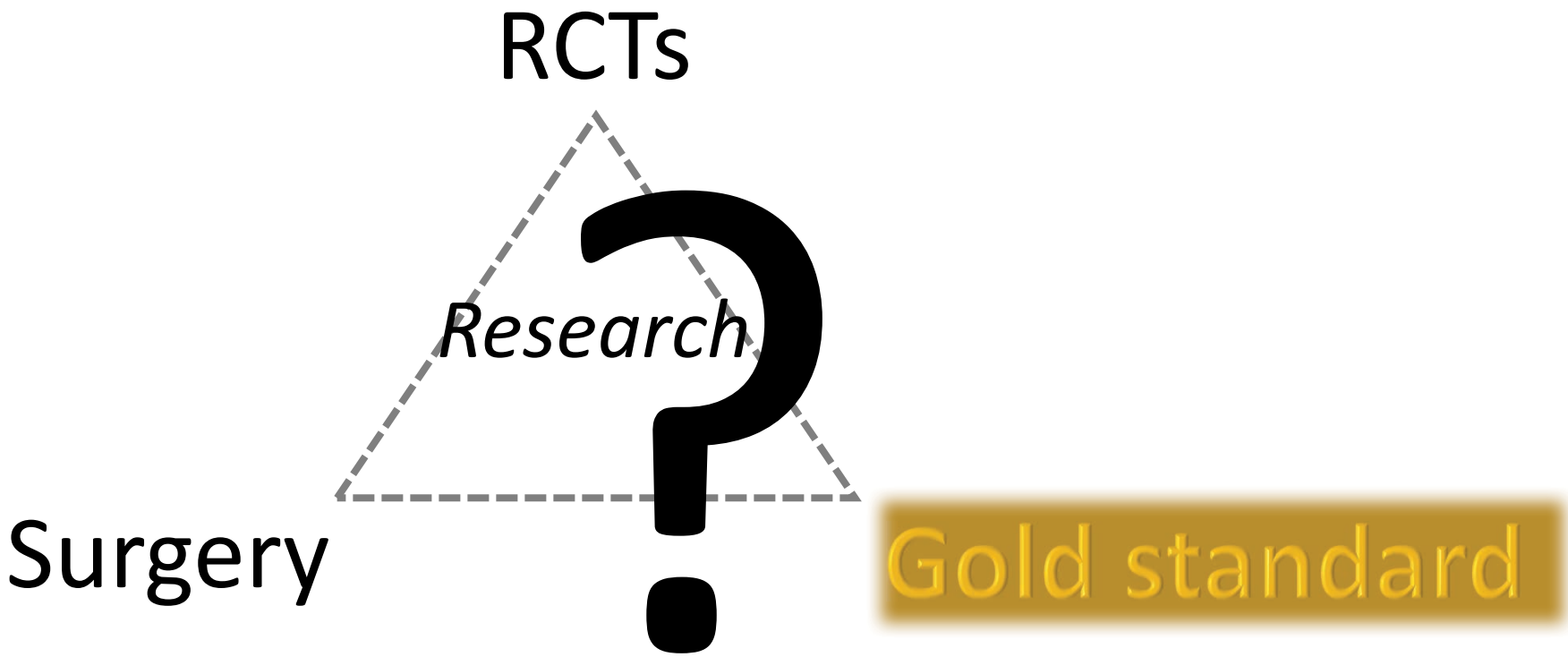


Dr Bill Sears

Medtronic Ageing Spine Conference

Sydney, August 18th 2017

“There are three kinds of lies: lies, damned lies and RCTs”

Benjamin Disraeli *circa*1890

What is the goal of Surgical research?

To determine if a surgical therapy makes a positive difference to the people receiving it.

Which people?

Which surgery?

removal of…

- Bias
- Placebo effect
- Confounding variables

Parachute Use to Prevent Death and Major Trauma Related to Gravitational Challenge: Systematic Review of Randomized Controlled Trials

Objectives

- To determine whether parachutes are effective in preventing major trauma related to gravitational challenge

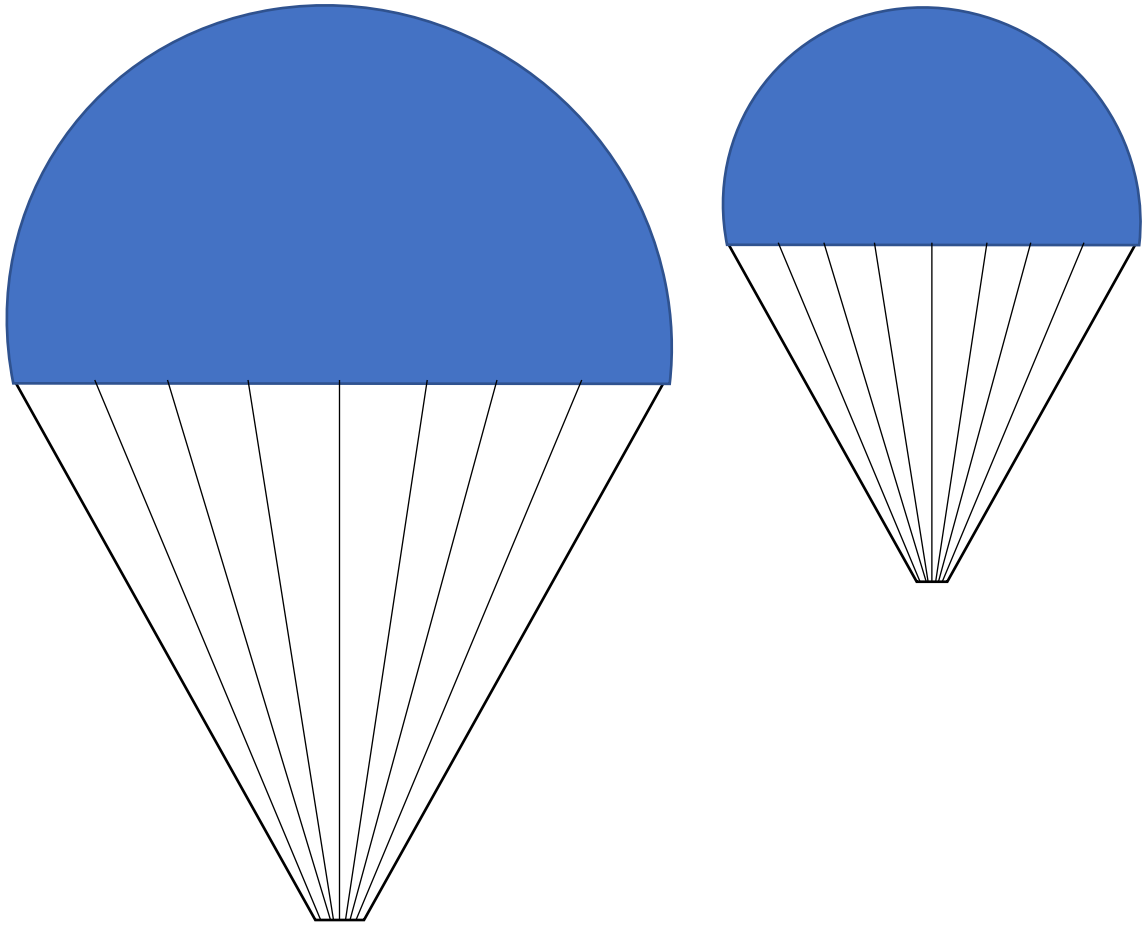
Results

- We were unable to identify any randomized controlled trials of parachute intervention

Conclusions

- As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomized controlled trials. Advocates of evidence-based medicine have criticized the adoption of interventions evaluated by using only observational data.
- We think that everyone might benefit if the most radical protagonists of evidence-based medicine organized and participated in a double-blind, randomized, placebo-controlled, crossover trial of the parachute.

BMJ 2003; 327:1459-61

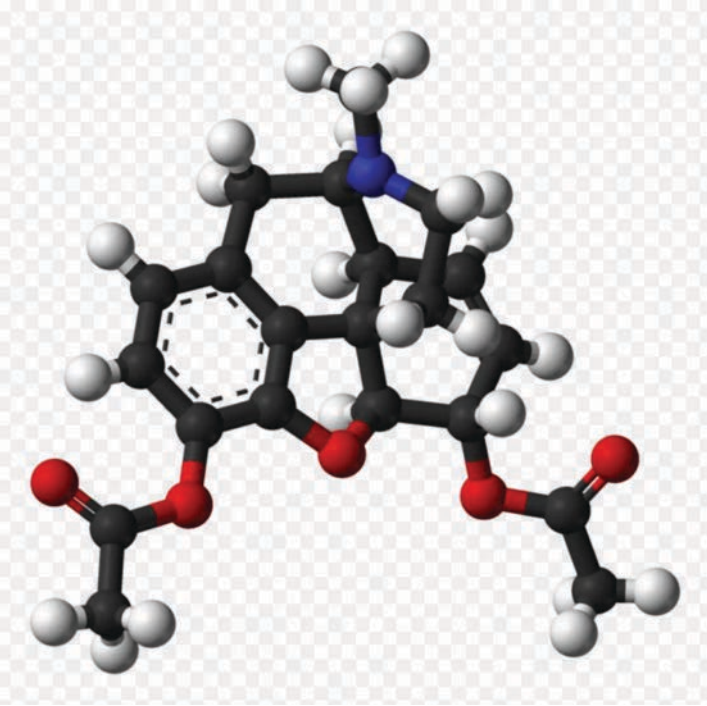


Relevant Factors:

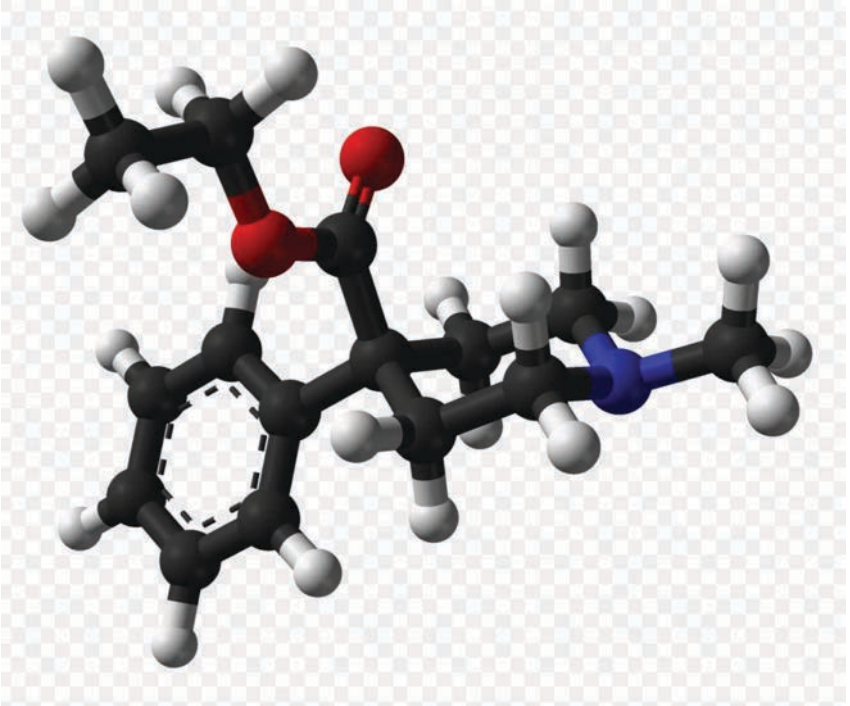
- Canopy
  - Design
  - Size
- Air density
  - Altitude
  - Temperature
- Load

Pharmaceutical research

Pharmaceutical research



vs.



‘New’ treatment A

‘Old’ treatment B

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Austin Bradford Hill

From Wikipedia, the free encyclopedia

For Massachusetts State Rep., see Bradford Hill.

Sir Austin Bradford Hill FRS[1] (8 July 1897 – 18 April 1991), English epidemiologist and statistician, pioneered the randomized clinical trial and, together with Richard Doll, demonstrated the connection between cigarette smoking and lung cancer. Hill is widely known for pioneering the "Bradford Hill" criteria for determining a causal association.[2][3]

Contents [hide]

Early life [edit]

Son of Sir Leonard Erskine Hill FRS a distinguished physiologist, Hill was born in London, lived as a child at the family home, Osborne House, Loughton, Essex; he was educated at Chigwell School, Essex. He served as a pilot in the First World War but was invalided out when he contracted tuberculosis. Two years in hospital and two years of convalescence put a medical qualification out of the question and he took a degree in economics by correspondence at London University.

Austin Bradford Hill

Born	8 July 1897
Died	18 April 1991 (aged 93)
Nationality	United Kingdom
Occupation	Epidemiologist statistician

Clinical trial design

- The study subjects - inclusion/exclusion criteria
- The treatment
- The comparitor
- The randomisation
- Crossover?
- The assessor
- The analysis
  - ‘Intention-to-treat’ *or* ‘as treated’
  - Statistics

Clinical trial design

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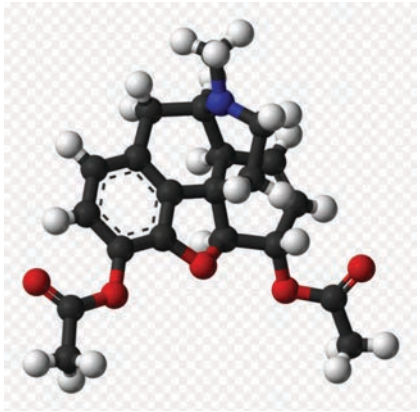
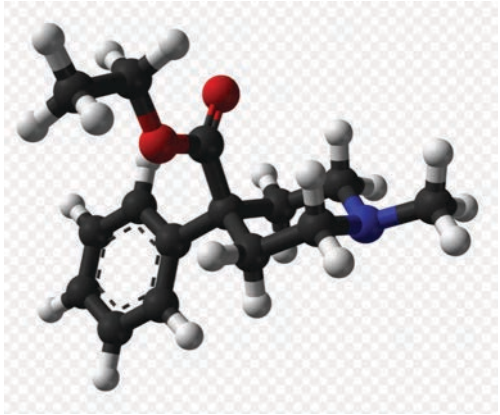
RCTs – standard in pharmaceutical research

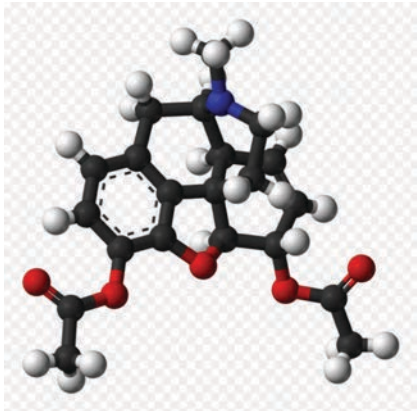


Treatment A



Treatment B

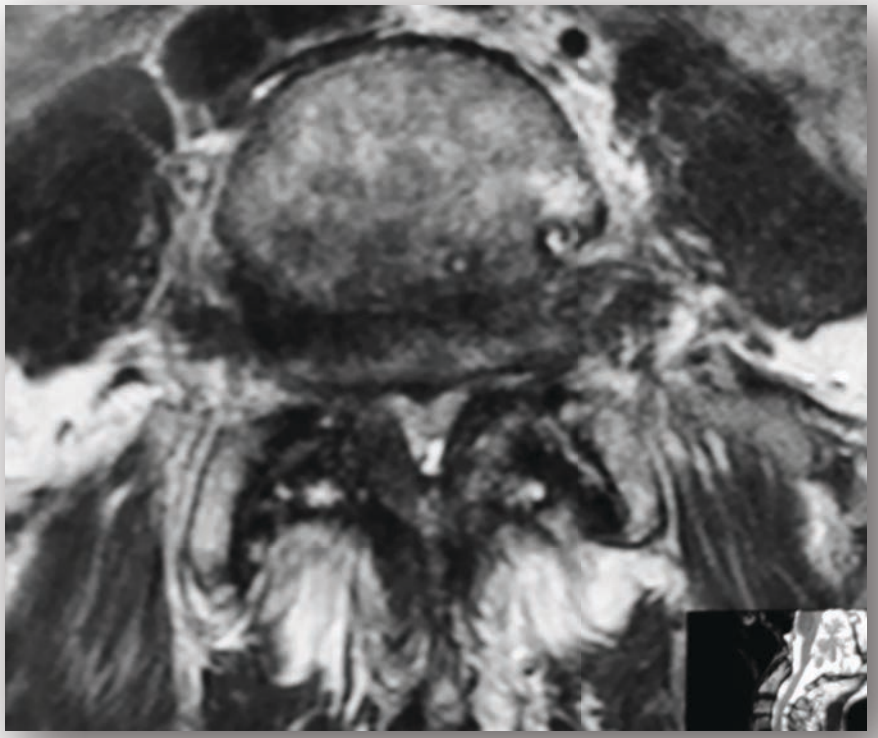
RCTs – standard in pharmaceutical research



Treatment A

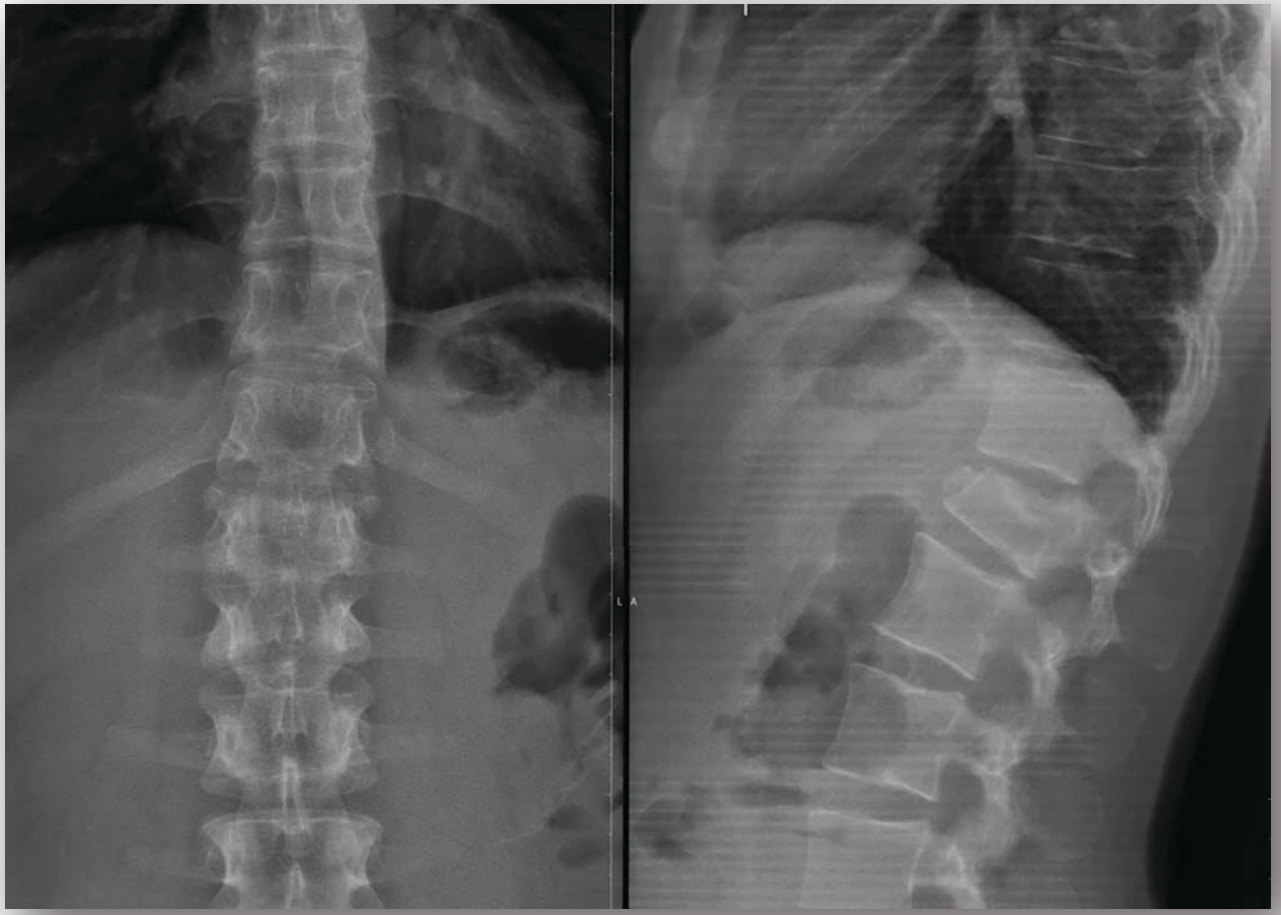
Placebo

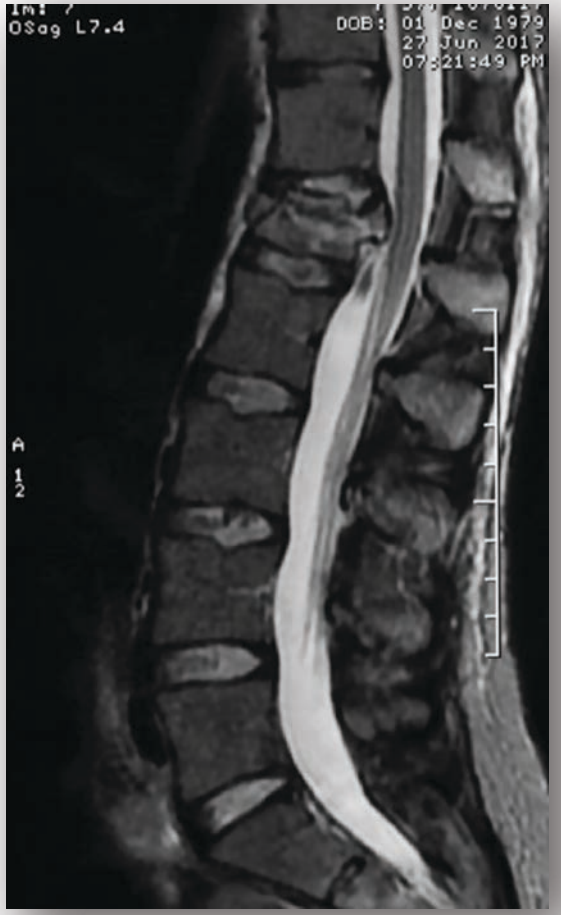
Spinal stenosis decompression?



Burst fracture without neuro deficit?

Treatment of thoraco-lumbar Burst Fractures, without neurological deficit





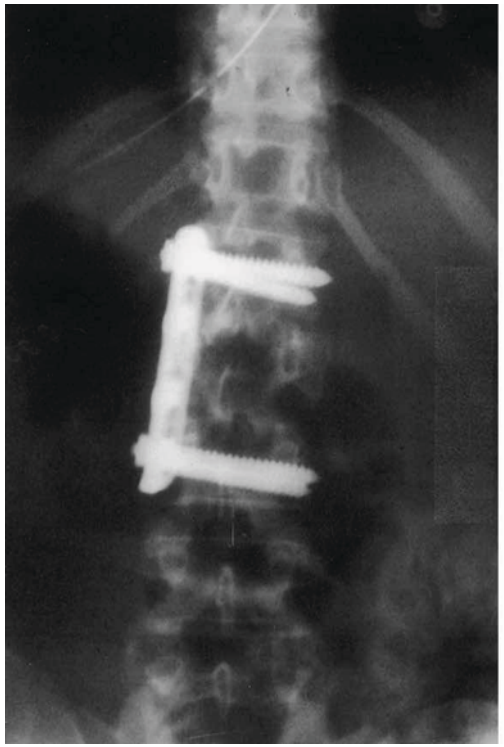
Treatment of thoraco-lumbar Burst Fractures, without neurological deficit

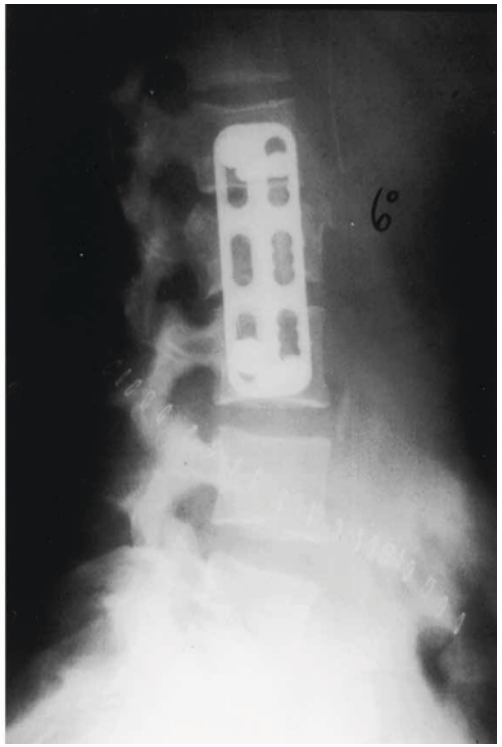
OPERATIVE COMPARED WITH NONOPERATIVE TREATMENT OF A THORACOLUMBAR BURST FRACTURE WITHOUT NEUROLOGICAL DEFICIT

Conclusion: We found that operative treatment of patients with a stable thoracolumbar burst fracture and normal findings on the neurological examination provided no major long-term advantage compared with nonoperative treatment.

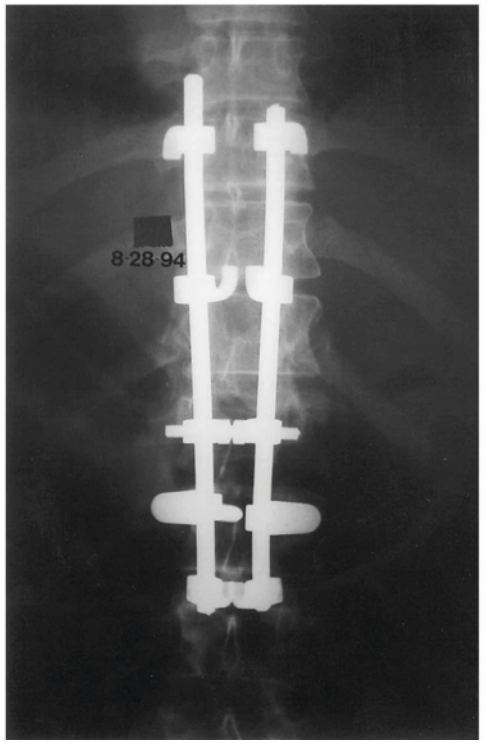
Level of Evidence: Therapeutic study, Level II-2 (poor-quality randomized controlled trial [e.g., <80% follow-up]). See

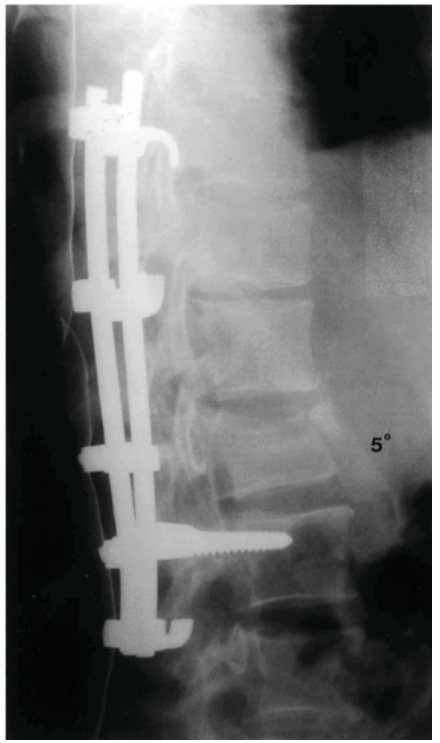
The ‘specific’ treatment



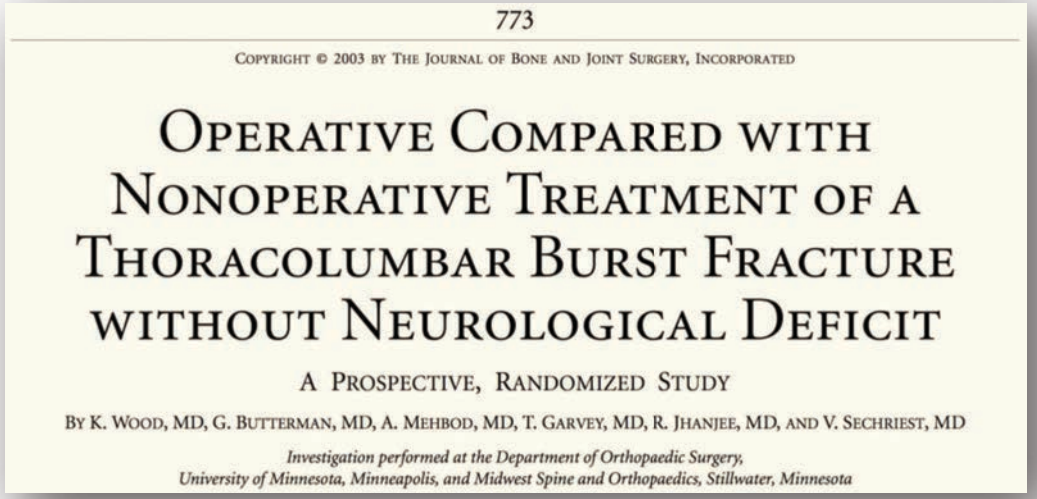


Treatment A





Treatment A



773

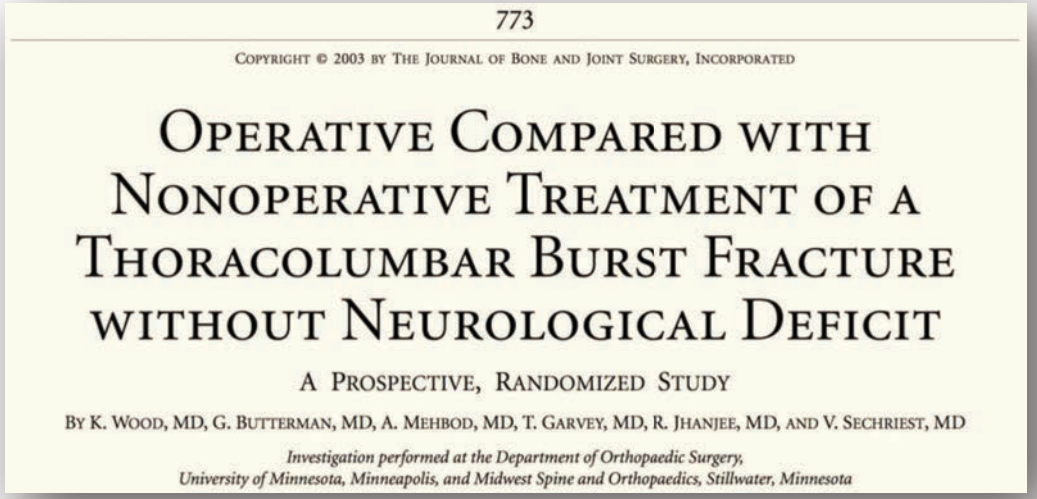
OPERATIVE COMPARED WITH NONOPERATIVE TREATMENT OF A THORACOLUMBAR BURST FRACTURE WITHOUT NEUROLOGICAL DEFICIT

A PROSPECTIVE, RANDOMIZED STUDY

BY K. WOOD, MD, G. BUTTERMAN, MD, A. MEHBOD, MD, T. GARVEY, MD, R. JHANJEE, MD, AND V. SECHRIEST, MD

Investigation performed at the Department of Orthopaedic Surgery, University of Minnesota, Minneapolis, and Midwest Spine and Orthopaedics, Stillwater, Minnesota

- 1992-1997
- Surgery
  - Posterior: ‘Short-segment’ – two to five levels, pedicle screw-hook instrumentation
  - Anterior: Two-level fibula & rib-strut graft



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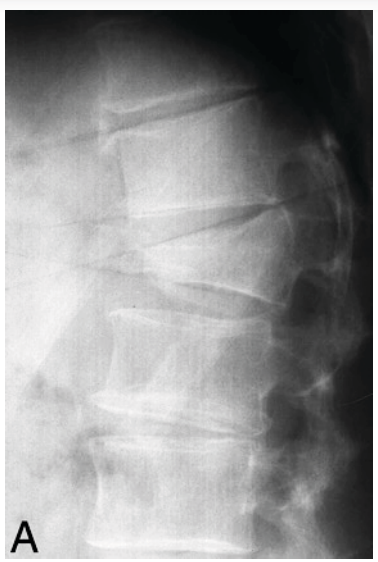
- Demographics
  - Smokers:
    - 16/24 (67%) surgery group
    - 4/23 (17%) non-surgery group ($p<0.01$)

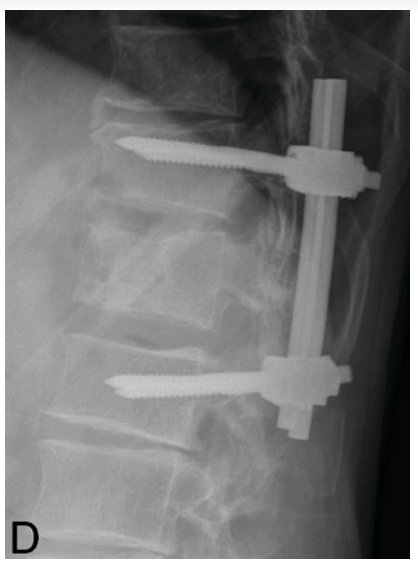
- “Because of the relatively small numbers involved, we could not determine whether there was any difference between those treated from an anterior or a posterior approach.”

SPINE Volume 31, Number 25, pp 2881–2890

Treatment of Traumatic Thoracolumbar Spine Fractures: A Multicenter Prospective Randomized Study of Operative *Versus* Nonsurgical Treatment

Jan Siebenga, MD,* Vincent J. M. Leferink, MD, PhD,† Michiel J. M. Segers, MD,‡ Matthijs J. Elzinga, MD,‡ Fred C. Bakker, MD, PhD,‡ Henk J. Th. M. Haarman, MD, PhD,‡ Pol M. Rommens, MD, PhD,§ Henk-Jan ten Duis, MD, PhD,† and Peter Patka, MD, PhD‖





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Results. … after a mean of 4.3 years. At the end of follow-up, both local and regional kyphotic deformity was significantly less in the operatively treated group. All functional outcome scores (VAS Pain, VAS Spine Score, and RMDQ-24) **showed significantly better results in the operative group**.

Conclusions. Patients with a Type A3 thoracolumbar spine fracture without neurologic deficit should be treated by short-segment posterior stabilization.

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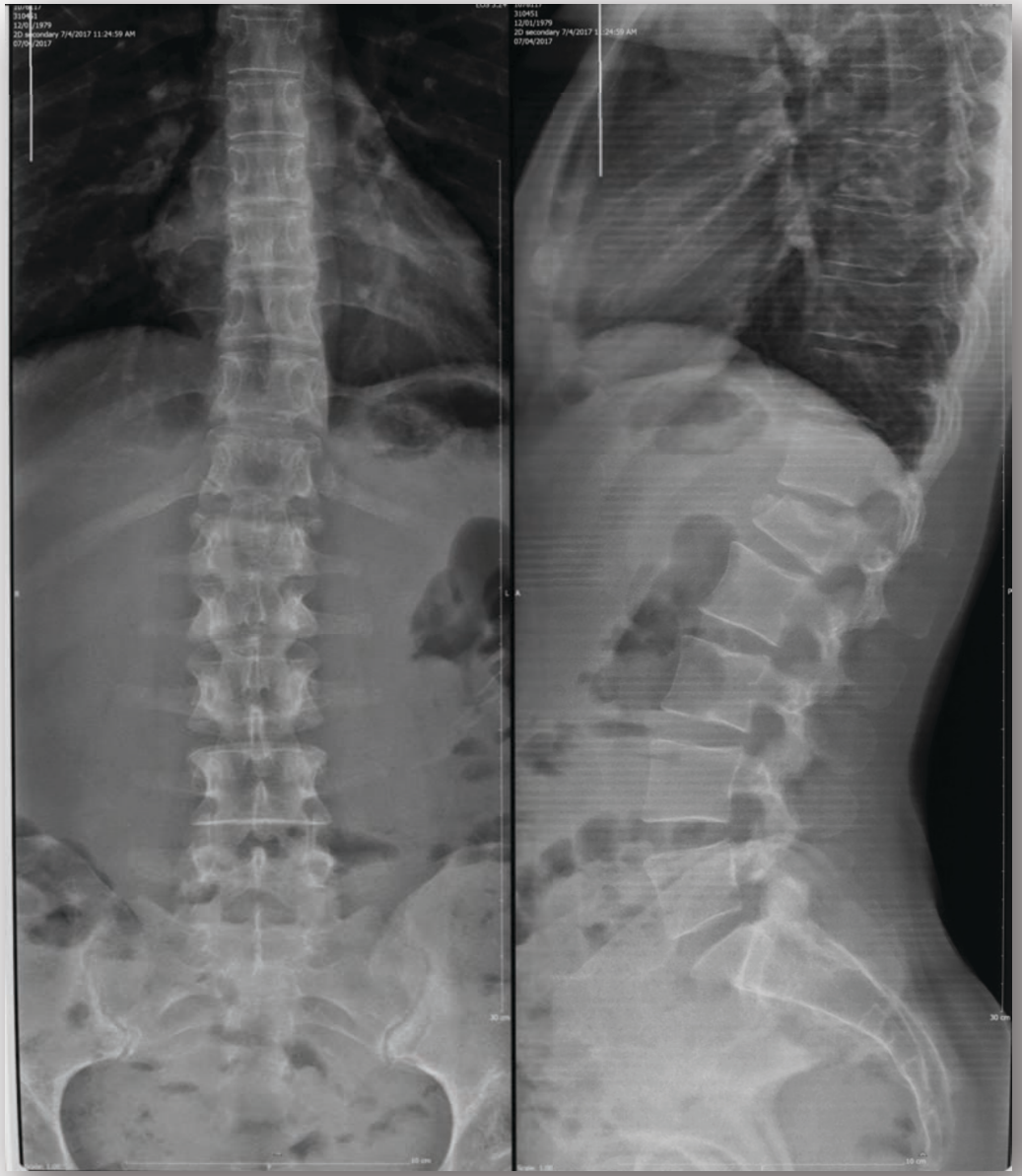
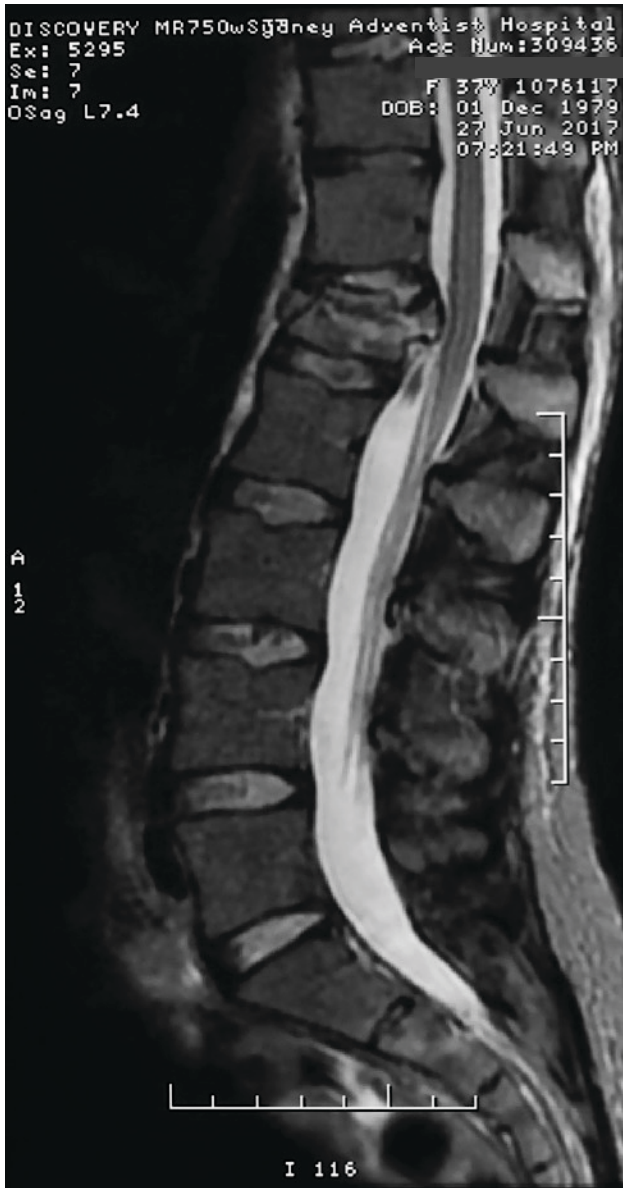
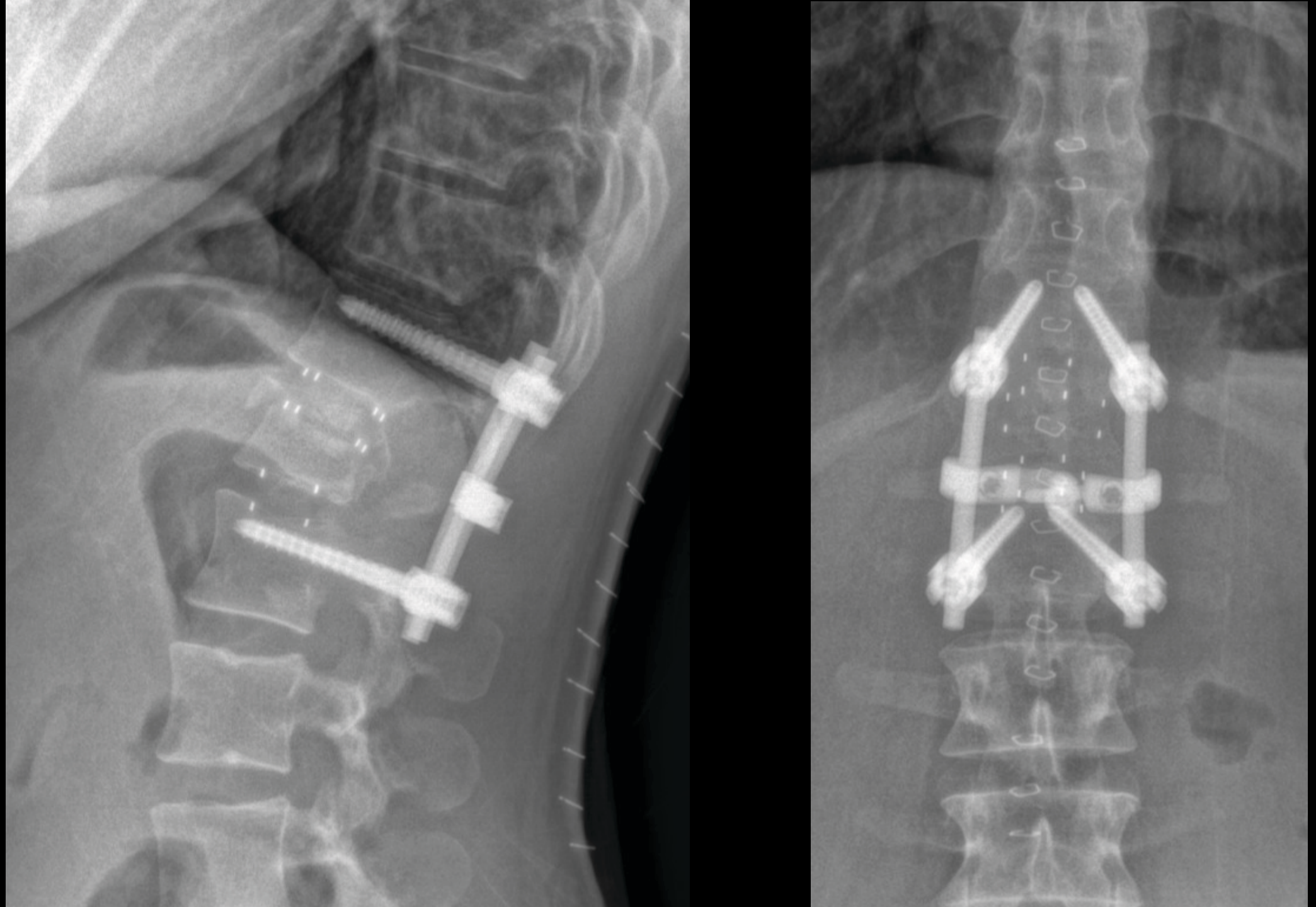
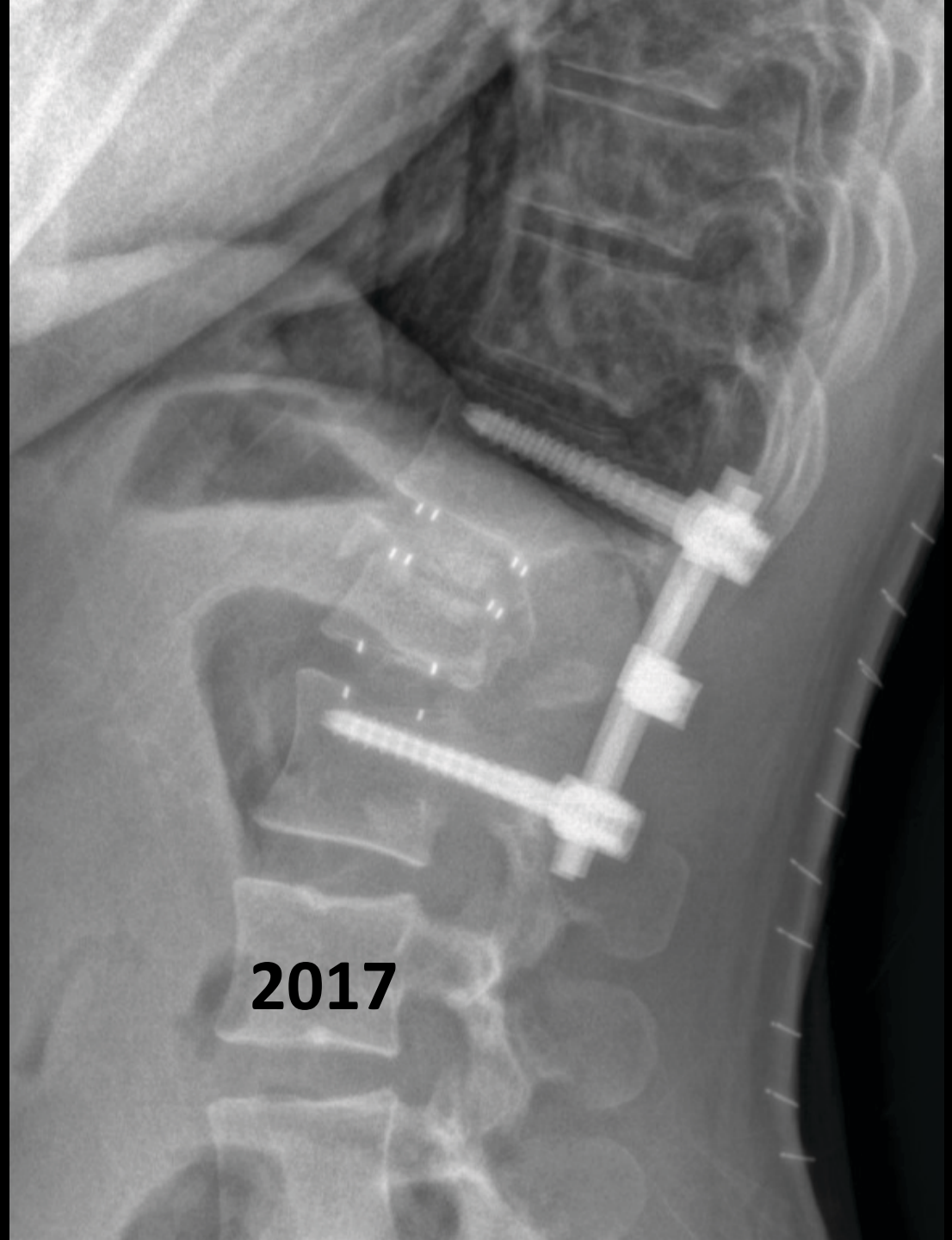
Conclusions. Patients with Type A3 thoracolumbar spine fracture without neurologic deficit **should be treated by short-segment posterior stabilization**.

Female, 40yrs








2017


1992

Internal *vs.* External Validity

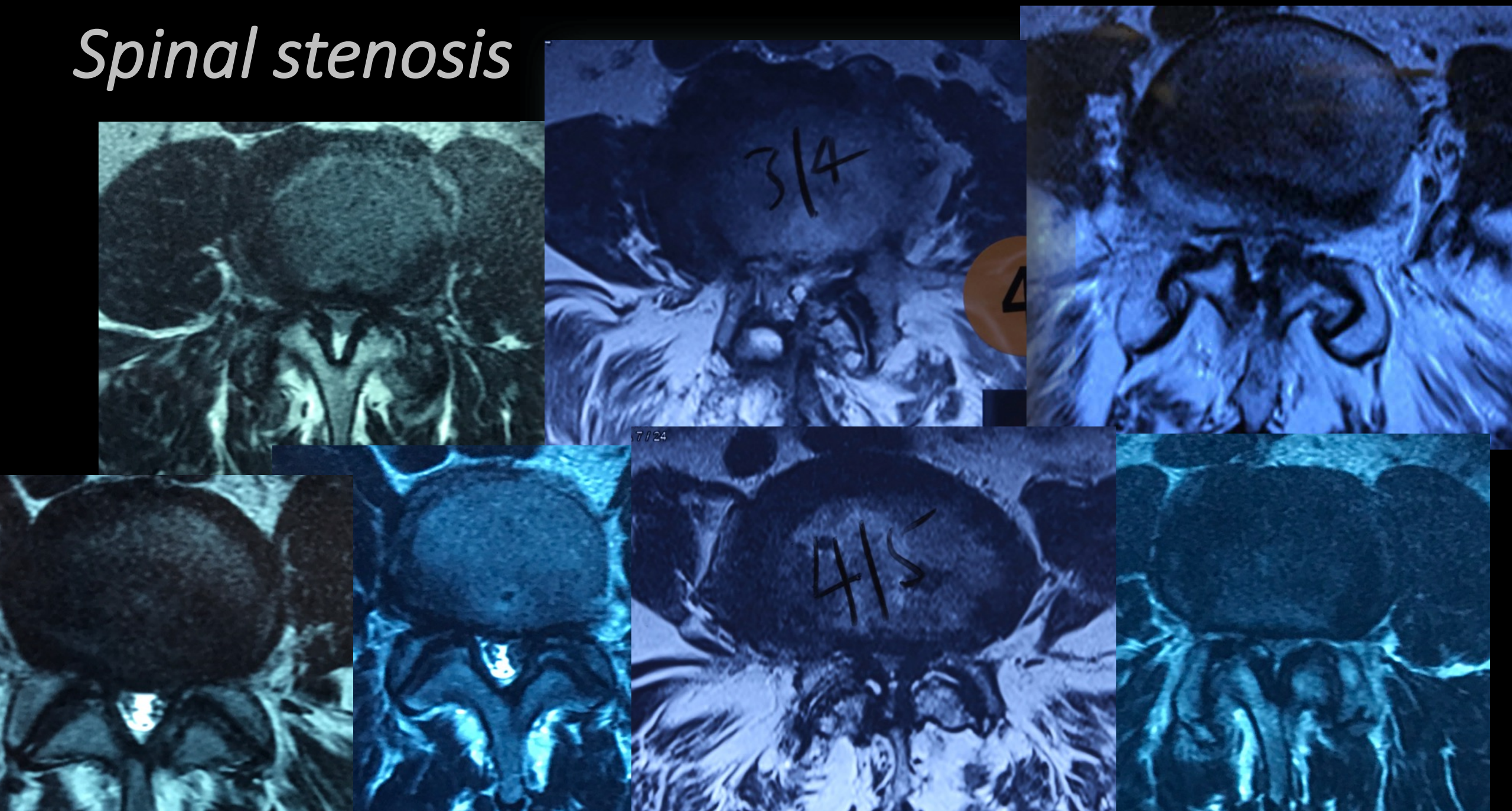
Bias should be removed and and the effects of confounding factors minimised, but…

it's also important to provide a focused research question – with limited heterogeneity of

1) the condition being treated and
2) the treatment provided.

The issue under investigation shouldn't be too general or the results may be attenuated by combining clinical outcomes from situations where a treatment doesn't work with those where it does.

Spinal stenosis



GRANT PROPOSAL – 2015 Project Grants

Application ID: APP1125140
CIA Surname: Ferreira

A. Research Proposal *(9 pages)*

SUcceSS: SUrgery for Spinal Stenosis – a randomised placebo-controlled trial

- ***"At present it is not possible to make sensible evidence-based decisions about the use of decompressive surgery for spinal stenosis as the evidence base is poor and surgical rationale unclear."***

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- ***"The results of this systematic review have revealed… to date there are no published randomised controlled trials comparing surgery to no treatment or placebo/sham surgery."*** Machado *et al.* PLOSone 2015

SPINE Volume 25, Number 11, pp 1424–1436

Lumbar Spinal Stenosis: Conservative or Surgical Management?

A Prospective 10-Year Study

Tom Amundsen, MD,* Henrik Weber, MD, DrMed,* Helge J. Nordal, MD, DrMed,* Bjørn Magnaes, MD, DrMed,† Michael Abdelnoor, MPH, PhD,‡ and Finn Lilleås, MD§

SPINE Volume 32, Number 1, pp 1–8

Surgical or Nonoperative Treatment for Lumbar Spinal Stenosis?

A Randomized Controlled Trial

Antti Malmivaara, MD, PhD,* Pär Slätis, MD, PhD,‖ Markku Heliövaara, MD, PhD,† Päivi Sainio, PT, MSc,† Heikki Kinnunen, MD,§ Jyrki Kankare, MD, PhD,§ Nina Dalin-Hirvonen, MD,‡ Seppo Seitsalo, MD, PhD,‖ Arto Herno, MD, PhD,¶ Pirkko Kortekangas, MD, PhD,# Timo Niinimäki, MD, PhD,** Hannu Rönty, MD,** Kaj Tallroth, MD, PhD,‖ Veli Turunen, MD,†† Paul Knekt, PhD,‡‡ Tommi Härkänen, PhD,† and Heikki Hurri, MD, PhD,‖ for the Finnish Lumbar Spinal Research Group

SPINE Volume 35, Number 14, pp 1329–1338

Surgical *Versus* Nonoperative Treatment for Lumbar Spinal Stenosis Four-Year Results of the Spine Patient Outcomes Research Trial

James N. Weinstein, DO, MS,*†‡ Tor D. Tosteson, ScD,*†‡ Jon D. Lurie, MD, MS,*†‡ Anna Tosteson, ScD,*†‡ Emily Blood, MS,*†‡ Harry Herkowitz, MD,§ Frank Cammisa, MD,¶ Todd Albert, MD,‖ Scott D. Boden, MD,** Alan Hilibrand, MD,‖ Harley Goldberg, DO,†† Sigurd Berven, MD,‡‡ and Howard An, MD§§

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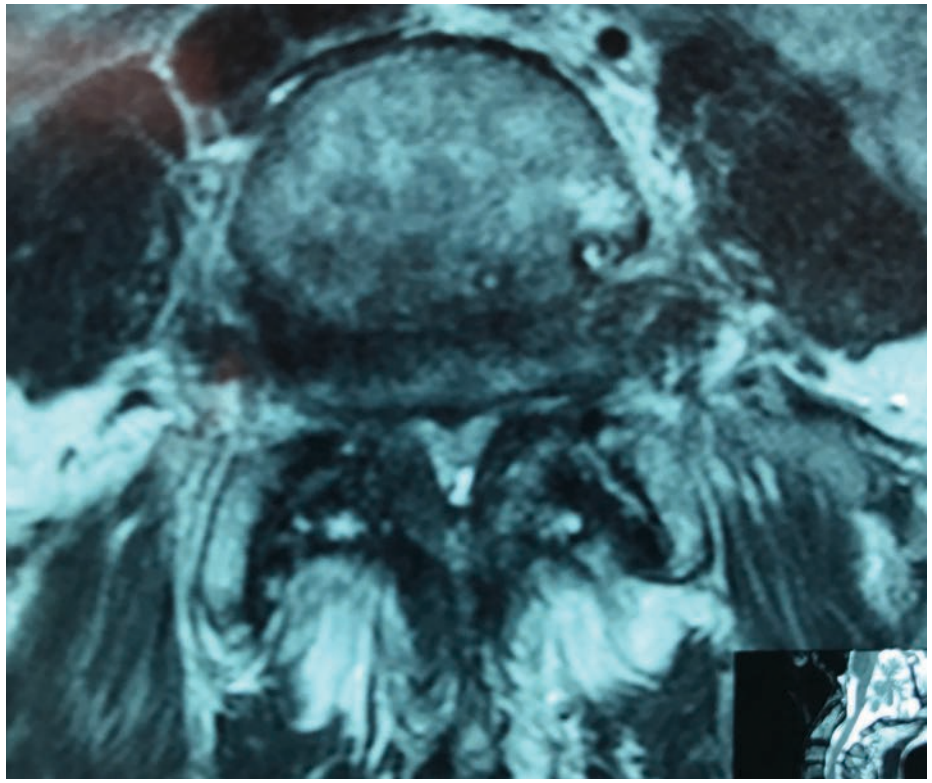
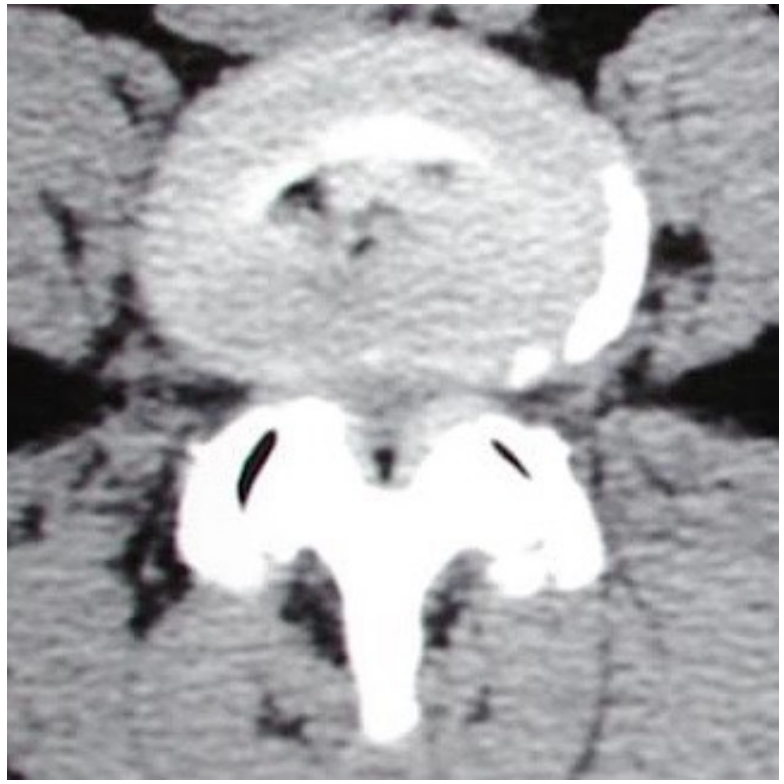
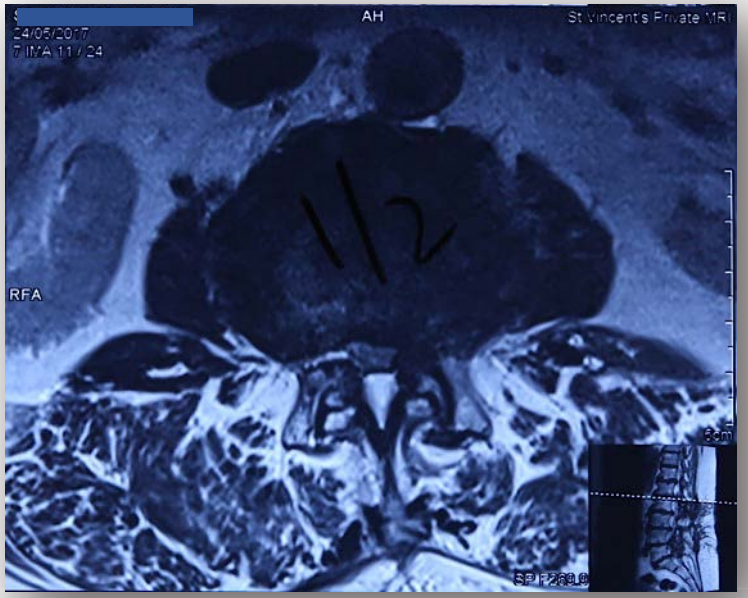
- ***"The trial is being carried out as we are currently unaware of which aspect of surgical decompression is therapeutic."***

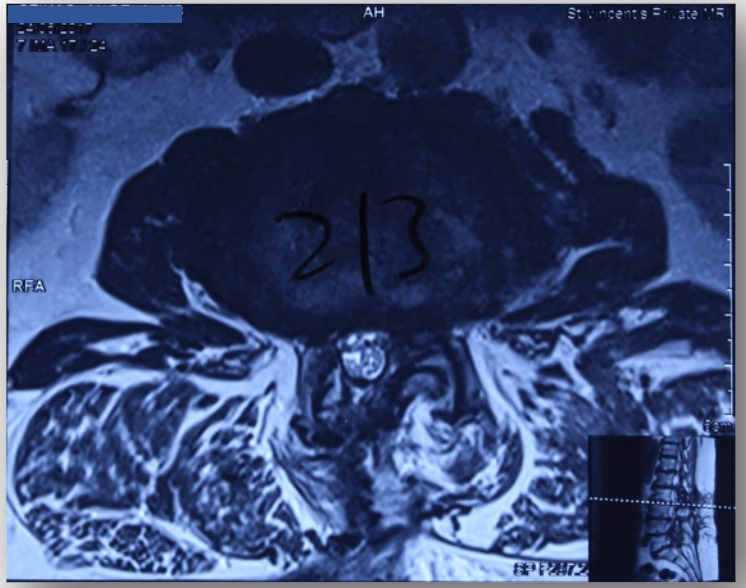
“… surgical rationale unclear” ???

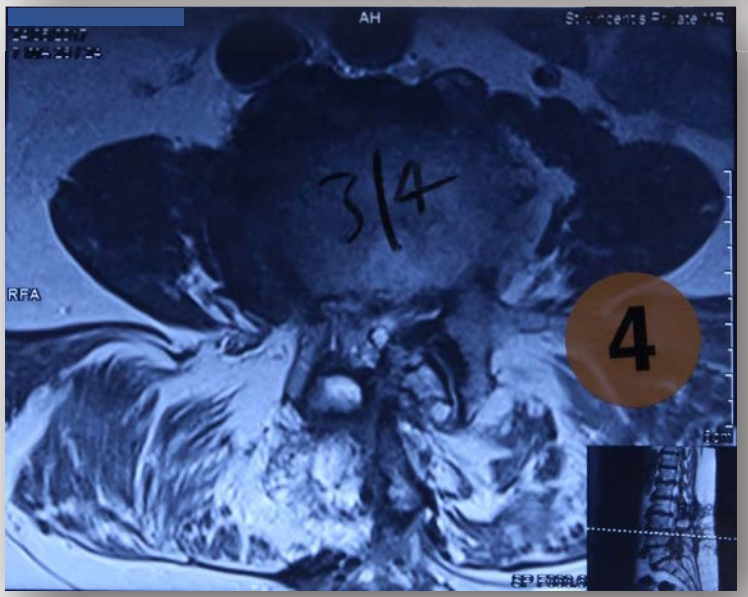


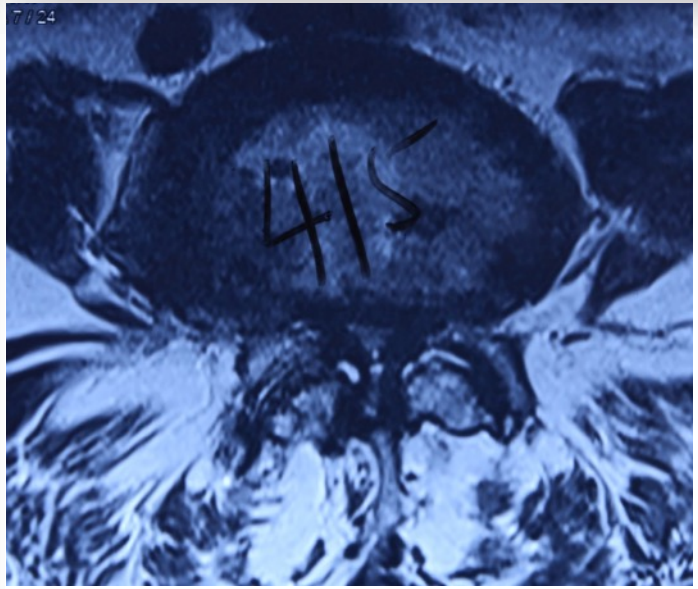


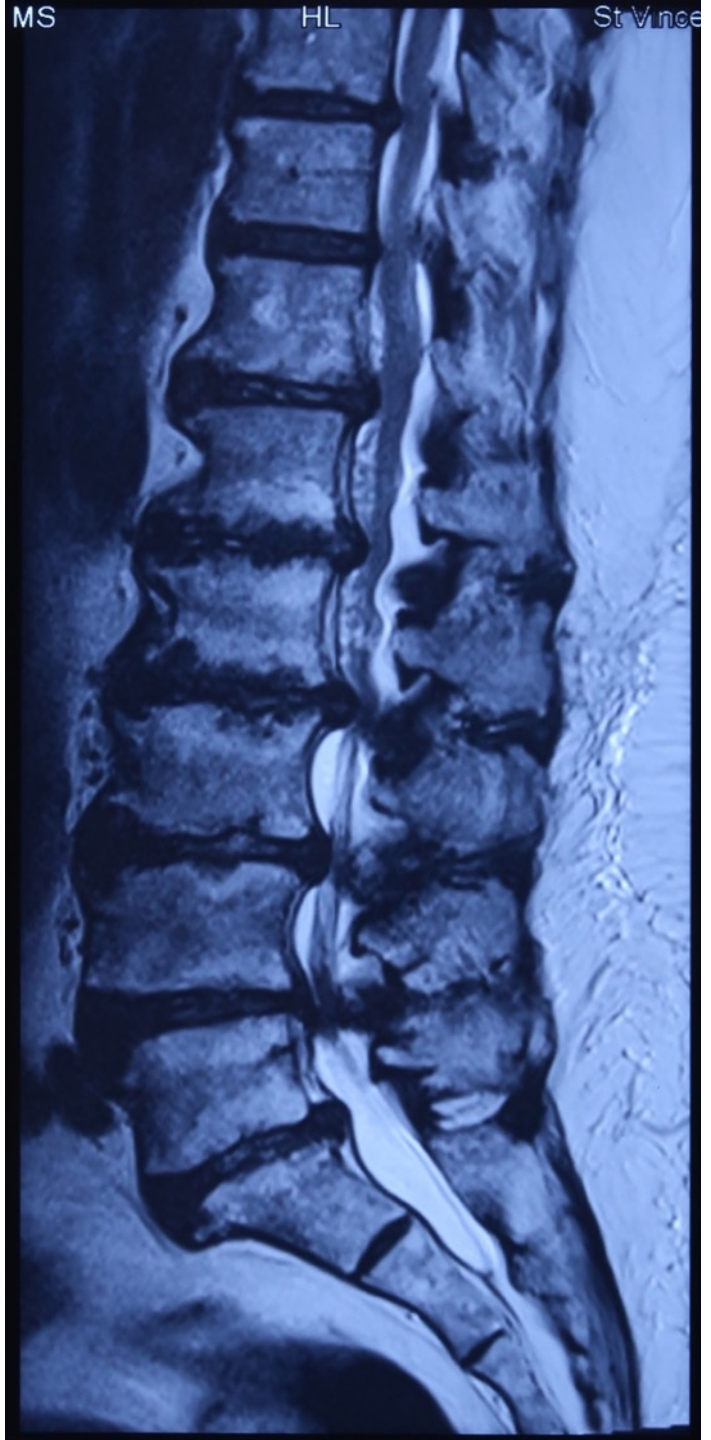
Female, 71yrs



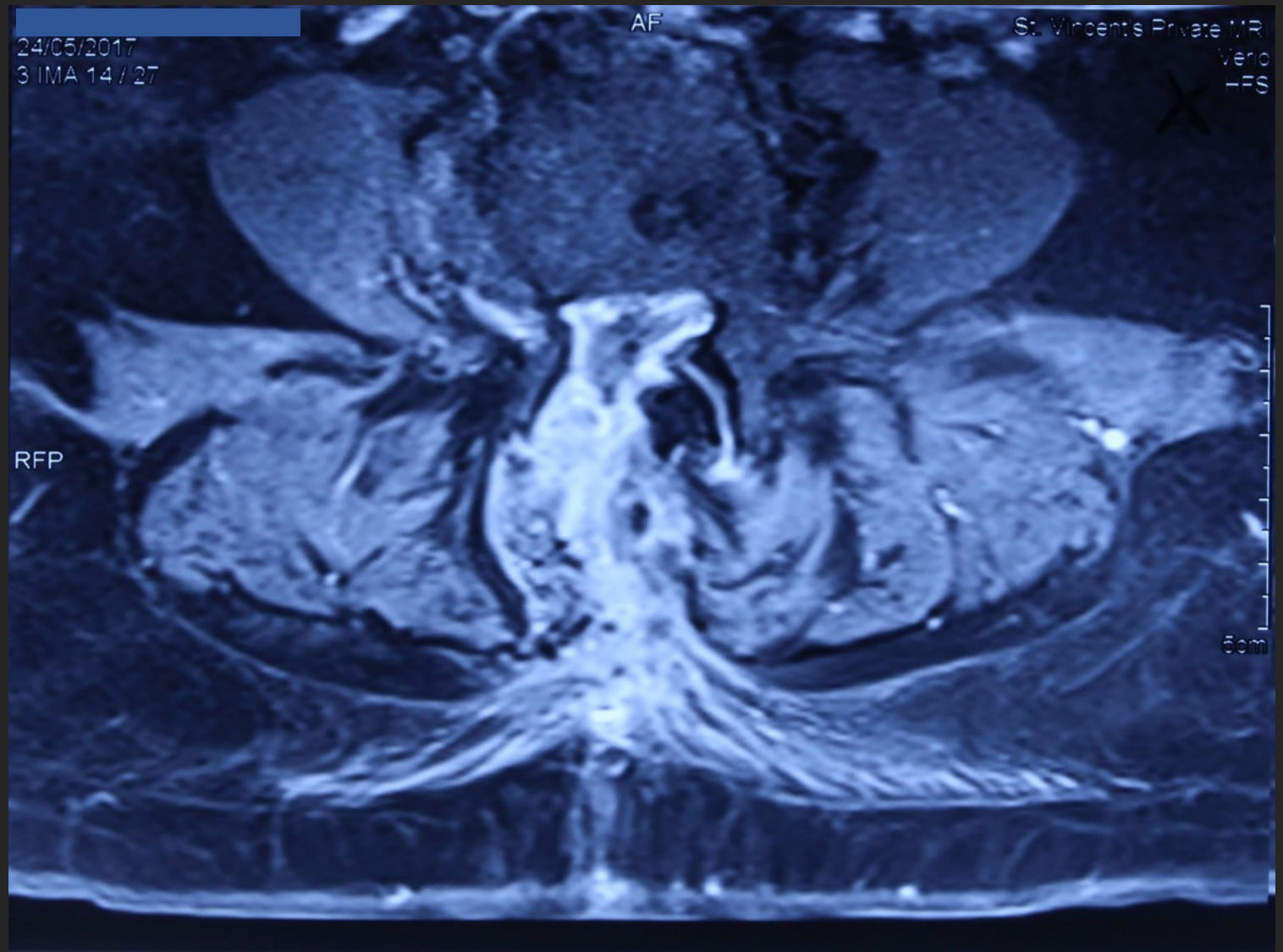






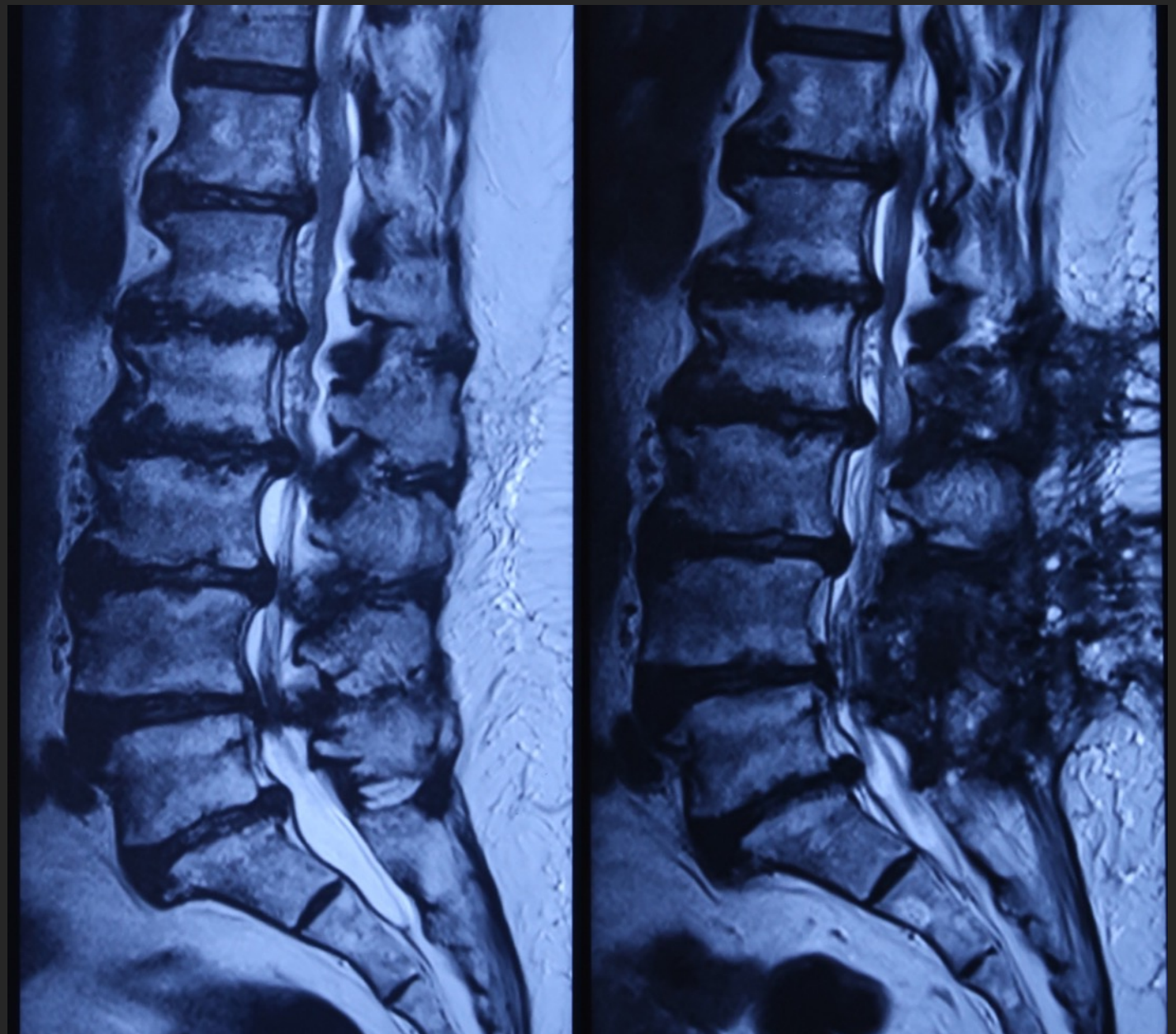


‘minimally invasive’ Treatment A



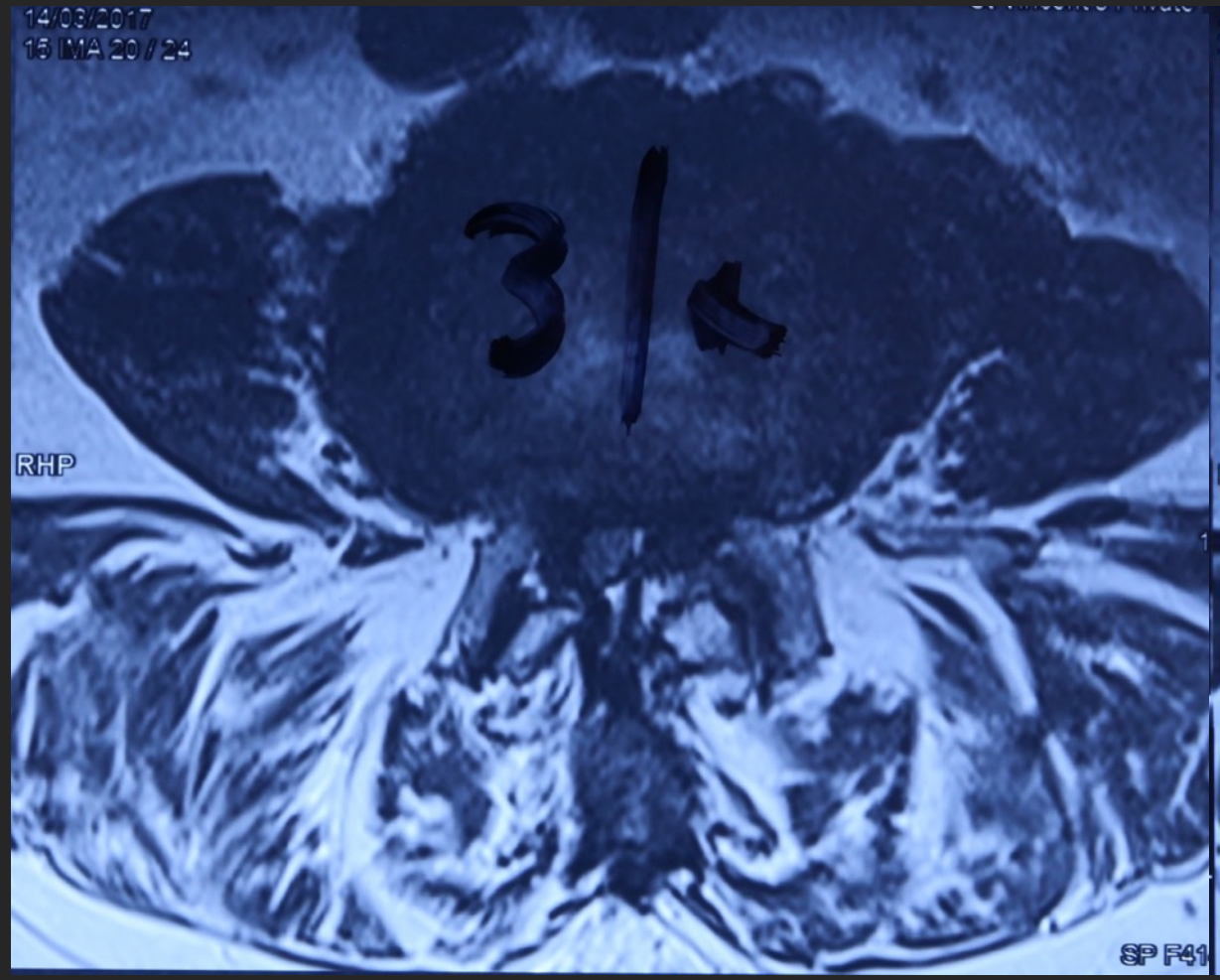
Pre Op

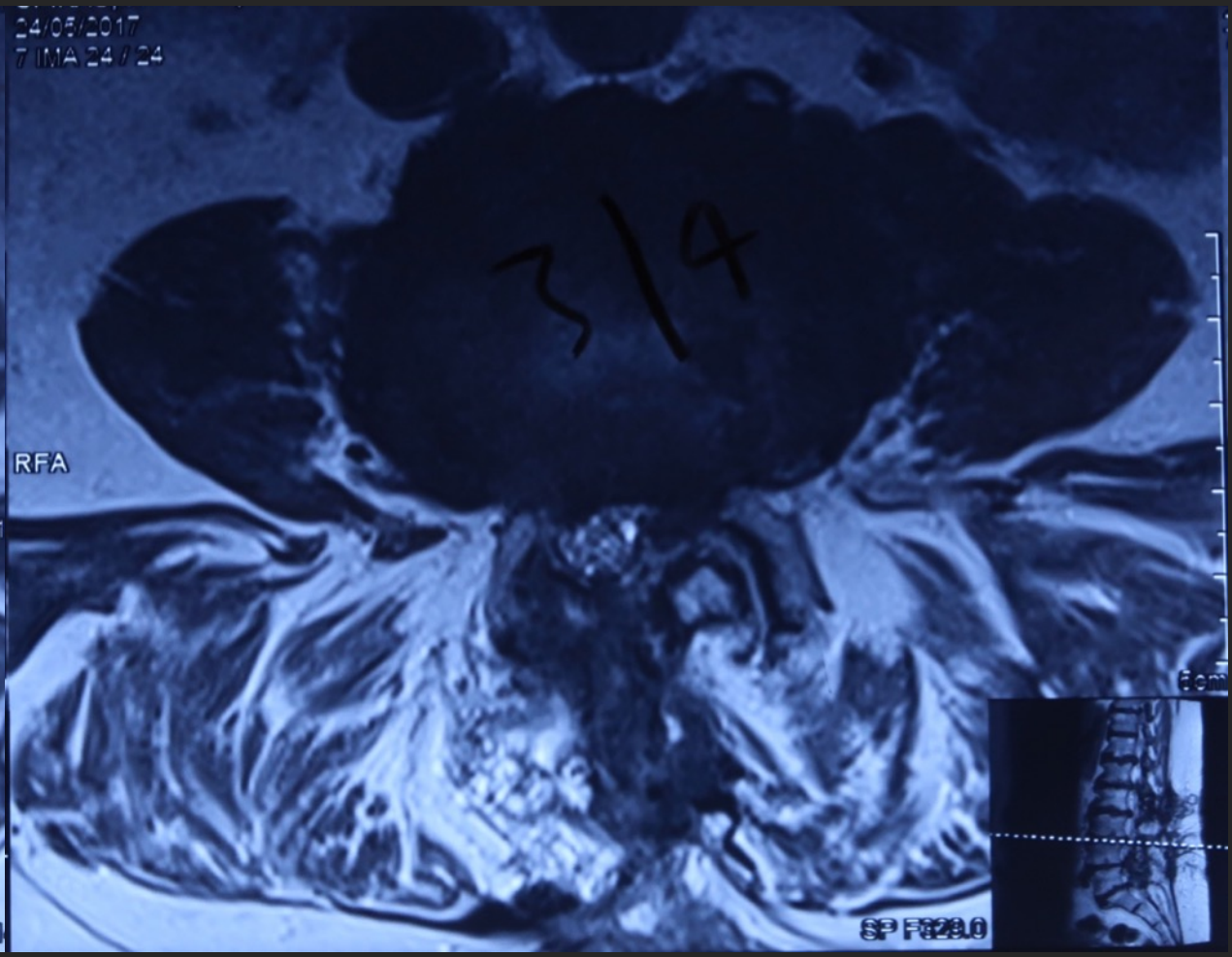
Teatment A



Pre Op

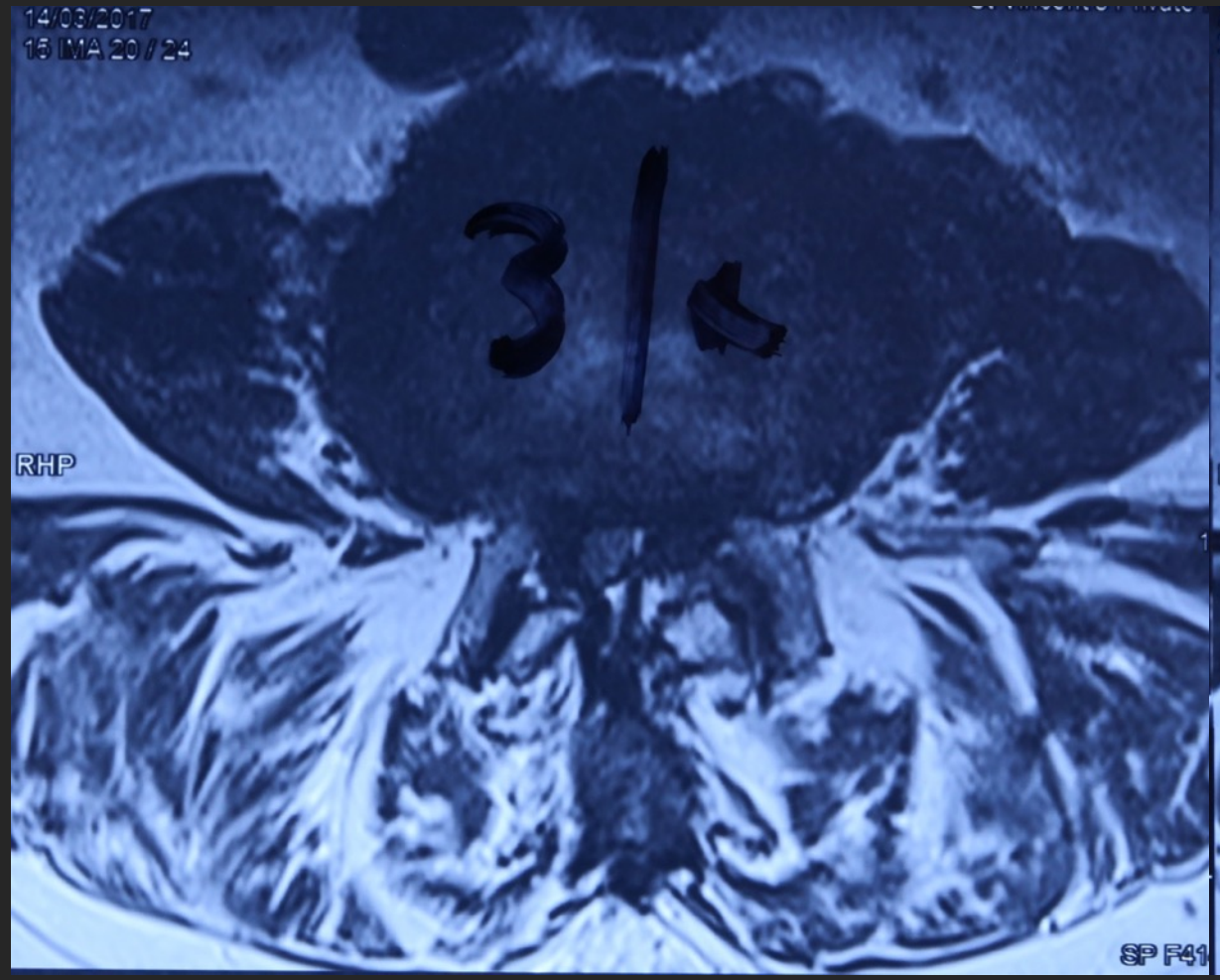
Treatment A

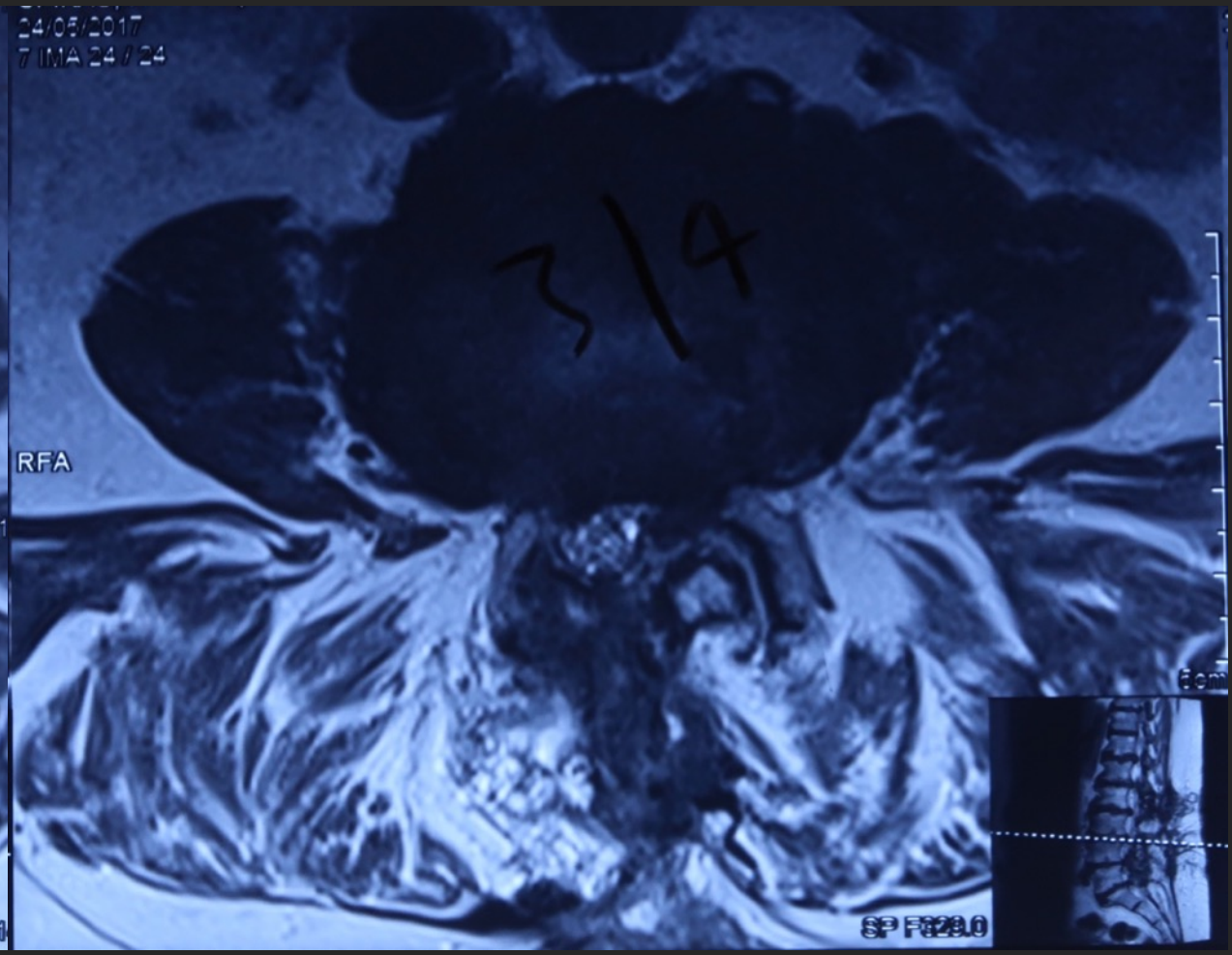




Pre Op

or… more correctly described:
‘Lack of’ Treatment A





removal of…

- Bias
- Placebo effect

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- *"At present it is not possible to make sensible evidence-based decisions about the use of decompressive surgery for spinal stenosis as* ***the evidence base is poor and surgical rationale unclear.***"

- ***"Health policy makers and clinicians only have access to the results from small trials that employ control interventions that are barely credible."***

GRANT PROPOSAL – 2015 Project Grants

Application ID: APP1125140
CIA Surname: Ferreira

A. Research Proposal *(9 pages)*

SUcceSS: SUrgery for Spinal Stenosis – a randomised placebo-controlled trial

- **Our trial will conform to the ethical framework** for the use of sham procedures in clinical trials proposed by Horng et al (New Engl J Med 2002;347:137-9).
- **All risks associated with surgery will be explained to the patient as per routine peri-operative care** and do not exceed a threshold of acceptable research risk.
- **There are no anticipated extra risks and hazards to patients allocated to the placebo intervention group**, since there will be no bone removal

BMJ. 2014; 348: g3253.
Published online 2014 May 21. doi: 10.1136/bmj.g3253
PMCID: PMC4029190

Use of placebo controls in the evaluation of surgery: systematic review

Karolina Wartolowska, NDORMS research fellow,[1,2] Andrew Judge, university research lecturer,[1,2,3] Sally Hopewell, senior research fellow,[2,4] Gary S Collins, NDORMS senior research fellow,[2,4] Benjamin J F Dean, DPhil student,[1,2] Ines Rombach, statistician,[1,2] David Brindley, DPhil student,[1,2,5,6] Julian Savulescu, Uehiro chair in practical ethics,[7] David J Beard, professor of musculoskeletal sciences,[1,2,8] and Andrew J Carr, professor of orthopaedic surgery[1,2,8]

- 53 trials
- Most investigated minor and not directly life threatening conditions
- Most common intervention was endoscopy
- ***No placebo controlled surgical trials*** *investigating* ***more invasive surgical procedures such as laparotomy, thoracotomy, craniotomy, or extensive tissue dissection*** *were identified*.

Risks of a general anaesthetic & placebo laminectomy

- **Sore throat**: up to 45 per cent of patients having anaesthesia requiring a breathing tube
- **Nausea and vomiting**: 20 to 30 per cent of the general surgical population
- **Damage to teeth:** fewer than 1 in 100 general anesthetic cases
- **Anaphylaxis:** reactions to anaesthetic agents in Australia is 1 in 10,000 to 1 in 20,000
- **Death:** for a healthy patient (known as ASA 1), incidence is about one in 100,000
- **Blindness:** approximately one in 1,250,000 anaesthetics

How common are skydiving accident deaths? Not very.

Only 8 in a million skydiving jumps result in a fatality

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- Serious adverse events were reported in the placebo arm in 18/53 trials (34%)
- Complications in the placebo group, related or likely to be related to some element of the procedure, were reported in 9/53 studies (17%).

Risks of a general anaesthetic & placebo laminectomy

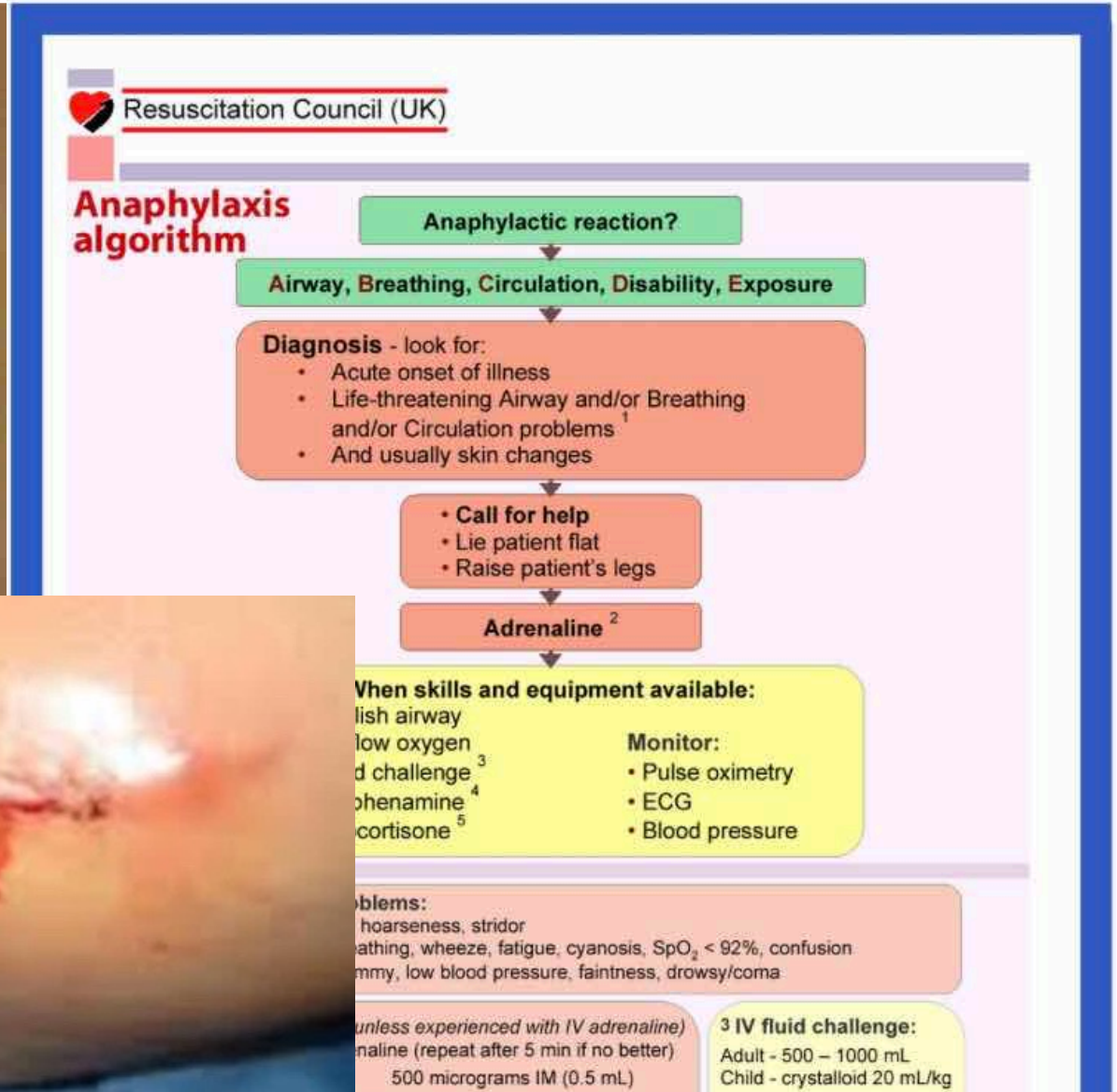
Complications of anaesthesia:

During anaesthesia:

- Respiratory depression
- Salivation, respiratory secretions
- Cardiac arrhythmias
- Fall in BP
- Aspiration
- Laryngospasm and asphyxia
- Awareness
- Delirium and convulsion

After anaesthesia

- Nausea and vomiting
- Persisting sedation
- Pneumonia
- Organ damage – liver,
- Nerve palsies
- Emergence delirium
- Cognitive defects



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SPINE Volume 25, Number 11, pp 1424–1436

Lumbar Spinal Stenosis: Conservative or Surgical Management?

A Prospective 10-Year Study

Tom Amundsen, MD,* Henrik Weber, MD, DrMed,* Helge J. Nordal, MD, DrMed,* Bjørn Magnaes, MD, DrMed,† Michael Abdelnoor, MPH, PhD,‡ and Finn Lilleås, MD§

SPINE Volume 32, Number 1, pp 1–8

Surgical or Nonoperative Treatment for Lumbar Spinal Stenosis?

A Randomized Controlled Trial

Antti Malmivaara, MD, PhD,* Pär Slätis, MD, PhD,‖ Markku Heliövaara, MD, PhD,† Päivi Sainio, PT, MSc,† Heikki Kinnunen, MD,§ Jyrki Kankare, MD, PhD,§ Nina Dalin-Hirvonen, MD,‡ Seppo Seitsalo, MD, PhD,‖ Arto Herno, MD, PhD,¶ Pirkko Kortekangas, MD, PhD,# Timo Niinimäki, MD, PhD,** Hannu Rönty, MD,** Kaj Tallroth, MD, PhD,‖ Veli Turunen, MD,†† Paul Knekt, PhD,‡‡ Tommi Härkänen, PhD,† and Heikki Hurri, MD, PhD,‖ for the Finnish Lumbar Spinal Research Group

SPINE Volume 35, Number 14, pp 1329–1338

Surgical *Versus* Nonoperative Treatment for Lumbar Spinal Stenosis Four-Year Results of the Spine Patient Outcomes Research Trial

James N. Weinstein, DO, MS,*†‡ Tor D. Tosteson, ScD,*†‡ Jon D. Lurie, MD, MS,*†‡ Anna Tosteson, ScD,*†‡ Emily Blood, MS,*†‡ Harry Herkowitz, MD,§ Frank Cammisa, MD,¶ Todd Albert, MD,‖ Scott D. Boden, MD,** Alan Hilibrand, MD,‖ Harley Goldberg, DO,†† Sigurd Berven, MD,‡‡ and Howard An, MD§§

ELSEVIER

The Spine Journal 8 (2007) 296–304

THE SPINE JOURNAL

2007 Outstanding Paper Award: Surgical Science

Assessment of health-related quality of life after surgical treatment of focal symptomatic spinal stenosis compared with osteoarthritis of the hip or knee

Y. Raja Rampersaud, MD[a,b,*], Bheesma Ravi, HBSc[c], Stephen J. Lewis, MD[a,b], Venessa Stas, MD[c], Ronald Barron[c], Roderick Davey, MD[c], Nizar Mahomed, MD, MPH[c]

[a]*Division of Orthopaedic Surgery, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada M5T-2S8*
[b]*Division of Neurosurgery, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada M5T-2S8*
[c]*Division of Orthopaedics, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada M5T-2S8; and Krembil Neuroscience Program and Musculoskeletal Health and Arthritis Program, Toronto Western Hospital, University Health Network, University of Toronto, 399 Bathurst Street, Toronto, Ontario, Canada M5T-2S8*

Received 12 February 2007; accepted 2 May 2007

ELSEVIER

The Spine Journal 10 (2010) 306–312

THE SPINE JOURNAL

Clinical Study

Health-related quality of life: a comparison of outcomes after lumbar fusion for degenerative spondylolisthesis with large joint replacement surgery and population norms

Sabarul A. Mokhtar, MD, MS (Orth)[a,*], Peter F. McCombe, MBBS, FRACS[b], Owen D. Williamson, MBBS, GradDipClinEpi, FRACS, FAOrthA[c], Michael K. Morgan, MD, MMedEd, FRACS[d], Gavin J. White[e], William R. Sears, MBBS, FRACS[a]

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Table 1
Cohort demographics

	FLSS	H-OA	K-OA
Age in years (range)	64.2 (42–84)	63.0 (40–84)	64.6 (43–83)
Sex (female/male)	51/39	51/39	51/39
Body mass index (range)	26.7 (16.3–54.2)	24.0 (18.3–40.1)	27.6 (18.2–56.1)
ASA physical status (median)	2	2	2

Table 2
SF-36 PCS and MCS scores for the entire cohort

SF-36 component summary	Time interval (years)	FLSS (n_0=90; n_1=80; n_2=80)	H-OA (n_0=90; n_1=80; n_2=80)	K-OA (n_0=90; n_1=80; n_2=78)
PCS	0	32.0	30.2	31.3
	1	39.6[a,1]	44.5[c,1]	38.5[1]
	2	38.6[a,2]	43.2[c,2]	37.1[2]

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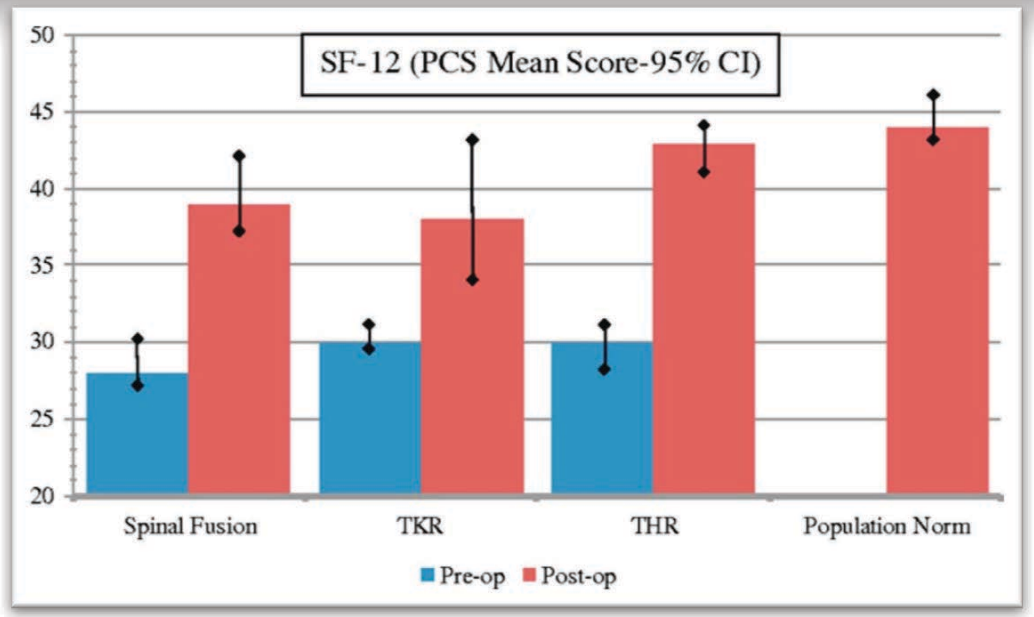

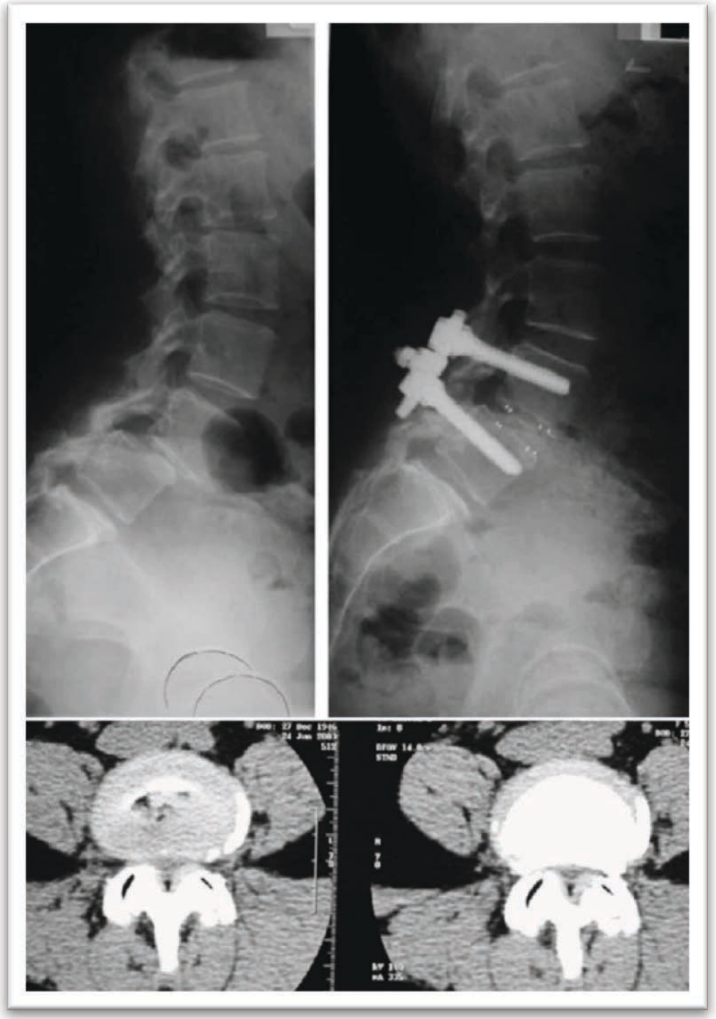

PLOS ONE

RESEARCH ARTICLE

Effectiveness of Surgery for Lumbar Spinal Stenosis: A Systematic Review and Meta-Analysis

Gustavo C. Machado[1]*, Paulo H. Ferreira[2], Ian A. Harris[3], Marina B. Pinheiro[2], Bart W. Koes[4], Maurits van Tulder[5], Magdalena Rzewuska[1], Chris G. Maher[1], Manuela L. Ferreira[1,6]

1 The George Institute for Global Health, Sydney Medical School, University of Sydney, Sydney, NSW, Australia, **2** Faculty of Health Sciences, University of Sydney, Sydney, NSW, Australia, **3** South Western Sydney Clinical School, Ingham Institute for Applied Medical Research, University of New South Wales, Sydney, NSW, Australia, **4** Department of General Practice, Erasmus Medical Centre, Rotterdam, The Netherlands, **5** Department of Health Sciences, VU University, Amsterdam, The Netherlands, **6** Institute of Bone and Joint Research, Sydney Medical School, University of Sydney, Sydney, NSW, Australia

- *" The most common methodological flaws were lack of blinding (therapist, patient and assessor) and failure to use an intention-to-treat analysis."*

This section features a recent systematic review that is indexed on PEDro, the Physiotherapy Evidence Database (http://www.pedro.org.au). PEDro is a free, web-based database of evidence relevant to physiotherapy.

No clinically important benefits of surgery over rehabilitation for lumbar spinal stenosis (PEDro synthesis)

Pooled mean differences (MD), standardised mean differences (SMD), risk ratios and associated 95% CIs were calculated using random-effects meta-analysis. Heterogeneity was evaluated using the χ^2 test and the I^2 statistic. A MD <10 (0–100 scale) or SMD <0.4 was defined as a small and not clinically important effect. Data from a large randomised controlled trial[5] not included in the meta-analysis were extracted and pooled following the methods described in the review using Comprehensive Meta-Analysis V2.02.

RESULTS

The review included 5 randomised trials with a total of 643 participants. The overall quality of the evidence was assessed using the GRADE approach. Three trials compared surgery with rehabilitation modalities, and two trials compared surgery with steroid injection. The additional trial not

“For this PEDro synthesis, we updated the pooled analyses by including data of a recently published randomised trial.5”

though this procedure has been associated with an increased

surgery is not superior to rehabilitation on disability at short

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4 Lurie J, Tomkins-Lane C. Management of lumbar spinal stenosis. *BMJ* 2016;352:h6234.

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Annals of Internal Medicine

ORIGINAL RESEARCH

Surgery Versus Nonsurgical Treatment of Lumbar Spinal Stenosis

A Randomized Trial

Anthony Delitto, PT, PhD; Sara R. Piva, PT, PhD; Charity G. Moore, PhD, MSPH; Julie M. Fritz, PT, PhD; Stephen R. Wisniewski, PhD; Deborah A. Josbeno, PT, PhD; Mark Fye, MD; and William C. Welch, MD

- Intention-to-treat analyses revealed no difference between groups (24-month difference, 0.9 [CI, 7.9 to 9.6]).

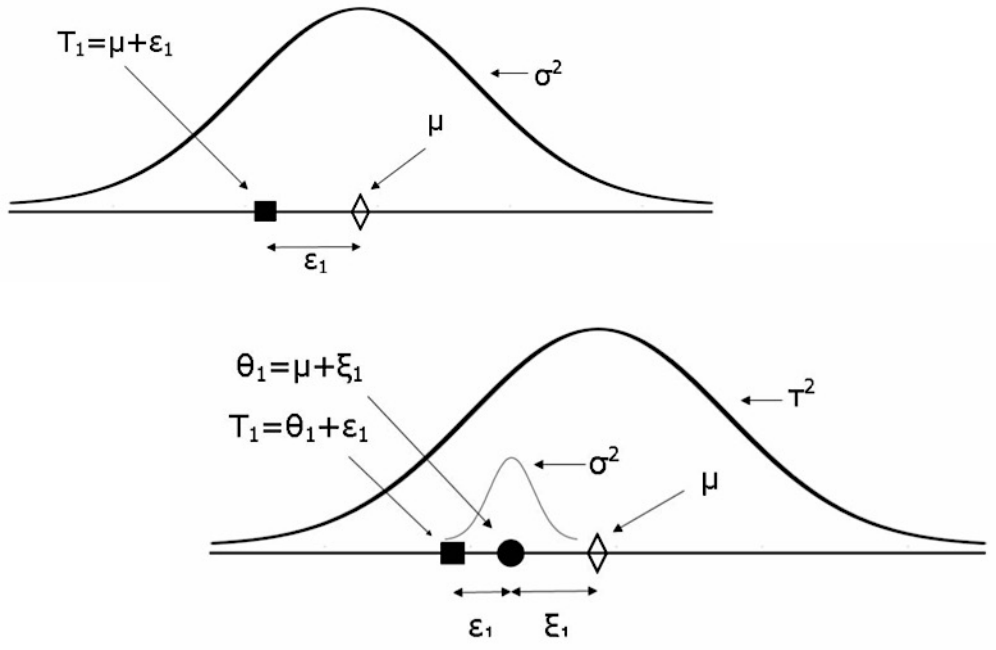
Table 2. Changes in Outcome Over Time in the Surgery and PT Groups*

Outcome	Baseline		10 wk		26 wk	
	Participants, *n*	Mean Score (95% CI)	Participants, *n*	Mean Score (95% CI)	Participants, *n*	Mean Score (95% CI)
Primary						
SF-36 physical function‡	–	–	–	–	–	–
Surgery	87	26.8 (23.2 to 30.4)	80	42.5 (37.1 to 47.9)	78	47.2 (41.1 to 53.3)
PT	82	28.2 (23.9 to 32.5)	73	41.0 (35.3 to 46.7)	75	45.4 (39.3 to 51.5)

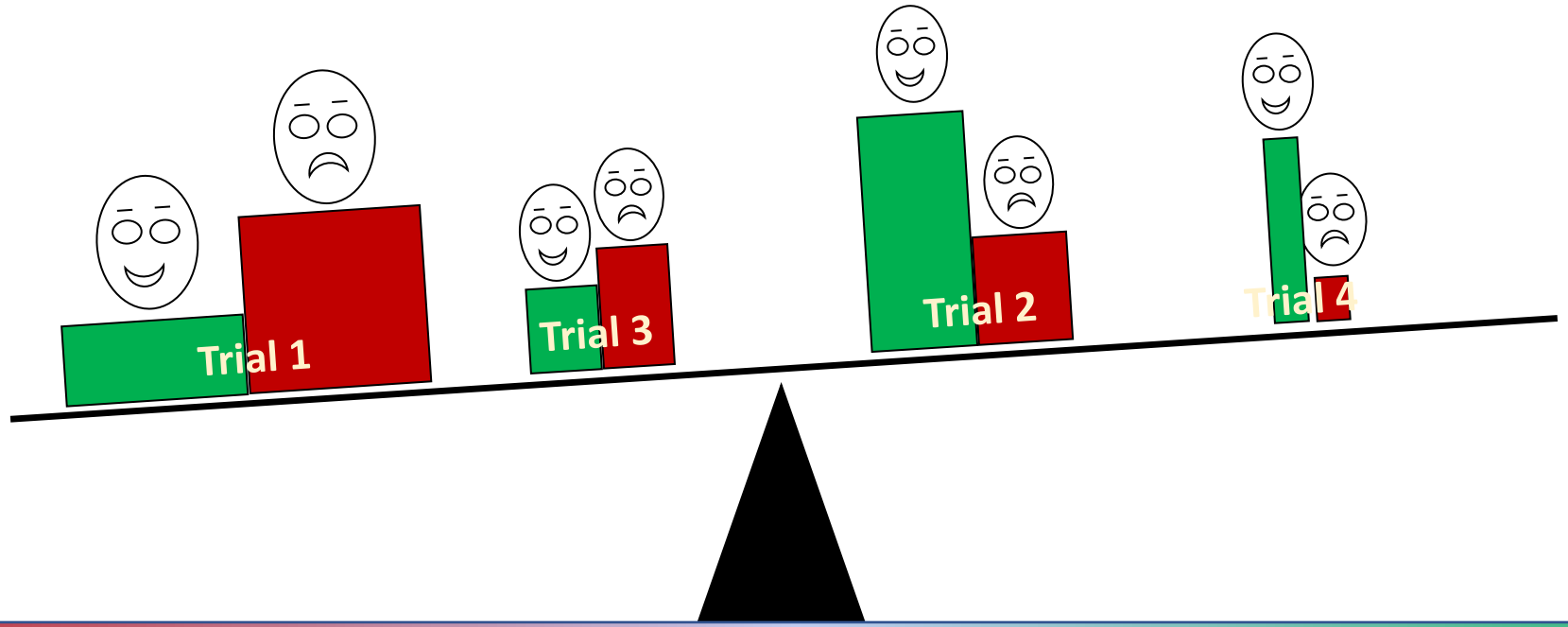
Meta analysis

The Meta-analysis

- Publication bias
- Agenda-driven bias
- Statistical approach
- Statistical models for aggregate data
  - Fixed effects
  - Random effects
  - IVhet
  - Quality effects
- Single-subject design
- Direct evidence
- Indirect evidence: Network meta-analysis methods
  - Bayesian framework
  - Frequentist multivariate framework
  - Generalized pairwise modelling framework
  - Inverse variance method
  - Mantel–Haenszel method
  - Peto method
  - Signed differential mapping



Treatment A *vs.* Treatment B



A < B

A > B

The Meta-analysis

- Random effects model
  - When heterogeneity becomes large, the individual study weights under the RE model become equal and thus the RE model returns an arithmetic mean rather than a weighted average.

Treatment of thoracolumbar Burst Fractures, without neurological deficit

OPERATIVE COMPARED WITH NONOPERATIVE TREATMENT OF A THORACOLUMBAR BURST FRACTURE WITHOUT NEUROLOGICAL DEFICIT

A PROSPECTIVE, RANDOMIZED STUDY

BY K. WOOD, MD, G. BUTTERMAN, MD, A. MEHBOD, MD, T. GARVEY, M

Investigation performed at the Department of Orth
University of Minnesota, Minneapolis, and Midwest Spine and Ort

SPINE Volume 31, Number 25, pp 2881–2890

Treatment of Traumatic Thoracolumbar Spine Fractures: A Multicenter Prospective Randomized Study of Operative *Versus* Nonsurgical Treatment

Jan Siebenga, MD,* Vincent J. M. Leferink, MD, PhD,† Michiel J. M. Segers, MD,‡ Matthijs J. Elzinga, MD,‡ Fred C. Bakker, MD, PhD,‡ Henk J. Th. M. Haarman, MD, PhD,‡ Pol M. Rommens, MD, PhD,§ Henk-Jan ten Duis, MD, PhD,† and Peter Patka, MD, PhD‖

Clin Orthop Relat Res (2012) 470:567–577
DOI 10.1007/s11999-011-2157-7

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

SURVEY

Nonoperative versus Operative Treatment for Thoracolumbar Burst Fractures Without Neurologic Deficit

A Meta-analysis

Sonali R. Gnanenthiran MBBS,
Sam Adie BSc(Med), MBBS, MSpMed MPH,
Ian A. Harris MBBS, MMed(Clin Epid), PhD, FRACS(Orth)

Received: 23 March 2011 / Accepted: 17 October 2011 / Published online: 5 November 2011

- "We found no difference in mean VAS pain at last f/u between non-op and operative groups (MD=-1.0; p=0.95; 95%CI -29.0 to 27.1; I^2=88%)"
- "There were no differences (p=0.89) in mean RMDQ (I^2=92%)"

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- "There were no differences (p=0.89) in mean RMDQ (**I^2=92%**)"
- "… two RCTs that yielded contrasting results"

The Meta-analysis

- A meta-analysis cannot correct for poor design and/or bias in original studies
- Only methodologically sound studies should be included
- Inconsistency of results across studies can be quantified and analyzed… e.g. Does inconsistency arise from sampling error, or are study results (partially) influenced by between-study heterogeneity?

The Meta-analysis

- The most severe fault in meta-analysis often occurs when the persons doing the meta-analysis have an economic, social, or political agenda such as the passage or defeat of legislation.
- The influence of such biases on the results of a meta-analysis is possible because the methodology of meta-analysis is highly malleable

Internal *vs.* External Validity

Important to

- remove bias and the effects of
- minimised confounding factors, but also

Important to provide

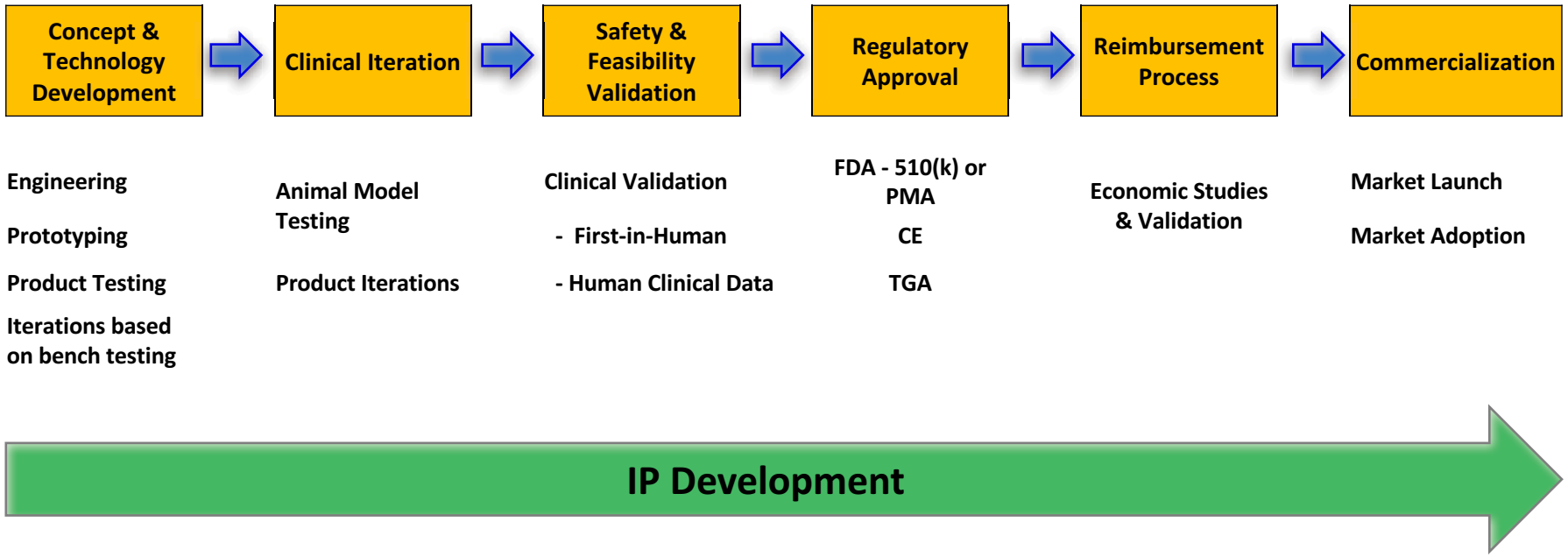
a sufficiently focused research question –
with limited heterogeneity of

- *the condition being treated and*
- *the treatment provided.*

The issue under investigation shouldn't be too general or the results may be attenuated by combining clinical outcomes from situations where a treatment doesn't work with those where it does.

RCTs – The cost

Medical Device Start-up's - The Process



Slide courtesy of Mr Tom Afzal, CEO Spinal Kinetics Inc

Today's Reality - FDA Pathway and Costs:

	YEARS											
	1	2	3	4	5	6	7	8	9	10	11	12
510(K)	Product Development	Clinical Device Development & Iteration	Safety & Feasibility Validation	FDA Submission Process	FDA Approval	Reimbursement Process						
Costs:	$6.5	$6.5M	$10.5-$12.0	$15.0-$20.0M	$4.0-$6.0M	$30.0-$40.0M						
Cumulative Costs	$6.5	$13.0	$23.5-$25.0M	$38.5-$45.0M	$39.5-$44.5M	$69.5-$84.5M						

4.5 -5.5 Yrs.

510(K)
FDA Related Cost:
$24M-$35M

PMA Class III Spine Implant	Product Development	Clinical Device Development & Iteration	Safety & Feasibility Validation	FDA Submission, Discussions & Approval for IDE Trial	Clinical Trial Patient Enrollment	Clinical Trial Follow-up	PMA Submission	FDA Review & Approval	Reimbursement Process
Costs:	$8.0M	$15.0M	$21.5M	$12.0M	$20.0-$25.0M	$12.0-$15.0M	$7.0M	$15.0-$22.0	$30.0-$40.0M
Cumulative Costs:	$8.00	$23.0M	$44.5M	$56.5M	$76.5-$81.5	$88.5-$96.5M	$93.5-$103.5M	$108.5-$125.5M	$138.5-$160.5M

9.5+ Yrs.

PMA
FDA Related Cost:
$80M- >$110M

Slide courtesy of Mr Tom Afzal, CEO Spinal Kinetics Inc

Venture Capital Fund Model

- **Venture Capital Funds**
  - Firm will set up a fund with a specific amount of capital
  - Typical VC fund size in Med-Tech: $200-$300+ Million
  - General Partners manage the funds
    - Responsible for setting up the legal entity
    - Raise funds from investors – Limited Partners
    - Find and evaluate investment opportunities
    - Manage investment portfolio
  - Limited Partners contribute capital
    - Often large companies, university endowments, insurance companies and pension funds, etc.
  - Fund life is 10 years
    - Need to make investments and provide returns within ***10 yrs.***

Slide courtesy of Mr Tom Afzal, CEO Spinal Kinetics Inc

Market Dynamics 2003-Present

- Spine – “Hot” Technology Sector in Med-Tech
  - SAS-2005, New York
    - Motion Preservation was “the” topic
    - 20+ artificial disc companies
    - 10+ dynamic stabilization companies
    - Multiple nucleus replacement companies
    - Numerous other technologies (interspinous, facet, etc.)

- VC’s invested heavily in *Spine*
  - Pent up demand for spine deals
  - Over 170+ start-up ***spine*** companies were funded between 2003-2007
  - $Billions invested

Slide courtesy of Mr Tom Afzal, CEO Spinal Kinetics Inc

Market Dynamics – TODAY

- Spine – "Hot" Technology Sector
  - SAS 2008 New York
  - Motion Preservation was "the" topic
  - 20+ disc companies
  - 10+ dynamic stabilization companies
  - Multiple nucleus replacement companies
  - Numerous other technologies
- VC's invested heavily in spine
  - Pent up demand for spine deals
  - Over 100 start-up spine companies were funded

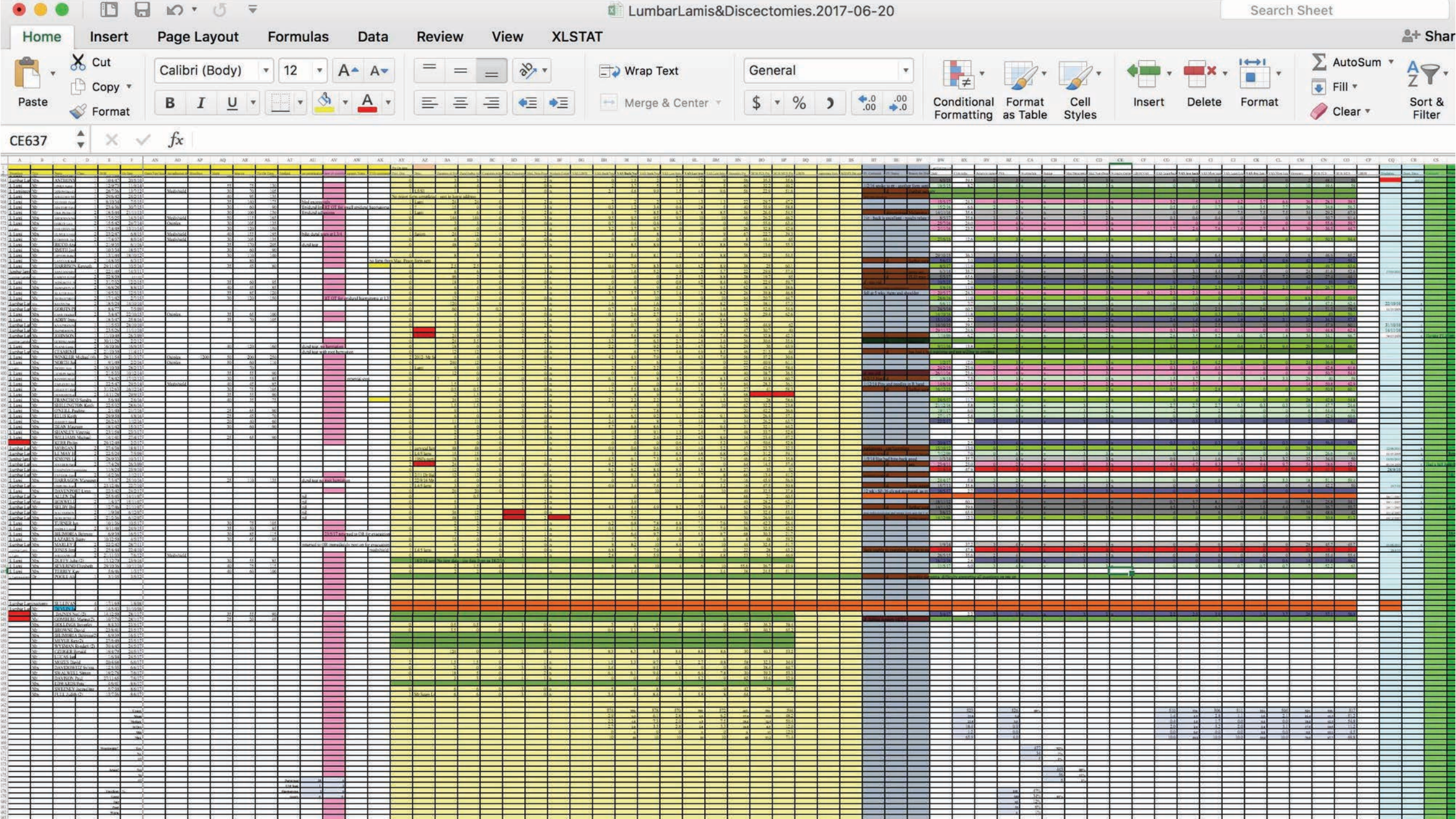
VERY FEW COMPANIES LEFT STANDING TODAY!

< 25 Companies

Slide courtesy of Mr Tom Afzal, CEO Spinal Kinetics Inc

RCTs – The cost

- RCTs have become massive bureaucratic and corporate enterprises.
- Created a $25 billion clinical trials industry
  - (Bodenheimer *et al*. N Engl J Med 2000)
- Unintended consequences:
  - High drug & implant costs
    - may inhibit drug and device introduction to 3rd world countries
  - Inhibit R & D
    - Impairing progress in patient treatment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Copy
Format
Calibri (Body)
12
Wrap Text
Merge & Center
General
Conditional Formatting
Format as Table
Cell Styles
Insert
Delete
Format
AutoSum
Fill
Clear
Sort & Filter
CE637

Pre-op

Op Date	VAS Back/Neck	VAS Back/Nec	VAS Back/Neck	VAS Leg/Arm L	VAS Leg/Arm /	VAS Leg/Arm M	Oswestry Pre	SF36 PCS Pre	SF36 MCS Pre
Count	574	596	578	570	590	572	603	594	594
Mean	2.9	4.3	6.1	2.8	4.5	6.2	37.4	33.5	48.2
Median	2.2	4.8	7.3	2.0	4.9	7.5	38.0	32.9	50.4
St Dev	2.7	2.8	3.3	2.8	2.8	3.3	16.8	8.5	12.0
Min	0	0	0	0	0	0	0	13	12.9
Max	10	10	10	10	10	10	88	57.2	71.4

Post-op (last f/u)

Op Date	VAS Least back	VAS Ave back/	VAS Most back	VAS Least Leg	VAS Ave Leg /	VAS Most Leg /	Oswestry	SF36 PCS	SF36 MCS
Count	510	516	506	511	514	504	524	516	517
Mean	1.4	1.9	2.8	1.1	1.5	2.1	21.4	41.3	51.2
Median	0.4	1.0	1.7	0.0	0.0	0.0	18.0	41.3	54.8
St Dev	2.0	2.4	3.2	2.0	2.4	3.1	17.9	10.5	11.2
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	15.1	4.5
Max	10.0	10.0	10.0	10.0	10.0	10.0	76.0	67.7	69.8

Lumbar laminectomy for stenosis

DOB	Op Date	F Up mths	Return to duties	PSA	Worthwhile	Repeat	Med Prescriptio
	Count	523		526	88%		
	Mean	23.8		3.2			
	Median	23.8		3.0			
	St Dev	18.4		0.9			
	Min	1.2		0.0			
	Max	65.9		4.0			
Worthwhile?	Yes				477	92%	
	No				34	7%	
	Q?				5	1%	
Again?	Yes					443	88%
	No					56	11%
	Q?					6	1%
Excellent	%			248	47%		
Good				180	34%	81%	
Fair				62	12%		
Poor				30	6%		
Worse				6	1%		

Pre-op

Post-op
(last f/u)

	VAS Back/N	VAS Avge Bacl	VAS Back/N	VAS Leg/Arr	VAS Avge Leg	VAS Leg/Arr	Oswestry P	SF36 PCS P	SF36 MCS P
Count	97	153	98	98	153	99	154	151	151
Mean	3.5	5.0	6.7	3.2	4.8	6.6	41.3	31.9	47.2
Median	3.0	5.2	7.9	2.0	5.0	8.0	42.0	31.0	49.0
St Dev	3.0	2.7	3.1	3.1	2.8	3.3	16.8	8.9	12.0
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.9	10.0
Max	10.0	10.0	10.0	10.0	10.0	10.0	88.0	59.6	67.8
Count	137	145	137	137	145	137	144	143	143
Mean	1.4	1.9	2.5	0.7	1.0	1.4	20.4	41.7	51.4
Median	0.3	0.5	1.0	0.0	0.0	0.0	16.9	41.7	53.0
St Dev	2.2	2.4	3.0	1.8					
Min	0.0	0.0	0.0	0.0					
Max	9.5	9.7	10.0	9.1					

PLIF for stenosis + degen. spondy

		F Up mths		PSA	Worthw	Repeat	
	Count	145		145	95%		
	Mean	43.9		3.5			
	Median	47.4		4.0			
	St Dev	31.0		0.9			
	Min	1.3		0.0			
	Max	121.2		4.0			
Worthwhile?	Yes				135	93%	
	No				8	6%	
	Q?				2	1%	
Again?	Yes					124	89%
	No					14	10%
	Q?					2	1%
Excellent	%			91	63%		
Good				39	27%	90%	
Fair				8	6%		
Poor				4	3%		
Worse				3	2%		

MONASH University

AUSTRALIAN SPINE REGISTRY (PILOT) AGREEMENT

THIS AGREEMENT is made on 2016

BETWEEN

MONASH UNIVERSITY (ABN 12 377 614 012) of Wellington Road, Clayton, VIC 3800, acting through its Department of Epidemiology and Preventive Medicine within its Faculty of Medicine, Nursing and Health Sciences (**Monash**)

and

THE SPINE SOCIETY OF AUSTRALIA (ABN 49 720 598 228) of C/o Australian Orthopaedic Association, Level 12, 45 Clarence Street Sydney NSW 2000 (**SSA**)

Australian Spine Registry

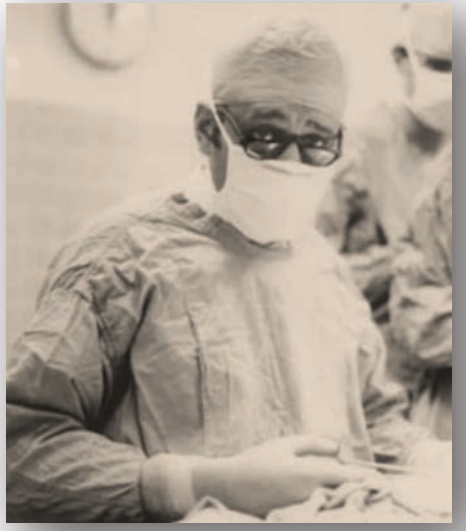
Protocol

Version 1.0

Dated 23 May 2016

“Randomized trials have developed such high scientific stature and acceptance that they are accorded an almost religious sanctification.”

René Favaloro



Internal validity

Bias

Cochrane

Placebo controlled

tau-squared

Collaboration

Statistical

Q statistic

Fixed effects

true effect θ1

Random effects

Meta-analysis

Quality effects

Intent-to-treat analysis

IVHet

Correctness

NICE

Systematic review

Triple blinded

Heterogeneity

$$Q = \sum_{i=1}^{k} w_i \left(T_i - \overline{T}_{\cdot} \right)^2$$

Level 1 evidence

sources of sampling error

Alternatives

- *ex vivo*
  - biomechanical
- Prospective observational research/Registries
  - the ‘real world’
  - eliminate psychological reward effect

RCTs are *not* an *appropriate Gold Standard* for determining the effectiveness of Surgical Treatment

Thank you