The Leeds Teaching Hospitals NHS
NHS Trust

Evaluating surgery versus SABR in clinical trials: New insights

Dr Kevin Franks

Consultant Oncologist/Honorary Clinical Associate Professor

Leeds Cancer Centre

UNIVERSITY OF LEEDS

Disclosure slide

- SJIO had a formal Research Agreement with ELEKTA inc.
- I have received funding for lectures, consultancy fees and funding to attend conferences from AZ, Boerhinger-Ingleheim, ELEKTA, GSK, Pierre-Fabre and Roche.

Evaluating surgery versus SABR in clinical trials: New insights

PAST- LUNG CANCER

Have we managed to do RCTs of Surgery versus RT?

Have we managed to do RCTs of SABR versus Surgery?

Evaluating surgery versus SABR in clinical trials: New insights

PAST- Have we managed to do RCTs of conventional RT versus surgery in Lung Cancer?

The Lancet · Saturday 6 September 1969

FIVE-YEAR FOLLOW-UP OF THE MEDICAL RESEARCH COUNCIL COMPARATIVE TRIAL OF SURGERY AND RADIOTHERAPY FOR THE PRIMARY TREATMENT OF SMALL-CELLED OR OAT-CELLED CARCINOMA OF THE BRONCHUS

A REPORT TO THE MEDICAL RESEARCH COUNCIL WORKING PARTY* ON THE EVALUATION OF DIFFERENT METHODS OF THERAPY IN CARCINOMA OF THE BRONCHUS

A. B. MILLER WALLACE FOX
RUTH TALL
Medical Research Council Tuberculosis and Chest Diseases Unit, Brompton Hospital, London S.W.3

THE LANCET, JULY 14, 1973

MEDICAL RESEARCH COUNCIL COMPARATIVE TRIAL OF SURGERY AND RADIOTHERAPY FOR PRIMARY TREATMENT OF SMALL-CELLED OR OAT-CELLED CARCINOMA OF BRONCHUS

Ten-year Follow-up

WALLACE FOX J. G. SCADDING
Medical Research Council Tuberculosis and Chest Diseases Unit and Cardiothoracic Institute, Brompton Hospital, Fulham Road, London SW3 6HP

Evaluating surgery versus SABR in clinical trials: New insights

PAST- Have we managed to do RCTs of SABR versus Surgery?

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang*, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†

Lancet Oncol 2015; 16: 630–37

Evaluating surgery versus SABR in clinical trials: New insights

PAST- Have we managed to do RCTs

Not really: this pooled analysis had very low numbers

Still need adequately powered RCT(s) to see if SABR is an alternative to Surgery

total of 58 pts randomised into both trials

Conclusion:

SABR may be better tolerated and give better survival??

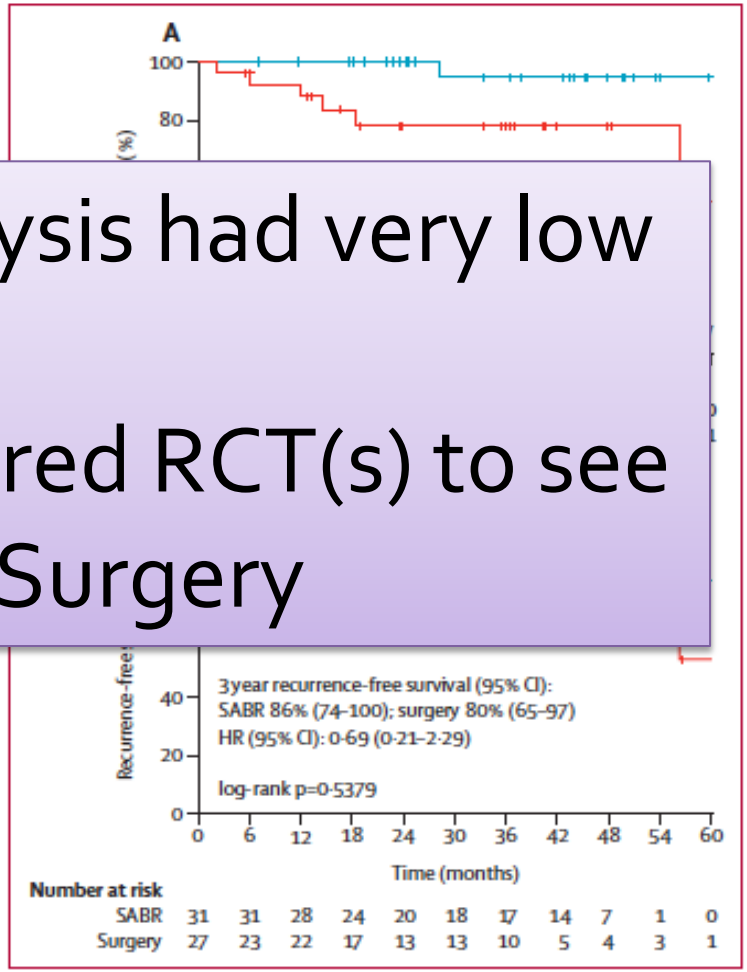


Figure 2: **Overall survival (A) and recurrence-free survival (B)**
One patient died and five had recurrence in the SABR group compared with six and six patients, respectively, in the surgery group. SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

Evaluating surgery versus SABR in clinical trials: New insights

- BASICALLY IT IS NOT EASY to do RCT of Surgery versus RT

- Lots of failures in the past and not just in lung cancer

  - PROSTATE BRACHYTHERAPY VERSUS SURGERY

  - SPARE- SURGERY VERSUS RADICAL RADIOTHERAPY

What can we learn from other Surgery versus RT trials?

- What can we learn from other Surgery versus RT trials?
- Some successes!
- PROTECT TRIAL
  - Randomised trial of surgery, radical radiotherapy and active surveillance for early stage prostate cancer.
  - Completed recruitment with ~ 1700 pts randomised.

What can we learn from other Surgery versus RT trials?

PROTECT Study

- Initially:
  - Randomisation rates variable between centres and individual clinicians – though numbers small
  - Overall - patients rejected randomisation and demonstrated a preference for surgery
  - Reluctance with conservative arm

Reasons patients participate

- Personal benefit (what will I get out of it?)
  - The best and most up to date treatment.
  - Better, more frequent monitoring.
- Hope
  - For more time.
  - In the absence of there being more options.
- Altruism
  - To help others in future.

Barriers to participation for patients

- Lack of trust in doctor.
- Lack of confidence in the information provided by the recruiter.
- Existing treatment preference.
- Terminology used and consistency of information given
- Randomisation is not presented well and patient perceives recruiter bias.

Barriers to recruitment
Known to professionals

- Lack of confidence to discuss scientific methodology.
- Ability to elicit and explore patients treatment preferences.
- System & organisational difficulties.
- Fewer than expected eligible patients.
- Enabling the patient to make a decision or being an agent for them rather than paternalistic approach.

Barriers to recruitment
Hidden from professionals

- Doctors had some discomfort about patient eligibility and intervention effectiveness.
- Nurses were anxious about approaching potential participants.
- All experienced conflict between clinical and research responsibilities.
- Lack of awareness of how personal views can contribute to recruitment difficulties.

What facilitates participation ?

Facilitator	Detail	Evidence (examples)
Altruism, hope & self-benefit	Patients choose to take part in trials to help themselves, others and to give them hope	Jenkins et al 2013
Equipoise	Treatments need to be presented in a balanced (neutral) way	Fletcher et al 2012 Donovan et al 2002 Jenkins et al 2014
Randomisation	Needs to be presented in a way that acknowledges that the computer makes the decision. Some references to chance may deter patients. Using "tossing a coin" has been viewed as trivialising	Jenkins et al 2002
Terminology	Terminology used could deter patients eg: in ProtecT trial when surgery and radiotherapy were presented as "aggressive treatments" Avoid being overly negative or positive about treatments	Donovan et al 2002

What facilitates participation 2?

Facilitator	Detail	Evidence (Examples)
Order in which treatments are presented	The order in which treatments are presented needs careful consideration	ProtecT study Donovan et al 2002
Recruiters confidence in scientific method	Recruiters need to be confident in the importance of the research question and the methods that is used to look at this	Blazeby et al 2014
Recruiters willingness to elicit preferences	Patients preferences are dynamic and subject to change. Patients can change their mind based on appropriate information exchange to make an informed decision	Mills et al 2014
Recruiter are self-aware of own bias	Recruiters are self-aware about how preferences and beliefs can influence the decisions they	Mills et al 2014

Slides Courtesy of Janine Bestall

What do Lung Cancer Patients feel about surgery?

- Patients' attitudes to risk in lung cancer surgery: A qualitative study HA Powell et al- Lung Cancer 2015
  - Participants reported being 'pleased' to hear that they were suitable for surgery
  - Felt that surgery was not a treatment to be turned down because they did not see any alternatives.
  - Participants had some knowledge of perioperative risks, including mortality estimates
  - However, many voiced a preference not to know these risks and to let the medical team decide their treatment plan.

What do Lung Cancer Patients feel about surgery?

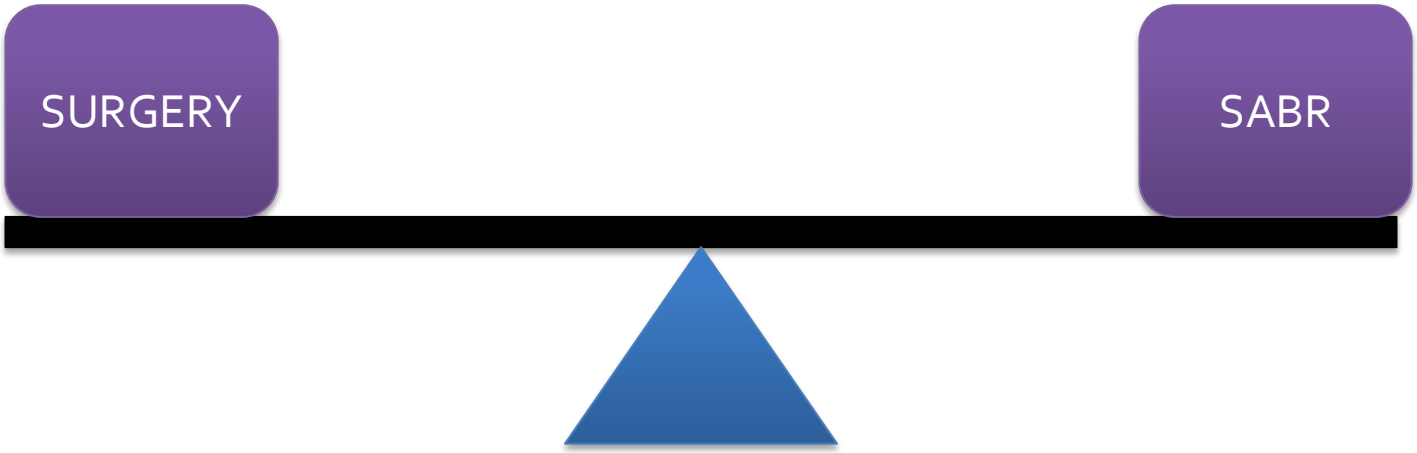
- Patients' attitudes to risk in lung cancer surgery: A qualitative study. HA Powell et al- Lung Cancer 2015
  - Some found it difficult to relate the potential risks and complications of surgery to their own situation and appeared willing to accept high perioperative mortality risks.
  - Generally, participants were willing to accept quite severe long-term postoperative breathlessness
  - However, it was apparent that many actually found this possibility difficult to imagine

SABR versus Surgery- does it have to be a battle?

What is the tipping point?

What is the tipping point?

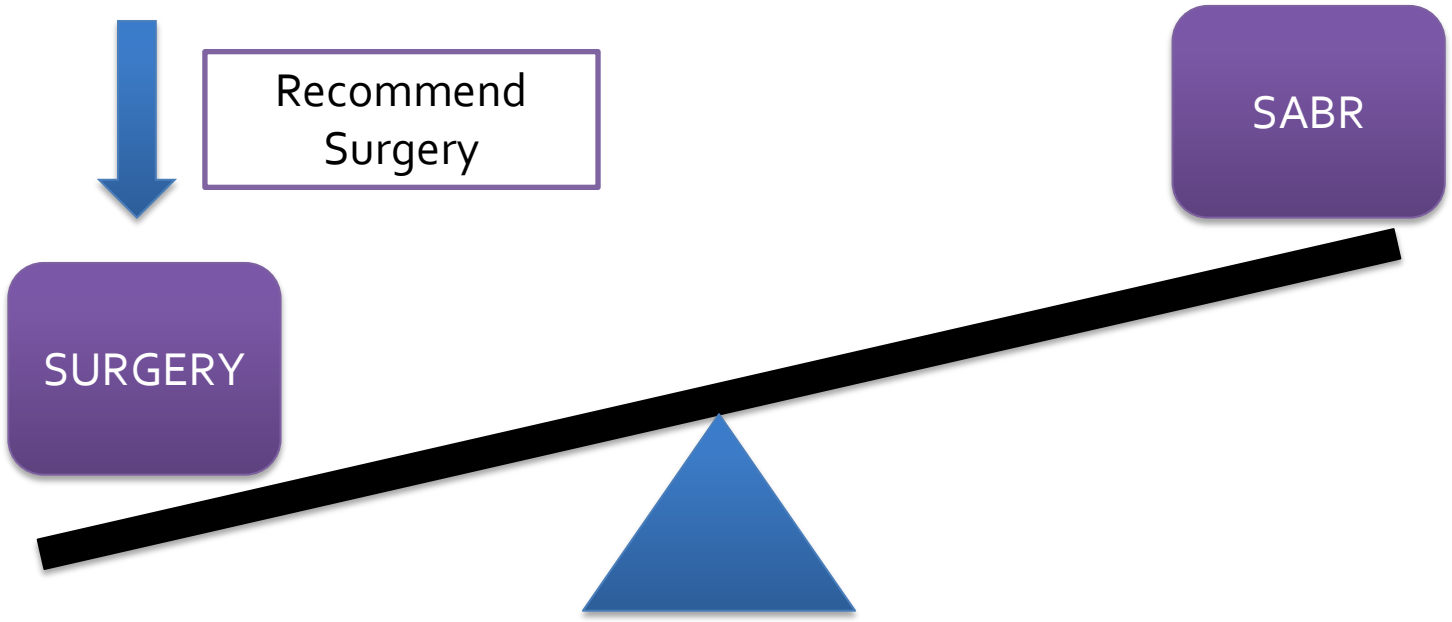
65yr old female with T1aNoMo AdenoCA
PS 1,FEV1 65%, Ex-smoker of 20 yrs and mild hypertension



What is the tipping point?

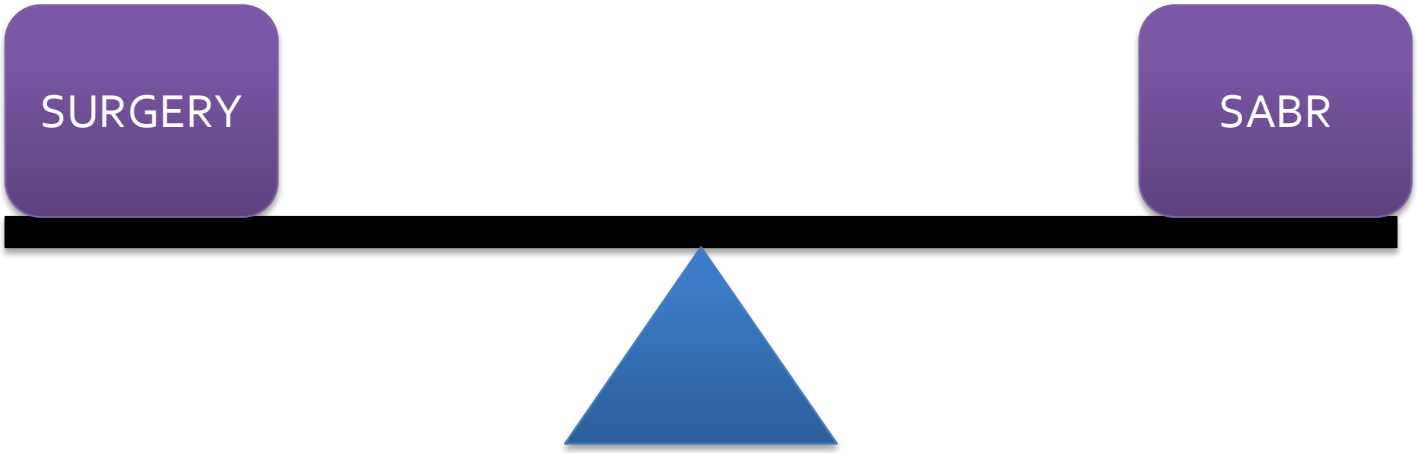
65yr old female with T1aNoMo AdenoCA
PS1,FEV1 >65%, Ex-smoker of 20 yrs and mild hypertension

Recommend Surgery



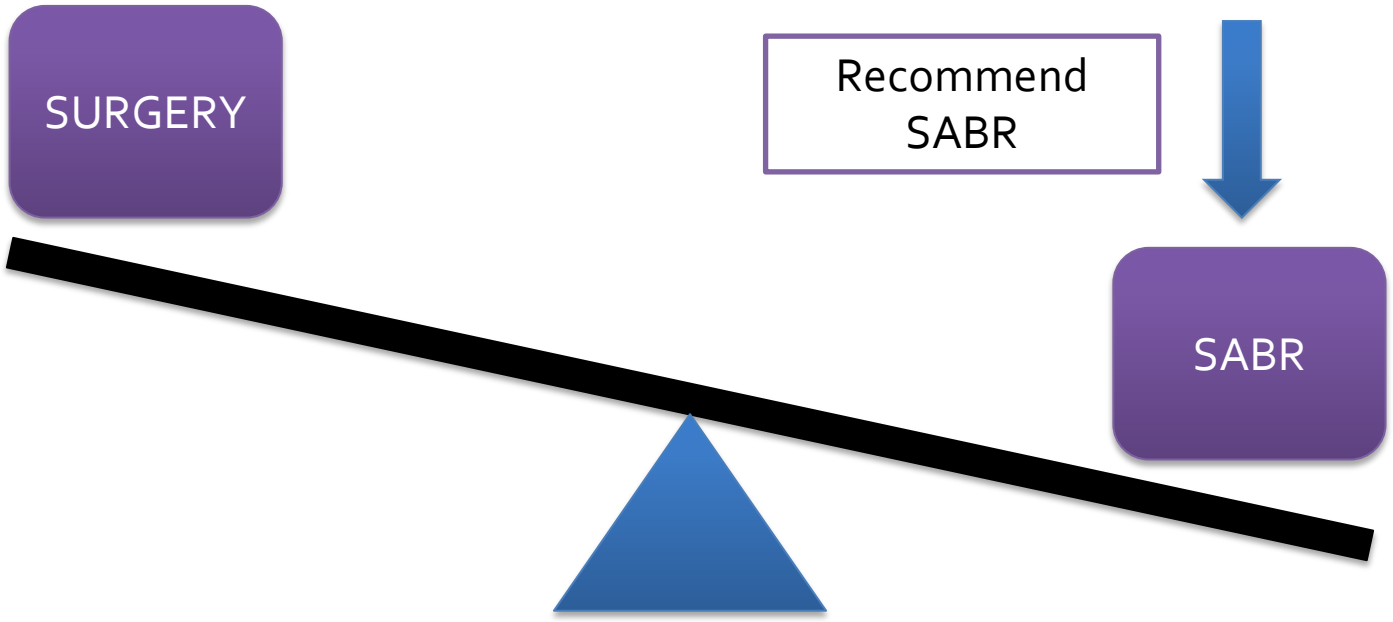
What is the tipping point?

85yr man T1bNo NSCLC and current smoker
PS2, FEV1 30% predicted, angina and mild CCF

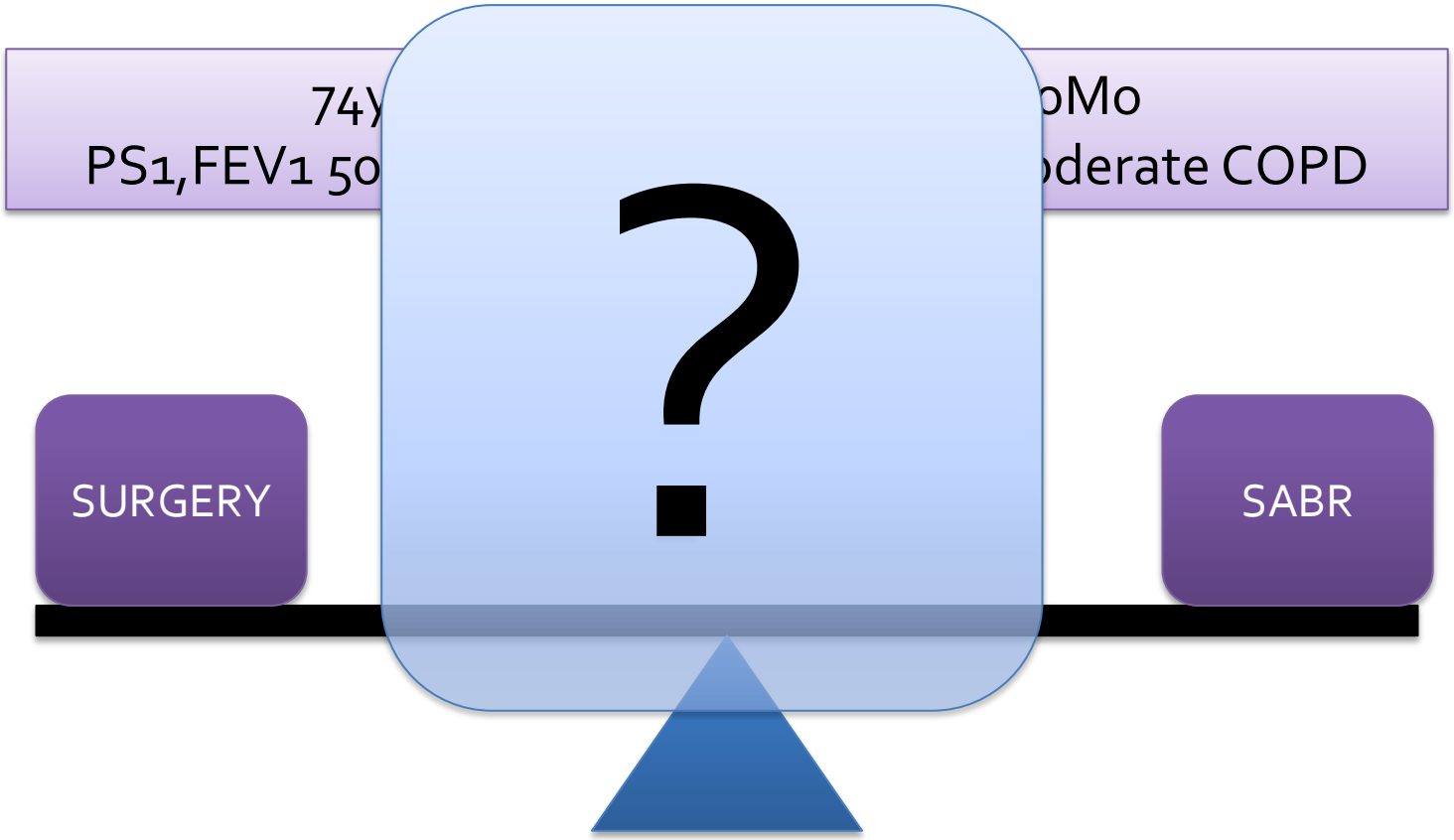


What is the tipping point?

85yr man T1bNo NSCLC and current smoker
PS2, FEV1 30% predicted, angina and mild CCF



What is the tipping point?



Current/Future Surgery versus SABR studies

- SABRTOOTH
- STABLE-MATES- pre-randomisation (LR vs SABR)- Robert Timmerman
- VETERANS STUDY –VALOR- Drew Moghanaki

Research for Patient Benefit (NIHR RfPB) Programme Ref PB-PG-0613-31114

SABRTooth

Stereotactic Radiotherapy vs. Surgery in early lung cancer

- A study to determine the feasibility and acceptability of conducting a phase III randomised controlled trial comparing **S**tereotactic **Ab**lative **R**adiotherapy (**SABR**) with surgery in pa**T**ients with peripheral stage I n**O**n-small cell lung cancer (NSCLC) c**O**nsidered To be at **H**igher risk of complications from surgical resection.

SABRTooth

Stereotactic Radiotherapy vs. Surgery in early lung cancer

- SABRTooth is funded by Research for Patient Benefit (NIHR RfPB) Programme

  Ref PB-PG-0613-31114

- The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health

SABRTooth
Stereotactic Radiotherapy vs. Surgery in early lung cancer

- **Issues Specific to SABRTOOTH**
  - Previous trials failed to recruit and closed prematurely
  - Needed to convey a convincing argument why our trial will work!
    - Multi-disciplinary support from all specialities
    - Non-fee paying system
    - MDT referral pathway unique to the UK

SABRTooth

Stereotactic Radiotherapy vs. Surgery in early lung cancer

- Getting the right question

- Initial question – is SABR as good as surgery in peripheral early lung cancer in patients?

SABRTooth

Stereotactic Radiotherapy vs. Surgery in early lung cancer

- Getting the right question

- Initial question – is SABR as good as surgery in peripheral early lung cancer in **higher risk** patients?

To get buy in from Pulmonologist/Thoracic Surgeons we we needed to find a group where all concerned had

EQUIPOISE

Use of evidence based approaches in SABRTooth

Evidence used to ensure trial management is as good as possible

Eg:

- Investigators workshops to discuss key issues with presenting trial equipoise and randomisation.
- Training video for recruiters and employment of clinical fellow to help ensure consistency of approach in consultation with patients.
- Launch event for trial to review any critical issues and to consider communication with participants.

Research for Patient Benefit (NIHR RfPB) Programme Ref PB-PG-0613-31114

Leeds Cancer Centre

SABRTooth

Stereotactic Radiotherapy vs. Surgery in early lung cancer

Eligibility

- Peripheral (>2 cm from the main airways), Stage I (T1a1b, T2a, N0M0 < 5 cm), NSCLC
- Lung cancer MDT consensus is the patient is suitable for surgery but at higher risk of complications

Seen by Respiratory Physician for diagnosis. SABRTooth discussed and information sheet provided

Seen by Respiratory Physician for diagnosis. SABRTooth discussed and information sheet provided

Consent with Research Nurse or Respiratory Physician

Seen by Surgeon

Seen by Clinical Oncologist

Patient or clinician decides against randomised treatment

Patient is invited to take part in Qualitative Feedback Interviews

Follow-up visits at 6 weeks, 3, 6, 9, 12, 18 & 24 months post-treatment or until the end of follow-up period (6 months after last participant randomised). Questionnaire data administered via post at 15m and 21m post-treatment and OS data collected at the end of the trial via the NCDR.

UNIVERSITY OF LEEDS

SABRTooth

Stereotactic Radiotherapy vs. Surgery in early lung cancer

- Opened July 2015
- All sites opened Oct/Nov 2015
- Slow initially to get RT Q/A, local set up and referral pathways in place
- Lots of additional actions done to improve this since November 2015

Strategies to Improve Recruitment

- Mock interviews filmed with actors and shared with recruitment sites
- Additional Face to Face meeting at BTOG (Jan 2016)
- Dedicated Nurses Meeting (Dec 2015) to provide additional information/confidence to help recruitment -further meeting planned (June 2016)
- Feedback from patient interviews discussed at TMG
- PI meeting (May 2016)

Strategies to Improve Recruitment

- Colour flipchart guide to aid discussions with patients
- Additional feedback questionnaire once patients have completed treatment
- Joint consultations at one of the sites
- Posters to go in the lung clinic to increase patient awareness

Strategies to Improve Recruitment

- Brailsford Strategy-‘small points/marginal gains’

- Short colour leaflet with team photo as introduction to trial
- Laminated eligibility cards available in clinic
- SABRTooth pens and “post-its” to keep trial visible.

Strategies to Improve Recruitment

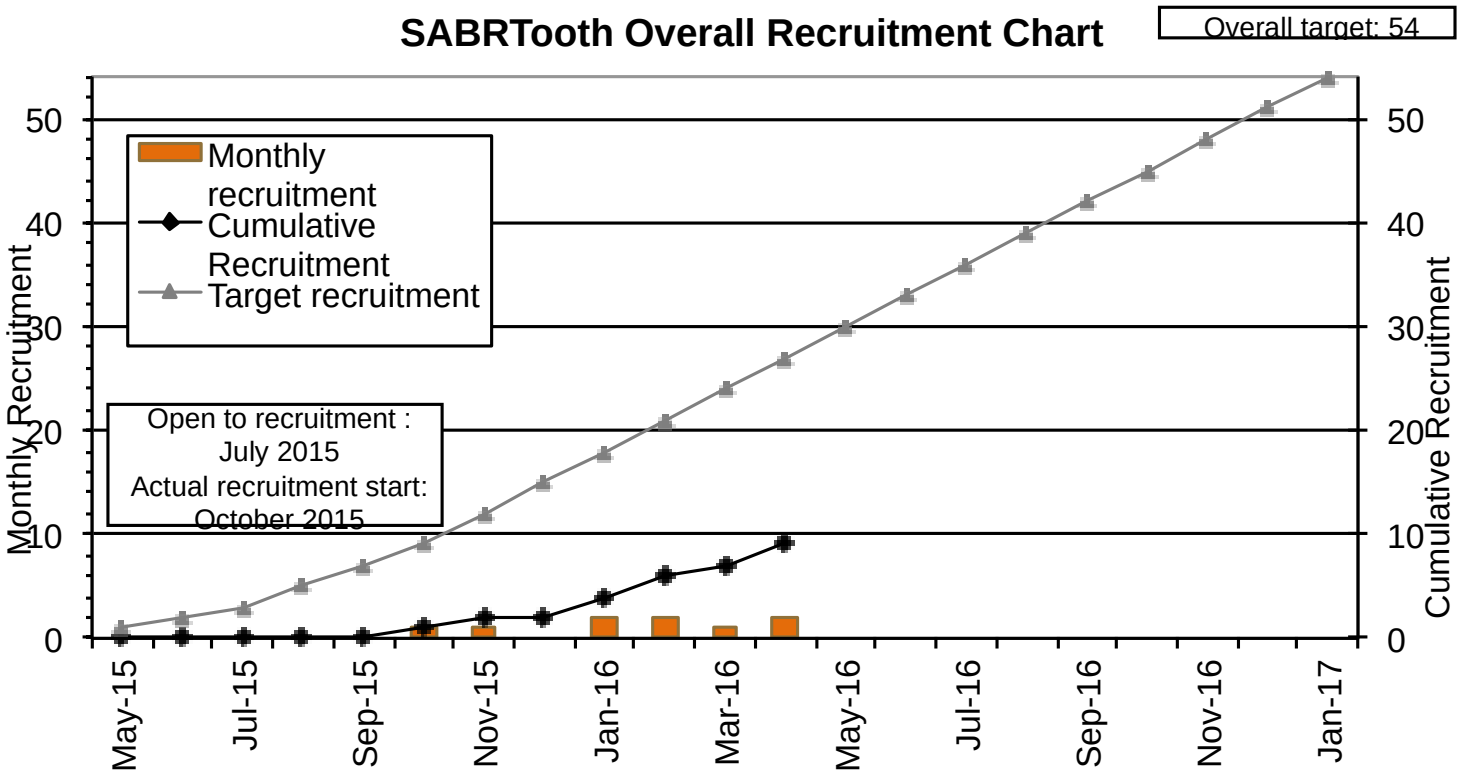
- Refinement of “Higher-risk” group
- Monthly news letter with “top tips”
- Patient information video in development
- SABRtooth on Tour (Feb 2016)

Research for Patient Benefit (NIHR RfPB) Programme Ref PB-PG-0613-31114

SABRTooth

Stereotactic Radiotherapy vs. Surgery in early lung cancer

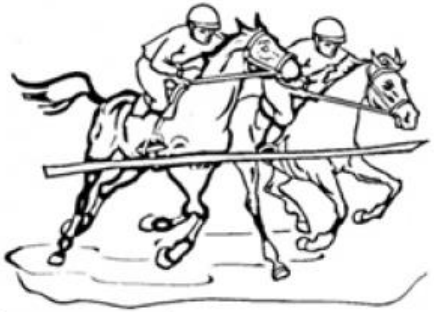
SABRTooth Overall Recruitment Chart



Leeds Cancer Centre

UNIVERSITY OF LEEDS

STABLEMATES Trial Schema



Defined High Risk Stage I NSCLC

Screen Eligible Patients/ Pre-Randomize

N = 258

Consent to Accept Randomization Assignment

Accept

N = 218

Arm 1: Sublobar Resection

N = 109

Arm 2: SAbR

N = 109

Follow for OS, Toxicity, and Patterns of Failure

Reject

N = 40*

Consent to Be Observed After Standard of Care Therapy

Accept

N = 36

Follow for OS, Toxicity, and Patterns of Failure

Reject

N = 4*

Failure to Consent (Off Study)

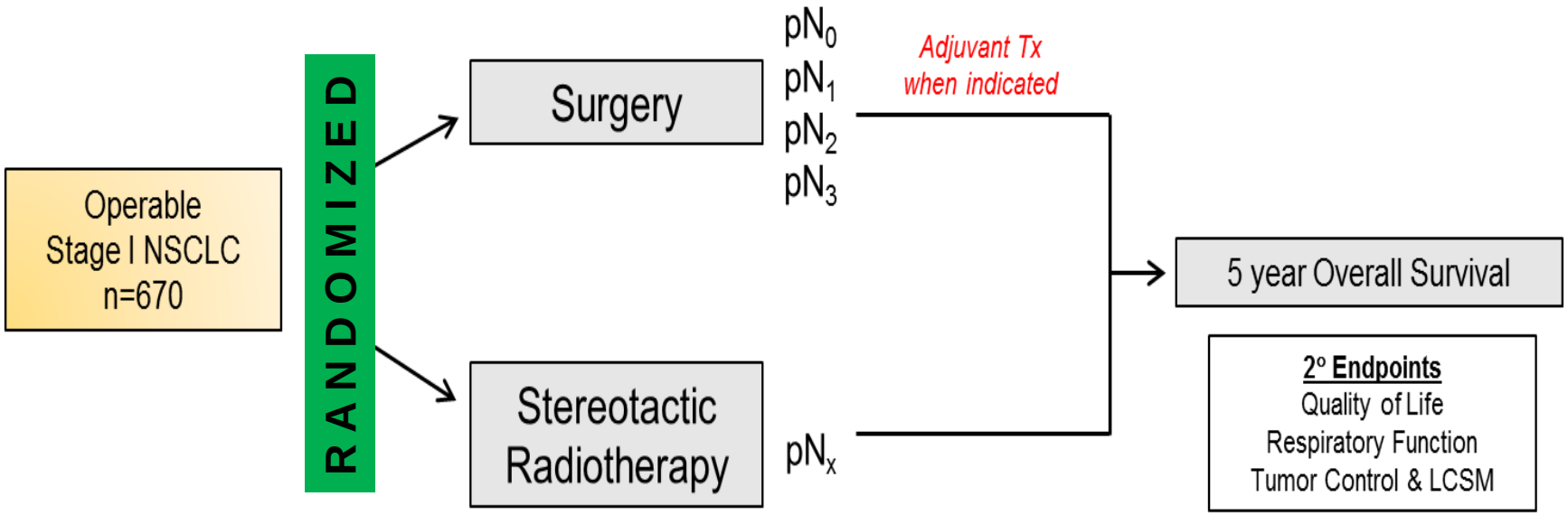
*Anticipated (actual assignment rate will be monitored)

Slide courtesy of Robert Timmerman

VALOR

Veterans Administration Lung cancer surgery Or stereotactic Radiotherapy Trial

A Department of Veterans Affairs Cooperative Study – CSP #2005



Stratified by
- Facility
- IA vs IB
- Central v Peripheral

Surgery
- Lobectomy
- Anatomic Segmentectomy

Salvage Surgery
- Bx first, recommended

Slide courtesy of Drew Moghanaki

Recruitment Strategy

- Select facilities with group equipoise
- Identify champion for each lung multi-D

- **Consent #1**: Counseled Screening
  - Dedicated research nurse
  - Educational video
  - Counseling & accompanying patients
    - Thoracic surgery consultation
    - Radiation oncology consultation
  - LN staging and **required biopsy**

- **Consent #2**: Willingness to be Randomized
  - Revisit local Site-PI and research nurse to review above

Slide courtesy of Drew Moghanaki

Conclusion

- Lung Cancer is a multi-disciplinary disease
- All curative modalities are improving
- We all want what is best for our patients
- That we should aim to be providing patient with a choice of treatment options based on the highest quality evidence

Conclusion

- Therefore we need Randomised Controlled Trials to define which patients in the future should receive

SURGERY

SABR

EITHER- patient choice

Conclusion

Acknowledgements

- Leeds SABR Team
- SABRtooth TMG/Investigators
- UK SABR Consortium
- BTOG
- PMH (Andrea Bezjak/David Jaffray)
- Suresh Senan/VU

POSTLIV (RTOG3502)

Phase 2 (76pts) Primary Endpoint 2 yr LC

Inclusion Criteria:

- -Pathologically (histologically or cytologically) proven diagnosis of Stage I NSCLC (AJCC, 7th ed.), T1N0M0; note: T1N0 disease must be confirmed by FDG-PET/CT
- Baseline FEV1 >60% predicted, postoperative predicted FEV1 >40% predicted;
- Diffusion capacity of the lung for carbon monoxide (DLCO) >60% predicted, postoperative predicted DLCO > 40 % predicted;
- No baseline hypoxemia and/or hypercapnia;
- If the estimated postoperative FEV1 or DLCO <40% predicted indicates an increased risk for perioperative complications, including death, from a standard lung cancer resection (lobectomy or greater removal of lung tissue), then cardiopulmonary exercise testing to measure maximal oxygen consumption (VO2max) must be >60%;