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Beyond randomisation – an EORTC academic perspective

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CDDF, Annual conference, 3-5 February 2025 Noordwijk aan Zee, NL

Declaration of interests

Murielle MAUER

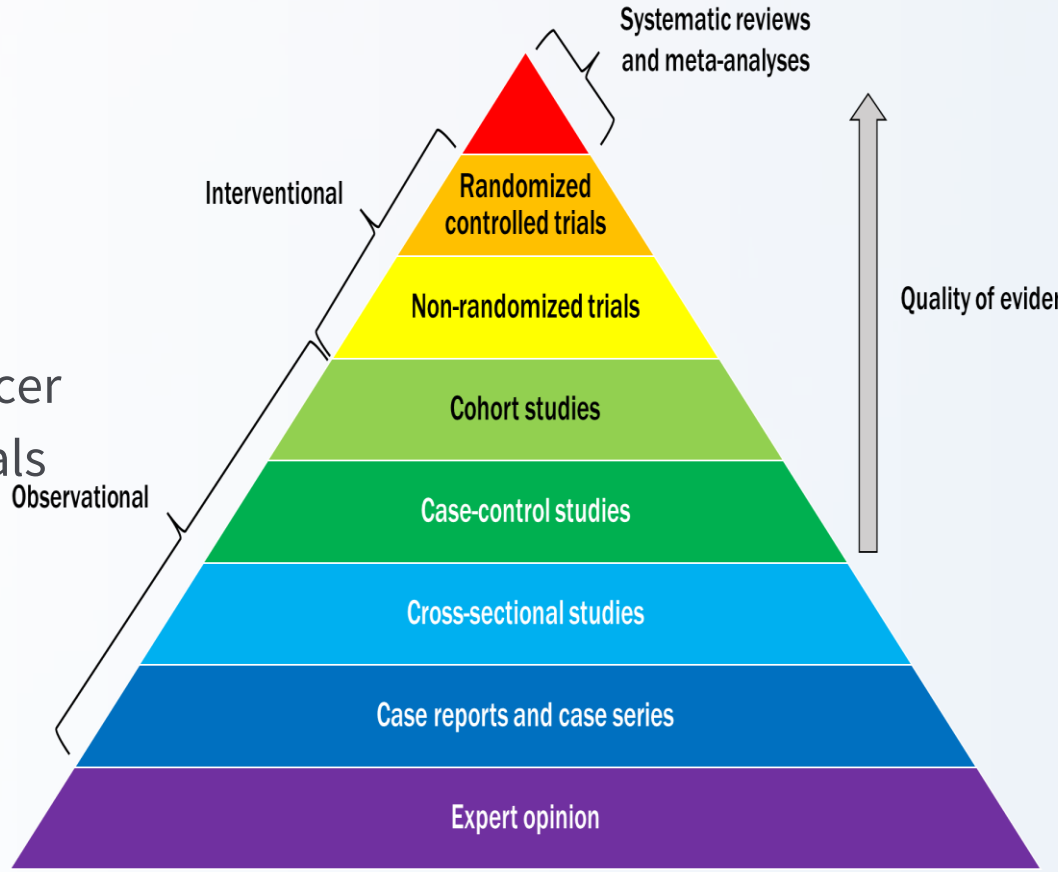
I have no conflicts of interest to disclose

The classical phase III cancer RCT

What does a typical phase III cancer RCT look like today?

- RCTs considered the ‘gold standard’ for evidence-based medicine
- Review of drug RCTs in breast, lung and colorectal cancer published between 2010 and 2020 in high-impact journals
  - 61% relied on surrogate outcomes as primary endpoints
  - 89% funded by industry
  - 73% investigated targeted or immunotherapeutic agents

Del Paggio et al. JAMA Oncol (2021)



The pyramid of evidence-based medicine

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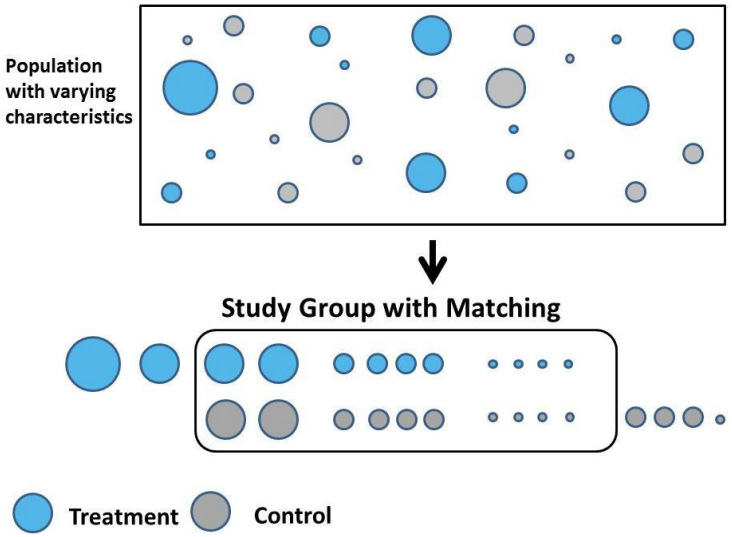
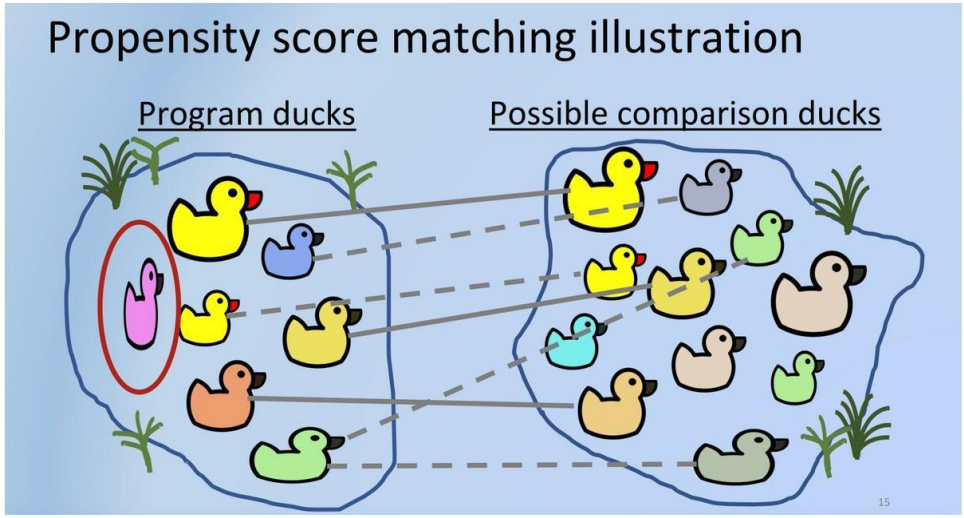
How to infer causality without RCT





"Which causal inference method and control data are best fit to assess new treatment effect in non randomized trials ?"

- *Propensity score matching*
- *Causal inference*

BUT

All come with some untestable assumptions!

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Only randomization (with large numbers) can control for UNKNOWN confounders

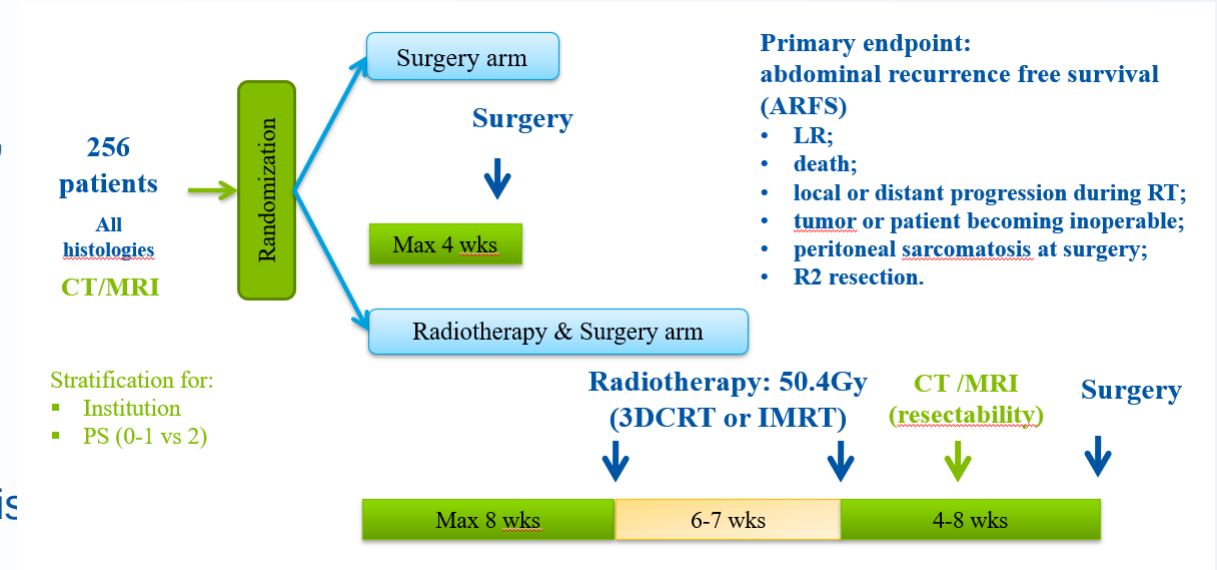
Beyond randomization: an EORTC case study

EORTC 62092-22092
A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma (STRASS)

EU funded project Eurosarc
"European clinical trials in Rare Sarcomas within an integrated translational trial network"

- **20 partners**
- **Started 1st Dec 2011 ended May 2018**
- **6 clinical trials in various type of sarcoma**

- Approximately 10-15% of adult soft tissue sarcomas aris the retroperitoneum
- Annual incidence is 2.7 cases per 10^6 persons
- Loco-regional relapse is the main cause of death



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Background

Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial

Sylvie Bonvalot, Alessandro Gronchi, Cécile Le Péchoux, Carol J Swallow, Dirk Strauss, Pierre Meeus, Frits van Coevorden, Stephan Stoldt, Eberhard Stoeckle, Piotr Rutkowski, Marco Rastrelli, Chandrajit P Raut, Daphne Hompes, Antonino De Paoli, Claudia Sangalli, Charles Honoré, Peter Chung, Aisha Miah, Jean Yves Blay, Marco Fiore, Jean-Jacques Stelmes, Angelo P Dei Tos, Elizabeth H Baldini, Saskia Litière, Sandrine Marreaud, Hans Gelderblom, Rick L Haas

Lancet Oncol 2020; 21: 1366–77

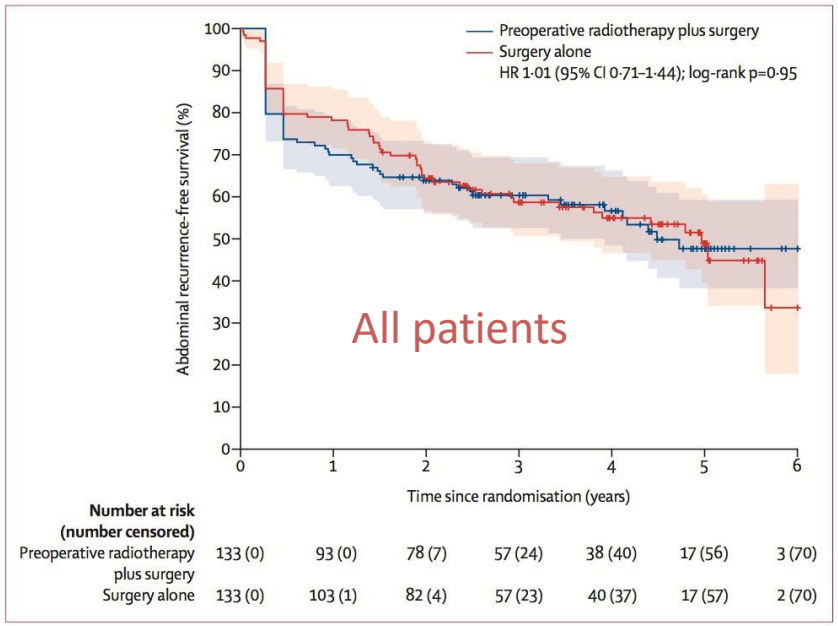

Figure 2: **Abdominal recurrence-free survival in all patients**
Shaded areas around the lines represent the 95% CI. HR=hazard ratio.

Sensitivity analysis recommended by IDMC when local progression not leading to inoperability was removed from the events.

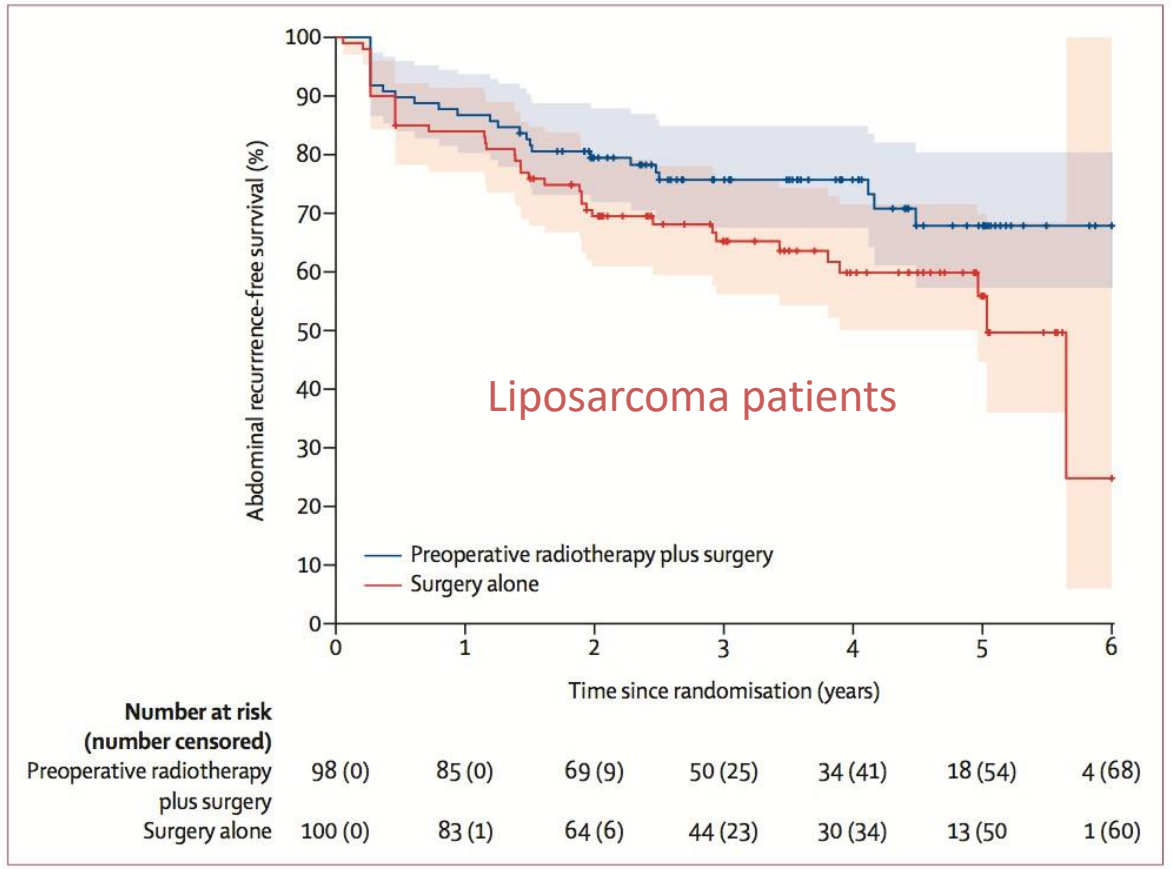

Figure 3: **Second sensitivity analysis of abdominal recurrence-free survival in the liposarcoma subgroup**
Shaded areas around the lines represent the 95% CI.

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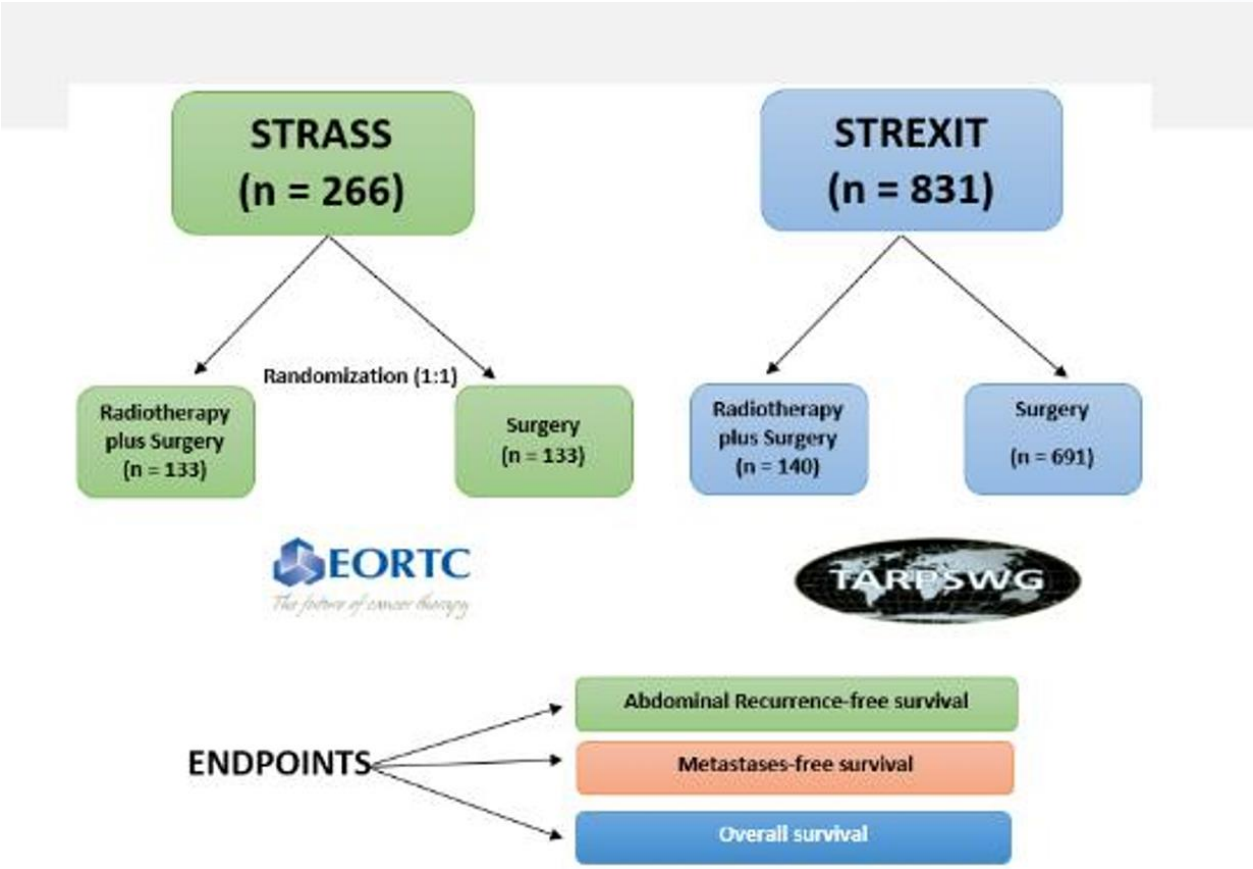
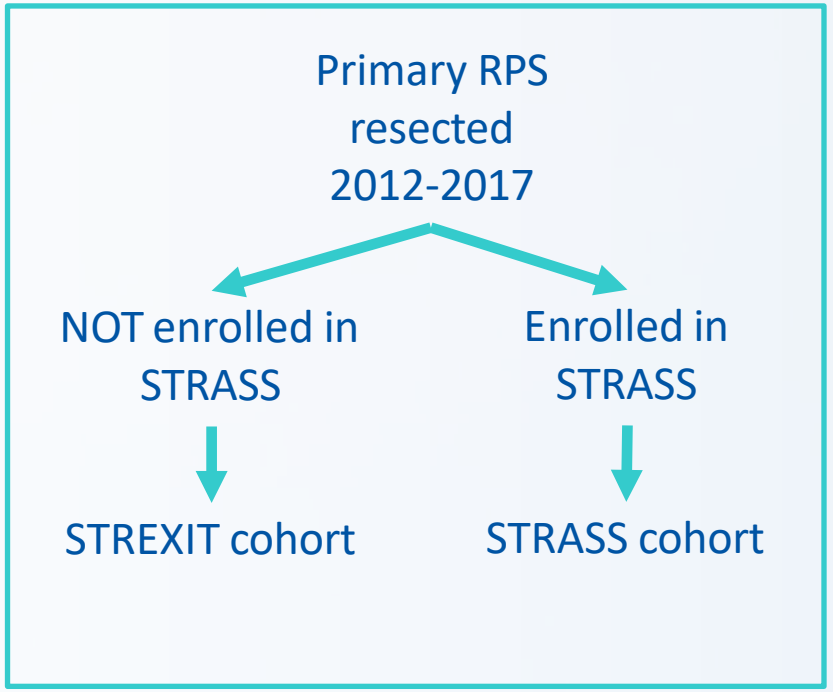
STRASS vs. STREXIT



- Some patients information were collected by TransAtlantic Retroperitoneal Sarcoma Working Group (TARPSWG) which led to the STREXIT study.



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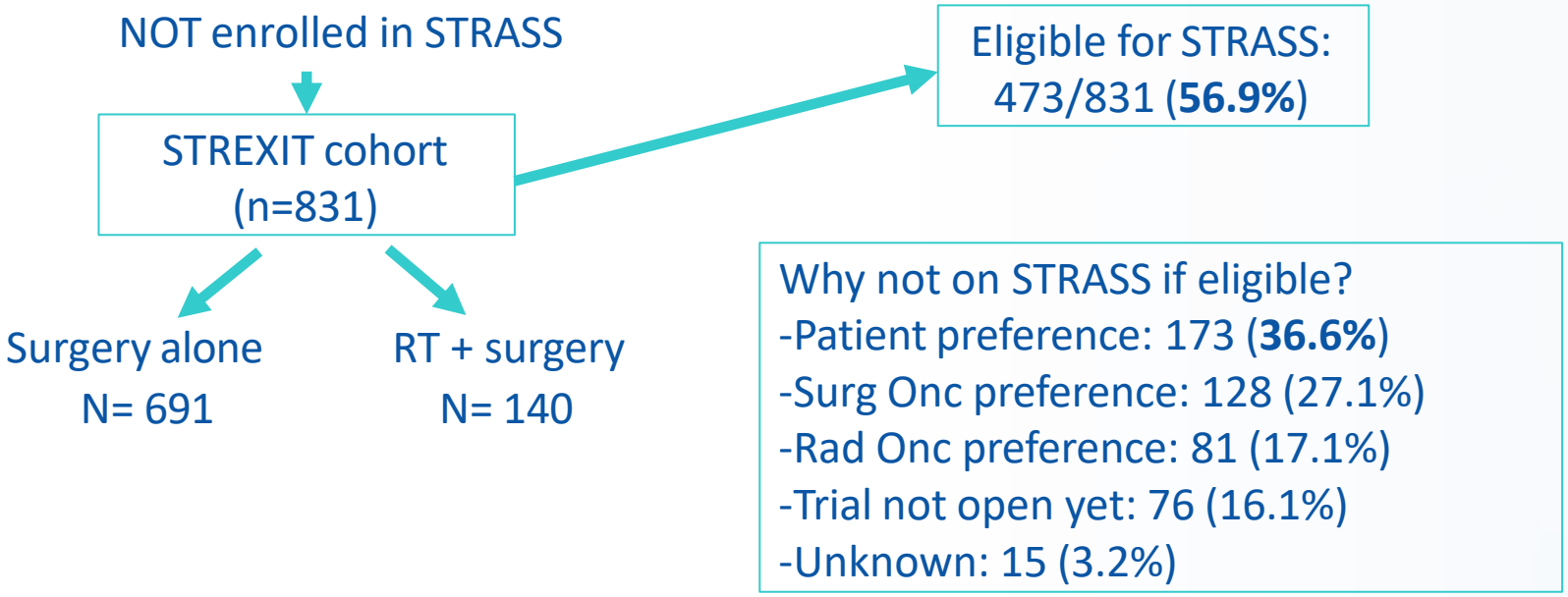
STRASS vs. STREXIT



The aim of this case study was to provide answers to the following objectives.

- Assess the impact of administration of Radiotherapy in the STREXIT cohort using a propensity score matching overall and in different liposarcoma subgroups.
- Compare the outcome of STRASS and STREXIT patient.
- Pool STRASS and STREXIT data and assess the impact of Radiotherapy.

Callegaro D, et al. Preoperative Radiotherapy in Patients With Primary Retroperitoneal Sarcoma: EORTC-62092 Trial (STRASS) Versus Off-trial (STREXIT) Results. Ann Surg. 2023 Jul 1;278(1):127-134. doi: 10.1097/SLA.0000000000005492. Epub 2022 Jul 14. PMID: 35833413.

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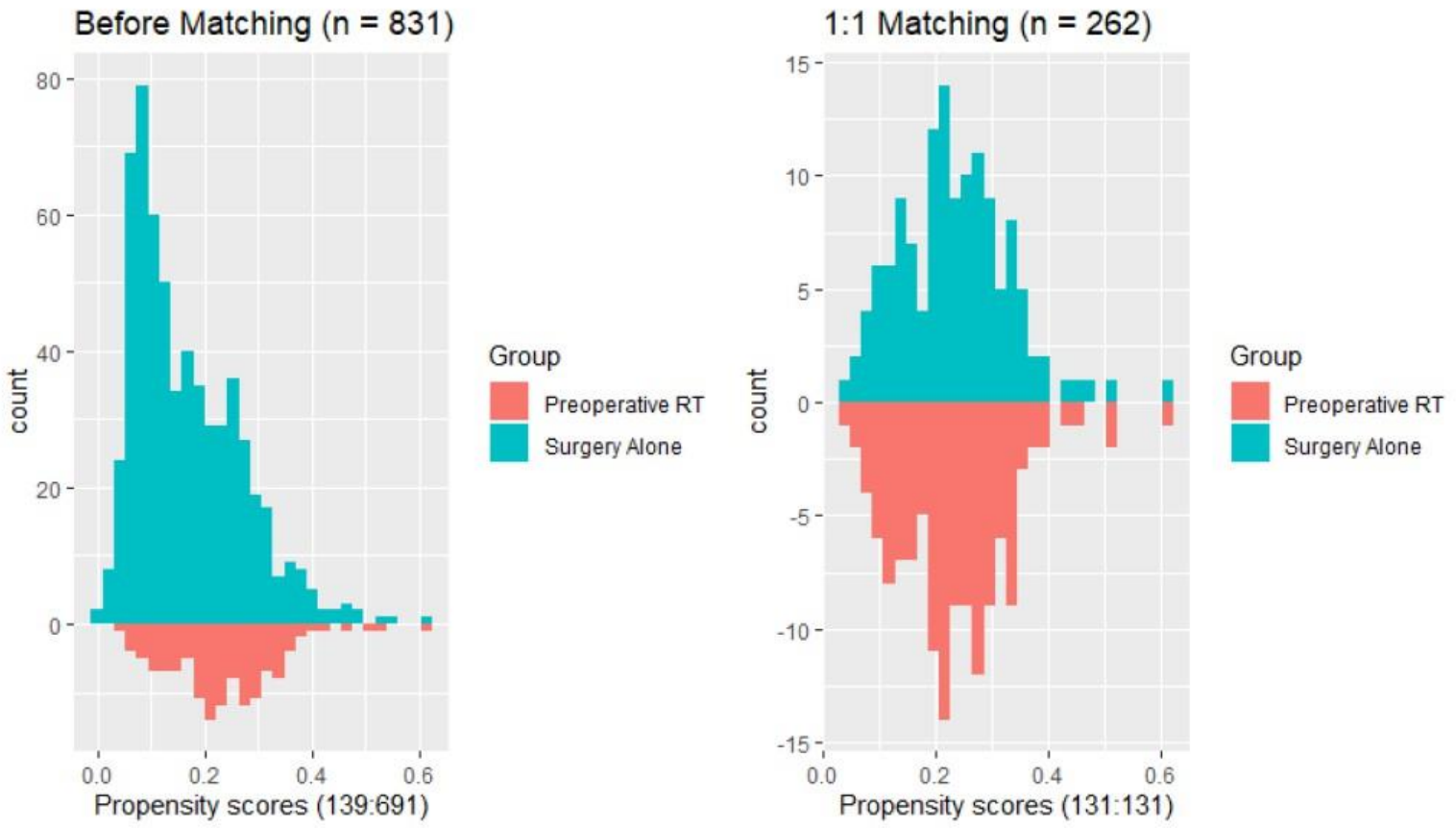
STRASS vs. STREXIT



The propensity score is the probability of treatment assignment conditioned on the measured baseline covariates.

$$Y_i \sim Bernoulli(\pi_i)$$

$$\pi_i = \frac{\exp(X_i\beta)}{1 + \exp(X_i\beta)}$$

Yi is a binary response of radiotherapy plus surgery (1) versus surgery alone (0), Xi are age, gender, size of the tumor, the grade of the tumor, multifocality, and histology as covariates.

β are vector of parameters.

This method produces unbiased estimates of the treatment effect and balance distribution of covariates provided all relevant confounding factors are considered.

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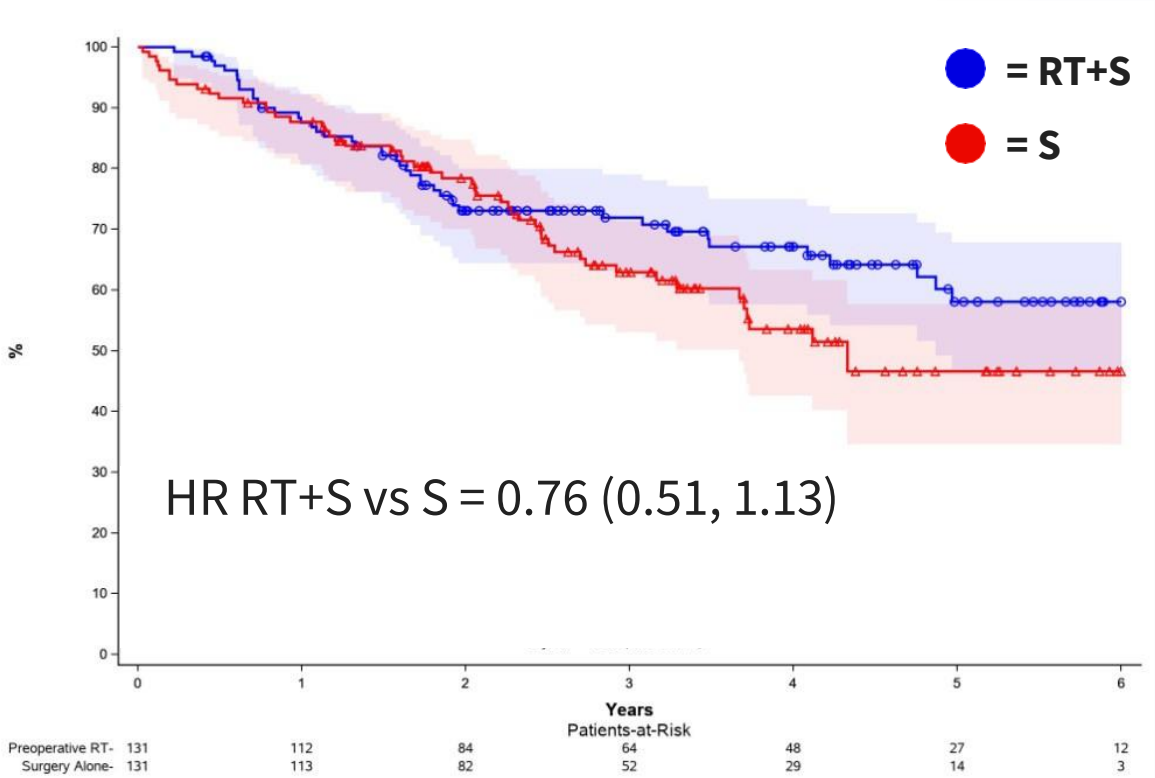
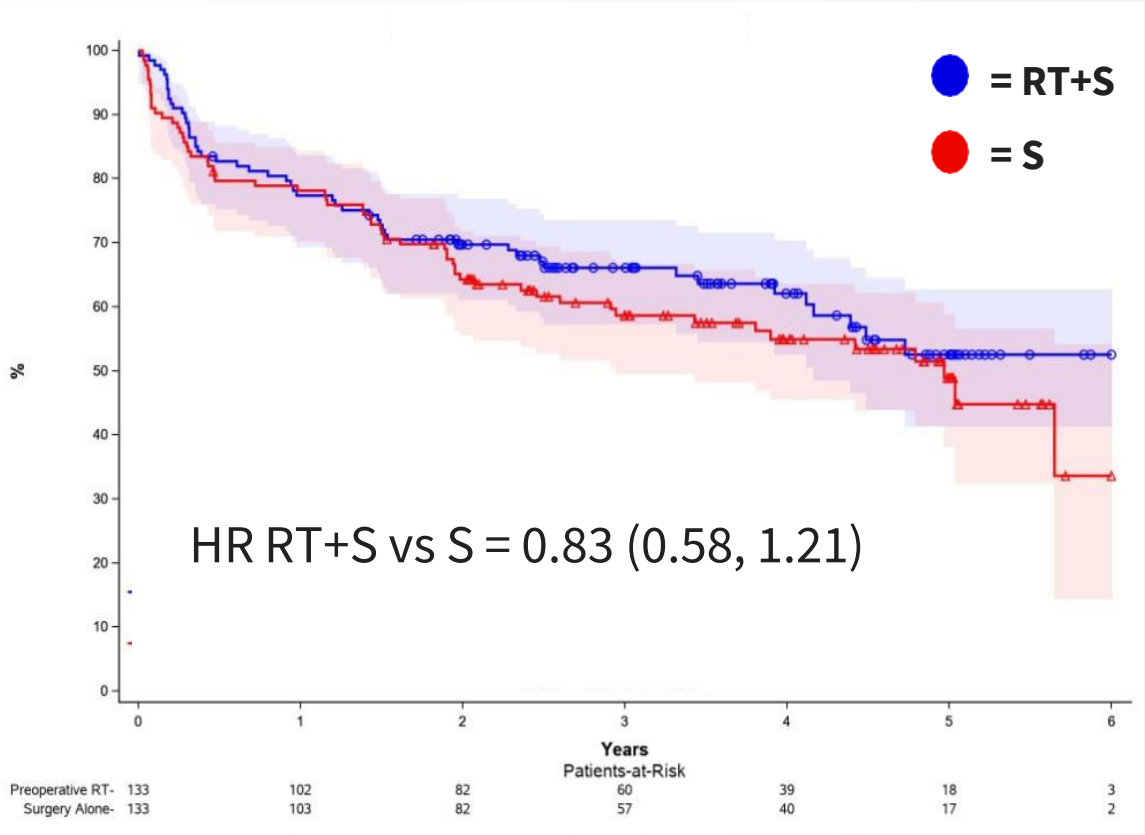
STRASS vs. STREXIT - ARFS (all histologies)

1:1 STREXIT (n=262)



HR RT+S vs S = 0.76 (0.51, 1.13)

STRASS (n=266)



HR RT+S vs S = 0.83 (0.58, 1.21)

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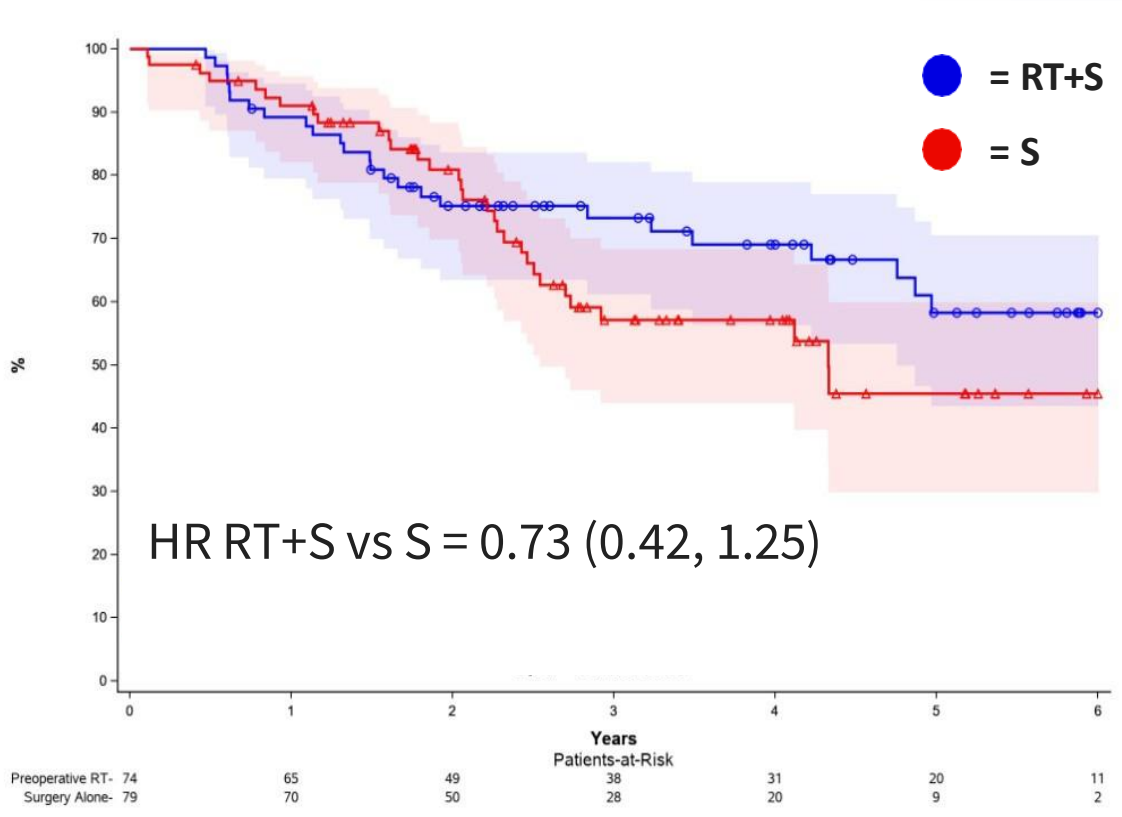
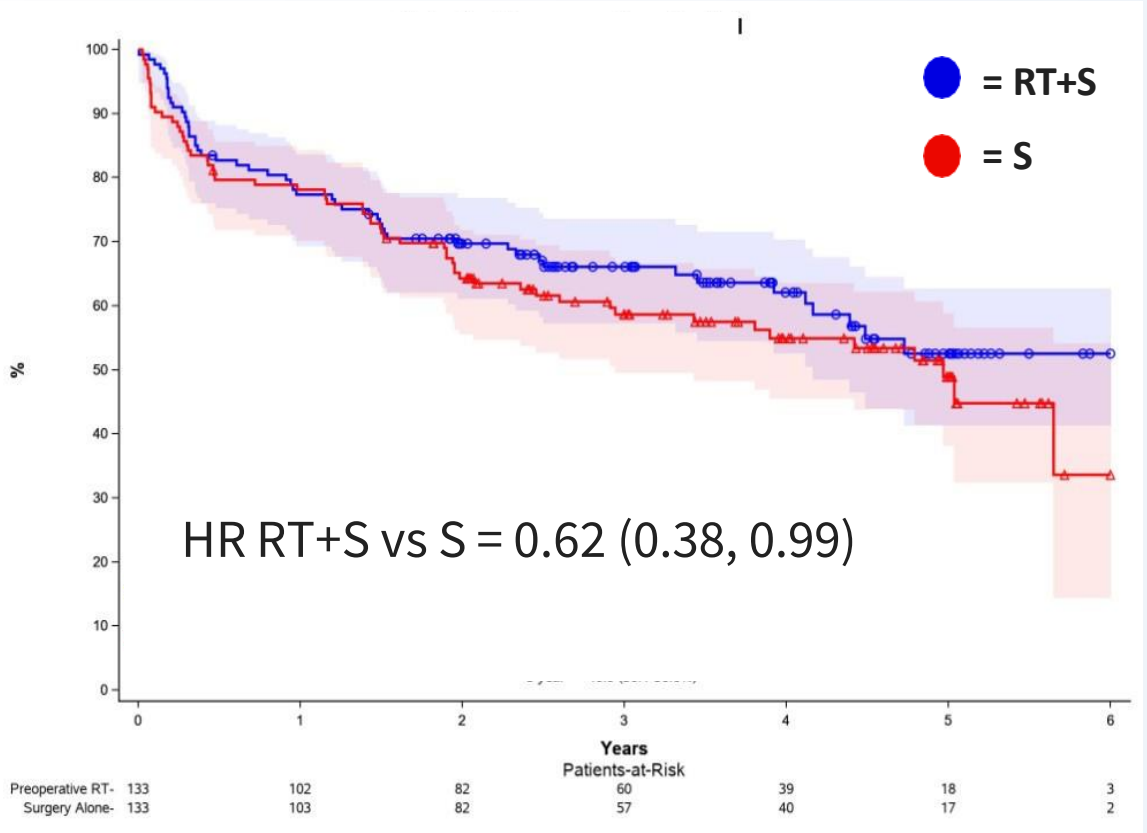
STRASS vs. STREXIT - ARFS (liposarcoma)

1:1 STREXIT (n=153)



HR RT+S vs S = 0.73 (0.42, 1.25)

STRASS (n=193)



HR RT+S vs S = 0.62 (0.38, 0.99)

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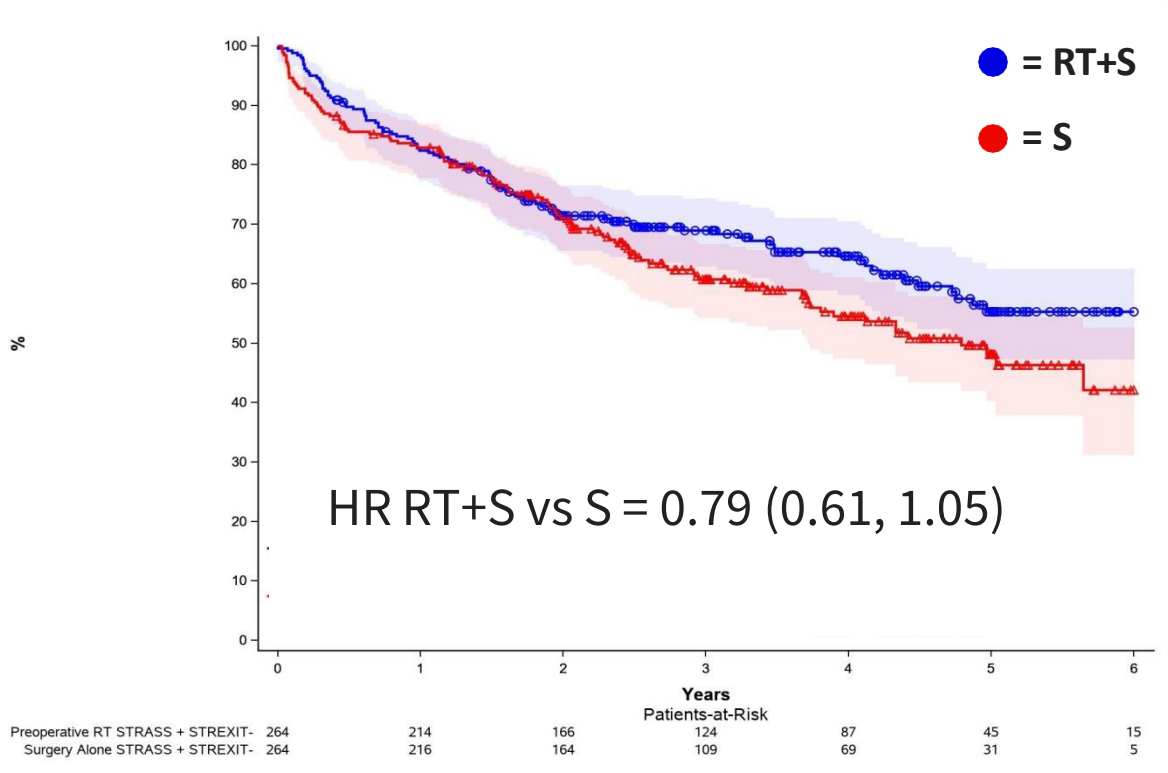
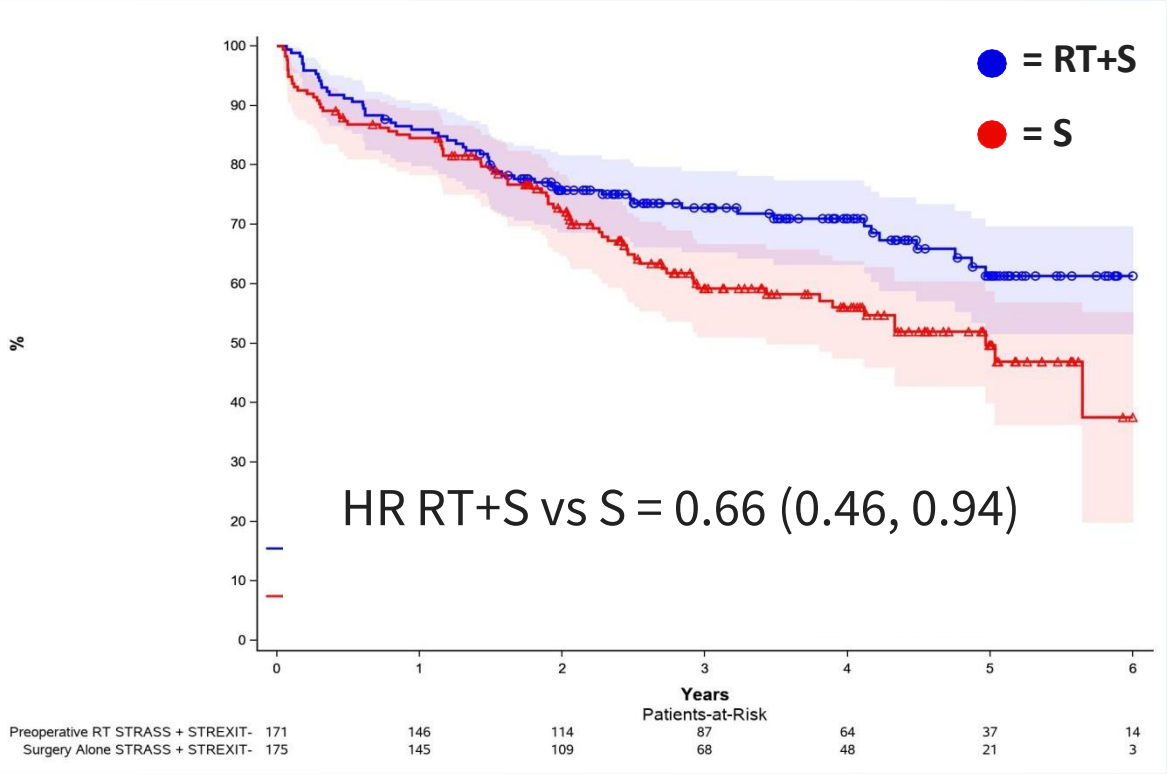
Pooled 1:1 STREXIT + STRASS (n=528)

All histologies (n=528)



HR RT+S vs S = 0.79 (0.61, 1.05)

Liposarcoma (n=346)



HR RT+S vs S = 0.66 (0.46, 0.94)

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STRASS vs. STREXIT

- The use of preoperative radiotherapy remains a subject of debate although there is growing evidence that there may be an effect on some histological subtypes.
- Real-life data in an orphan disease may help a lot to understand the result of a randomised study.
- The collection of real-life data may help to address the question of the external validity of the results.
- STRASS 2 addressing the impact of preoperative chemotherapy on RPS patients is ongoing.

Pragmatic trials

For patient-centric trials, addressing public health questions on treatment optimisation and treatment de-escalation

- **EORTC study 2227:** Lomustine with or without reirradiation for first progression of glioblastoma: a pragmatic randomized phase III study (LEGATO)
  - To assess whether the addition of radiation treatment to lomustine chemotherapy has superior efficacy as compared to lomustine chemotherapy alone for treatment of patients with recurrent glioblastoma.
  - To perform cost-effectiveness analysis assessing the economic value of the addition of radiation treatment to lomustine chemotherapy.
  - Study coordinators: M Preusser (AT), G Minniti (IT)

- **EORTC study 1809:** A pragmatic clinical study of neoadjuvant chemotherapy followed by surgery versus surgery alone for patients with high-risk retroperitoneal sarcoma (STREXIT2)
  - To validate the added value of neoadjuvant chemotherapy prior to surgery using high-quality real-world data (STREXIT2) collected in an observational cohort added under the umbrella of a classical phase 3 randomized clinical protocol (STRASS2).
  - To compare the clinical outcomes between STRASS2 and STREXIT2
  - To perform a health economics analysis assessing the economic value of different treatment scenarios based on STRASS2 and STREXIT2.
  - Study coordinators: A Gronchi (IT), W van Houdt (NL)

- **EORTC study 2238:** Intermittent androgen deprivation therapy in the era of androgen receptor pathway inhibitors; a phase 3 pragmatic randomised trial (DE-ESCALATE)
  - To evaluate whether intermittent androgen deprivation treatment in metastatic prostate cancer is not inferior to continuous treatment in terms of oncological benefit while minimizing side effects and resource utilization and improving patients' quality of life.
  - To perform health economic research assessing the economic value of intermittent treatment for metastatic prostate cancer compared to continuous treatment.
  - Study coordinators: B Tombal (BE), S Gillessen (CH)

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Patient selection in RCTs

- **Overly restrictive selection criteria to studies**
  - Liu R et al (Nature 2021): using the nationwide Flatiron Health EHR database of 61094 trials with advanced NSCLC to emulate trial entry criteria
  - Entry conditions on comorbidities or strict requirements on lab values may exclude up to 30% of otherwise eligible pts
  - Effect lost on average 0.05 on HR scale

https://www.nature.com/articles/s41586-021-03430-5

Table 1 | Comparisons of eligibility criteria

Trial name	Original trial criteria			Fully relaxed criteria		Data-driven criteria		
	No. of criteria	No. of patients	HR	No. of patients	HR	No. of criteria	No. of patients	HR
FLAURA	10	2,277	0.81	3,819	0.82	4	2,546	0.75
LUX8	11	129	0.65	1,350	0.81	5	141	0.58
Checkmate017	17	523	0.67	4,900	0.71	7	4,085	0.71
Checkmate057	19	792	0.75	4,900	0.71	9	2,594	0.66
Checkmate078	18	1,509	0.74	4,900	0.71	9	3,348	0.68
Keynote010	13	806	0.56	1,950	0.51	1	1,948	0.51
Keynote189	15	4,066	0.88	8,818	0.94	7	4,595	0.85
Keynote407	13	2,031	1.13	10,437	1.07	4	9,173	1.04
BEYOND	12	2,902	1.09	9,310	1.14	4	3,043	1.08
OAK	19	493	0.88	1,288	0.87	6	620	0.80
Average	15	1,553	0.82	5,167	0.83	6	3,209	0.77

The number of inclusion/exclusion criteria, the number of eligible patients and the hazard ratio of the overall survival of emulated aNSCLC trials with eligibility criteria under three scenarios: the original criteria used in the trial, fully relaxed criteria and data-driven criteria. The fully relaxed criteria correspond to evaluating the hazard ratio of the overall survival of all of the patients in the Flatiron database who took the treatments in the relevant line of therapy. The data-driven criteria were selected by Shapley values. HR, hazard ratio.

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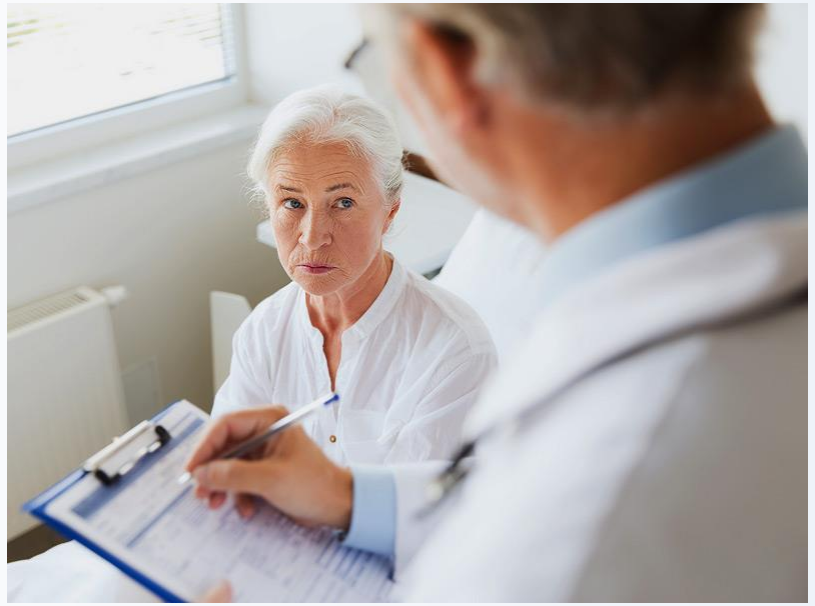
Patient selection in RCTs



A specific need in geriatric oncology

- The elderly are underrepresented in cancer clinical trials.
- In USA, though the elderly aged ≥65 years account for 61% of all new cancer cases and 70% of all cancer deaths, in the clinical trials active between 1993 and 1996, the elderly comprised only 25% of oncology trial participants.

Ref. Premnath at al. Elderly patients' participation in clinical trials. Perspect Clin Res. 2015 Oct-Dec; 6(4): 184–189

Patient selection in RCTs

CLINICAL CANCER RESEARCH | PERSPECTIVES

Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO–Friends of Cancer Research Joint Research Statement

Edward S. Kim[1], Thomas S. Uldrick[2], Caroline Schenkel[3], Suanna S. Bruinooge[3], R. Donald Harvey[4], Allison Magnuson[5], Alexander Spira[6], James L. Wade[7], Mark D. Stewart[8], Diana Merino Vega[8], Julia A. Beaver[9], Andrea M. Denicoff[10], Gwynn Ison[9], S. Percy Ivy[10], Suzanne George[11], Raymond P. Perez[12], Patricia A. Spears[13], William D. Tap[14], and Richard L. Schilsky[3]

Results: The four working groups, ASCO Board of Directors, and *Friends* leadership support the recommendations included in this statement to modernize EC related to washout periods, concomitant medications, prior therapies, laboratory references ranges and test intervals, and performance status to make trial populations more inclusive and representative of cancer patient populations.

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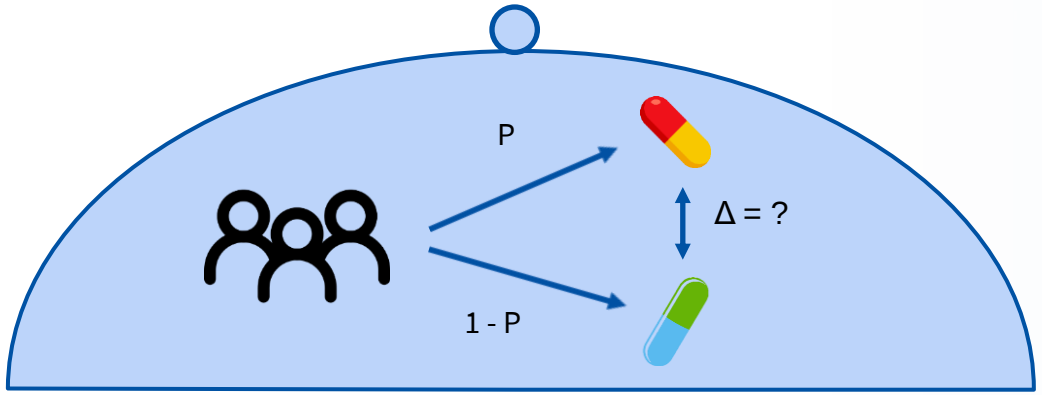
The need for pragmatic trials

Explanatory trials address the question:

Can the treatment work, if it is applied under ideal circumstances?

→ treatment *efficacy*



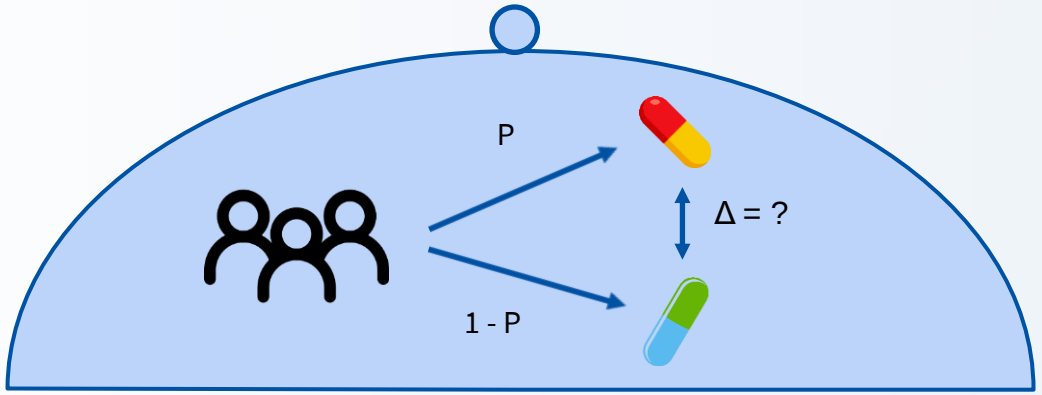
Ensuring a controlled environment by:

- Rolling the trial out in university hospitals only
- Recruiting a homogeneous sample of participants
- Giving extensive training to investigators/study staff
- Monitoring participants according to a fixed schedule
- Keeping track of participants' compliance with treatment

Pragmatic trials address the question:

Will the treatment work, if it is applied in real-world clinical practice?

→ treatment *effectiveness*



Mimicking real-life conditions by:

- Rolling the trial out in multiple different types of hospitals
- Recruiting a heterogeneous sample of participants
- Giving little to no training to investigators and study nurses
- Monitoring participants according to a flexible schedule
- Tolerating participants' lack of compliance with treatment

Schwartz and Lellouch. *J Chronic Dis* (1967); Roland and Torgerson. *BMJ* (1998); Tunis et al. *JAMA* (2003); Patsopoulos. *Dialogues Clin Neurosci* (2011); Sedgwick. *BMJ* (2014); Ford and Norrie. *N Engl J Med* (2016); Loudon et al. *BMJ* (2015); Eichler et al. *Nat Rev Drug Discov* (2011)

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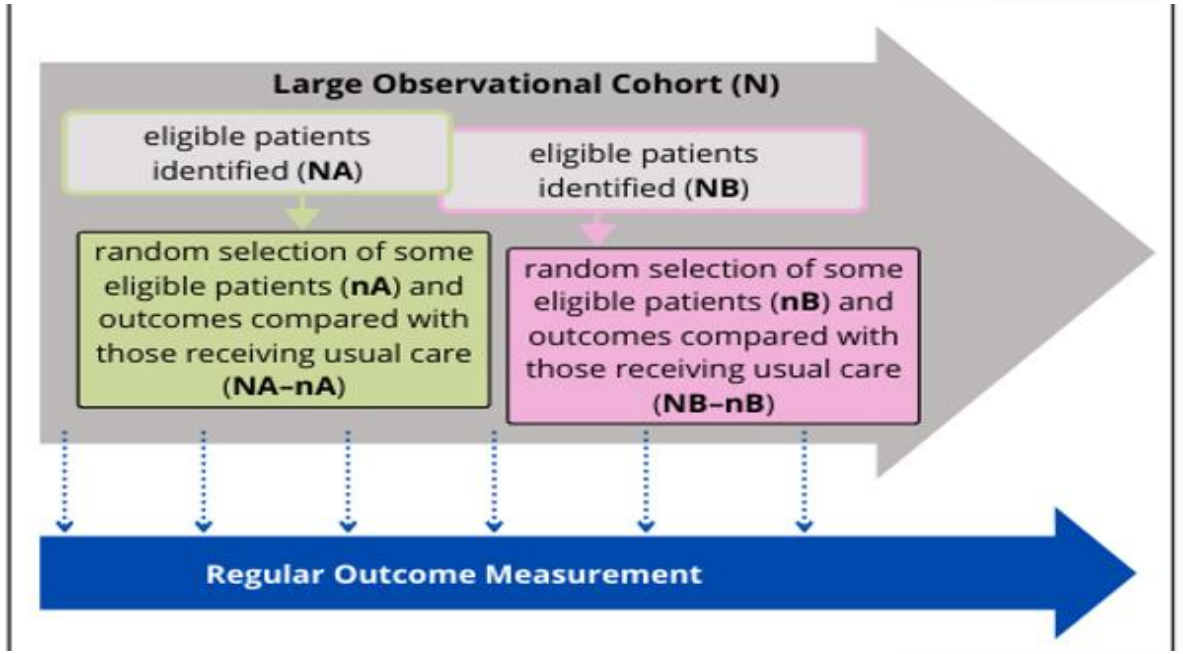
TWICS design



van der Velden et al. BMC Cancer (2016) 16:909
DOI 10.1186/s12885-016-2947-0

BMC Cancer

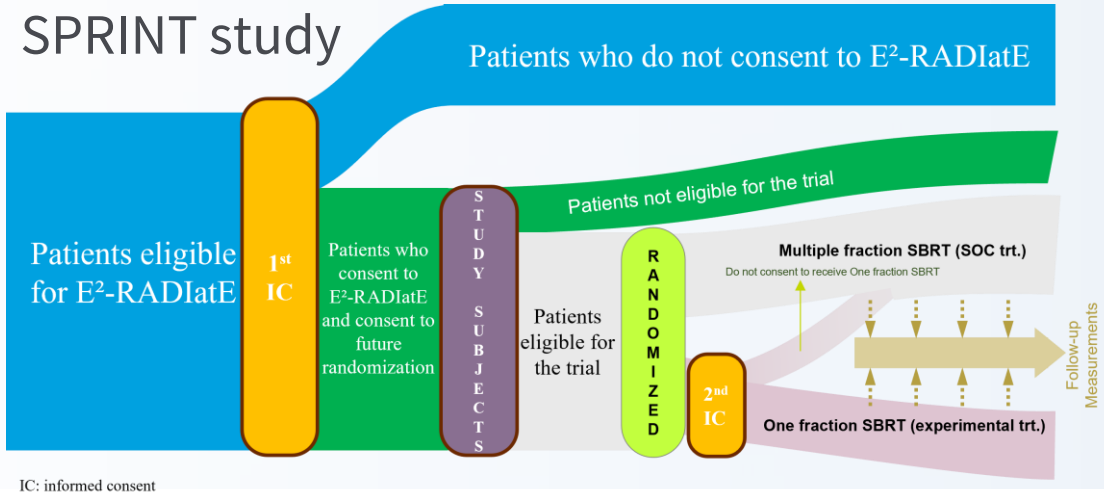
STUDY PROTOCOL Open Access

Comparing conVEntional RadioTherapy with stereotactIC body radiotherapy in patients with spinAL metastases: study protocol for an randomized controlled trial following the cohort multiple randomized controlled trial design

Joanne M. van der Velden[1*], Helena M. Verkooijen[1,2], Enrica Seravalli[1], Jochem Hes[1], A. Sophie Gerlich[1], Nicolien Kasperts[1], Wietse S. C. Eppinga[1], Jorrit-Jan Verlaan[3] and Marco van Vulpen[1]

Clare Relton et al. BMJ 2010; 340:bmj.c1066

EORTC 2387 SPRINT study



IC: informed consent

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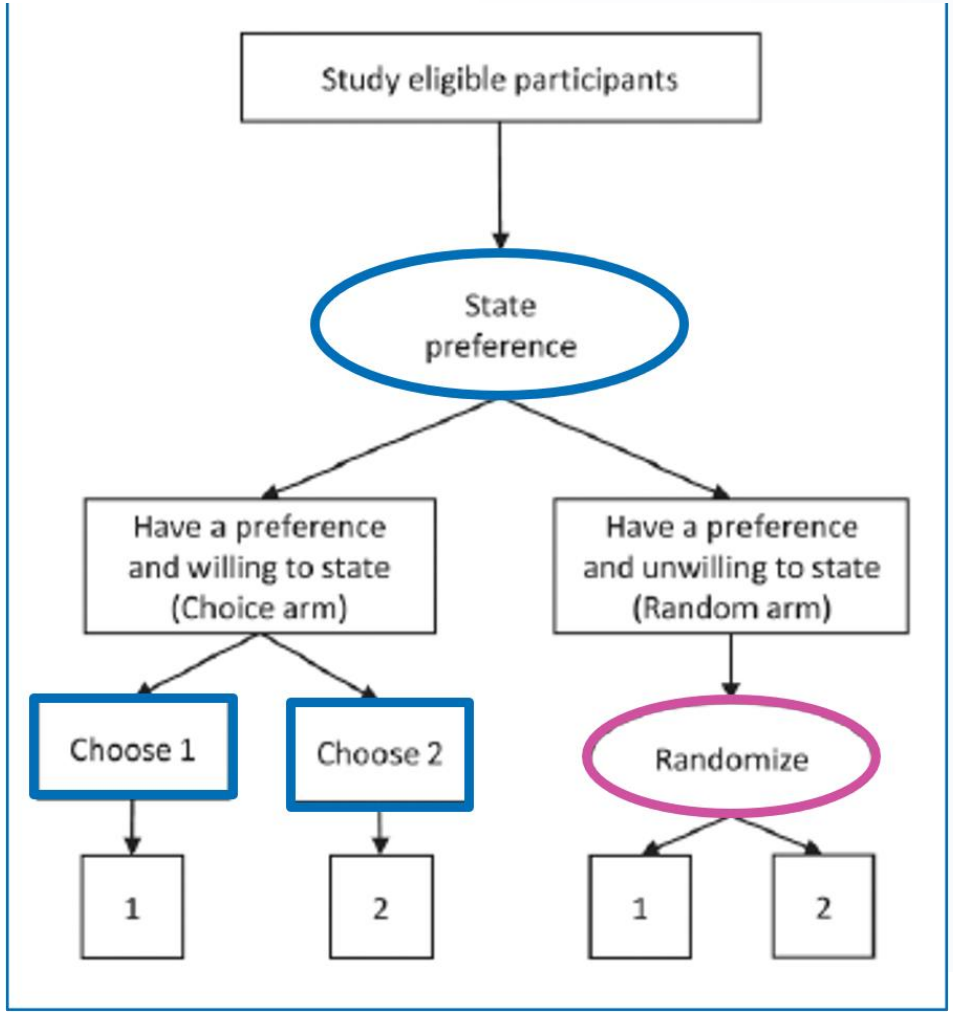
Designs including patients' preference



Partially randomized preference design (propensity score methodology)

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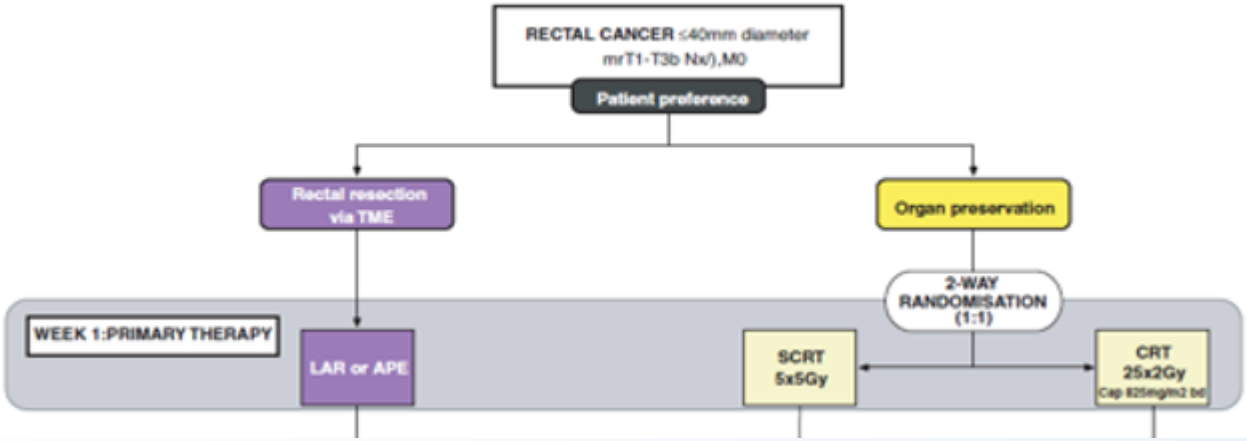
Designs including patients' preference

- SOC in rectal cancer = surgery alone by TME (total resection)
- Organ preserving approaches in early rectal cancer is a top research priority
- 2-step study
  - External phase 2 trial : feasibility of a 3-way randomisation
  - Modified phase 3 trial: switch to a partially randomised, patient preference design
    - TME preferred
    - Organ preserving approach preferred: randomisation to neoadjuvant CRT or SCRT

STAR-TREC TRIAL



Bach SP. STAR-TREC: An International Three-arm Multicentre, Partially Randomised Controlled Trial Incorporating an External Pilot. Clin Oncol (R Coll Radiol). 2023 Feb;35(2):e107-e109. doi: 10.1016/j.clon.2022.12.006. Epub 2022 Dec 26. PMID: 36577551.

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In conclusion

- Randomization is considered gold standard but patients included in RCTs are often highly selected and not representative of patients treated in clinical practice
- Conducting RCTs addressing questions on treatment optimisation and treatment de-escalation post marketing authorization is very challenging
- The additional collection of non-randomized data may help to strengthen the results of RCTs and may help to better assess the external validity of the results
- There is the need for pragmatic trials to address public health questions on treatment optimisation and treatment de-escalation and dedicated to patients not included in RCTs
- Pragmatic trials going beyond classical randomization are currently implemented in specific situation (radiotherapy trials, surgery trials, …) when classical randomization is not deemed feasible.

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