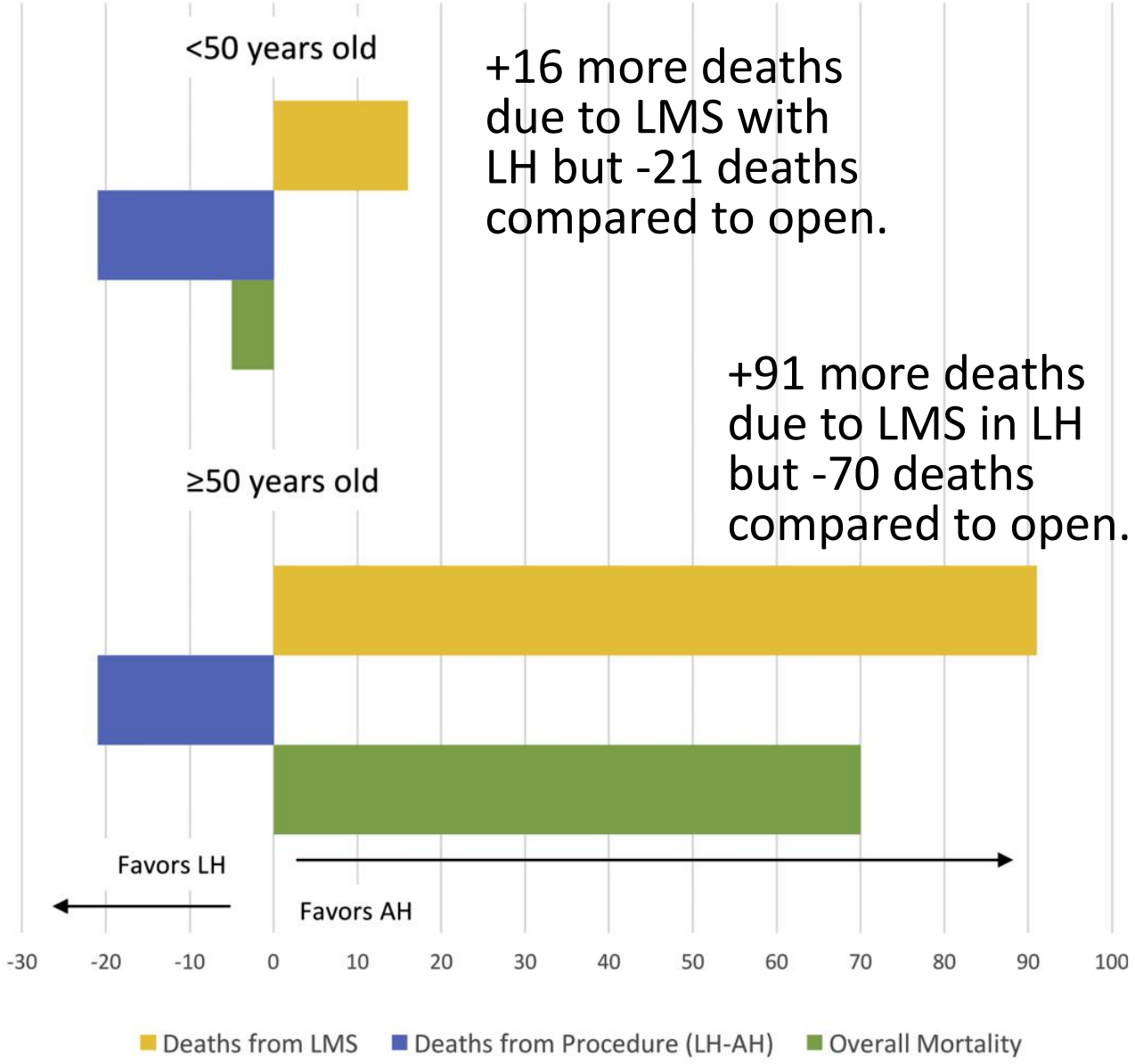

FIGURE 2. Mortality estimates stratified by age
Number of incremental deaths per 100,000 in laparoscopic hysterectomy (LH) and abdominal hysterectomy (AH), stratified by age.
LMS, leiomyosarcoma.
Siedhoff. Updated laparoscopic vs abdominal hysterectomy decision analysis. Am J Obstet Gynecol 2017.

Laparoscopic approach remains a safe option especially for women <50

- How is the risk of occult leiomyosarcoma?
  - Very low 2 in 10,000
- What is the risk of dissemination of leiomyosarcoma with morcellation?
  - Evidence suggests that there is an increased risk but it is NOT proven. Need more data
- What are the options?
  - LH is associated with lower morbidity and mortality in women <50

MORCELLATION-

To or not to, that is the question
Whether 'tis nobler in the mind to morcellate
The fibroids of outrageous uteri,
Or to take Arms against a Sea of lawyers and the FDA,
And by opposing end them

That is the question

"I can no other answer make, but thanks, and thanks, and ever thanks."
– William Shakespeare