Sublobar wedge resection or stereotactic radiotherapy treatment of high-risk patients with early-stage lung cancer - a randomized, controlled trial – The STRADOS trial

Sublobær kileresektion eller stereotaktisk strålebehandling af højrisikopatienter med tidlig lungekræft – et randomiseret, kontrolleret studie STRADOS studiet

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DEPARTMENT OF CLINICAL MEDICINE

CTVS
Cardiothoracic and Vascular Surgery
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- Has been on the speaker bureaus for AstraZeneca and GlaxoSmithKline
- Has been in an Advisory Board for AstraZeneca

Hvorfor et nationalt RCT?

- Der er etableret en gruppe med viden, logistik set-up mv. omkring RCT studier i Danmark med deltagelse af bl.a. lungemedicinere og thoraxkirurger
- Igangværende studier:
  - *Intrapleural Fibrinolysis and DNase versus VATS for the treatment of pleural empyema: a randomized, controlled trial – FIVERVATS (status: 109 patienter inkluderet pr. 26. maj 2026)*
- Kommende studier:
  - *STRADOS*
  - *High risk lung nodule, management with biopsy route or direct to surgery - The BIO-CUT trial*

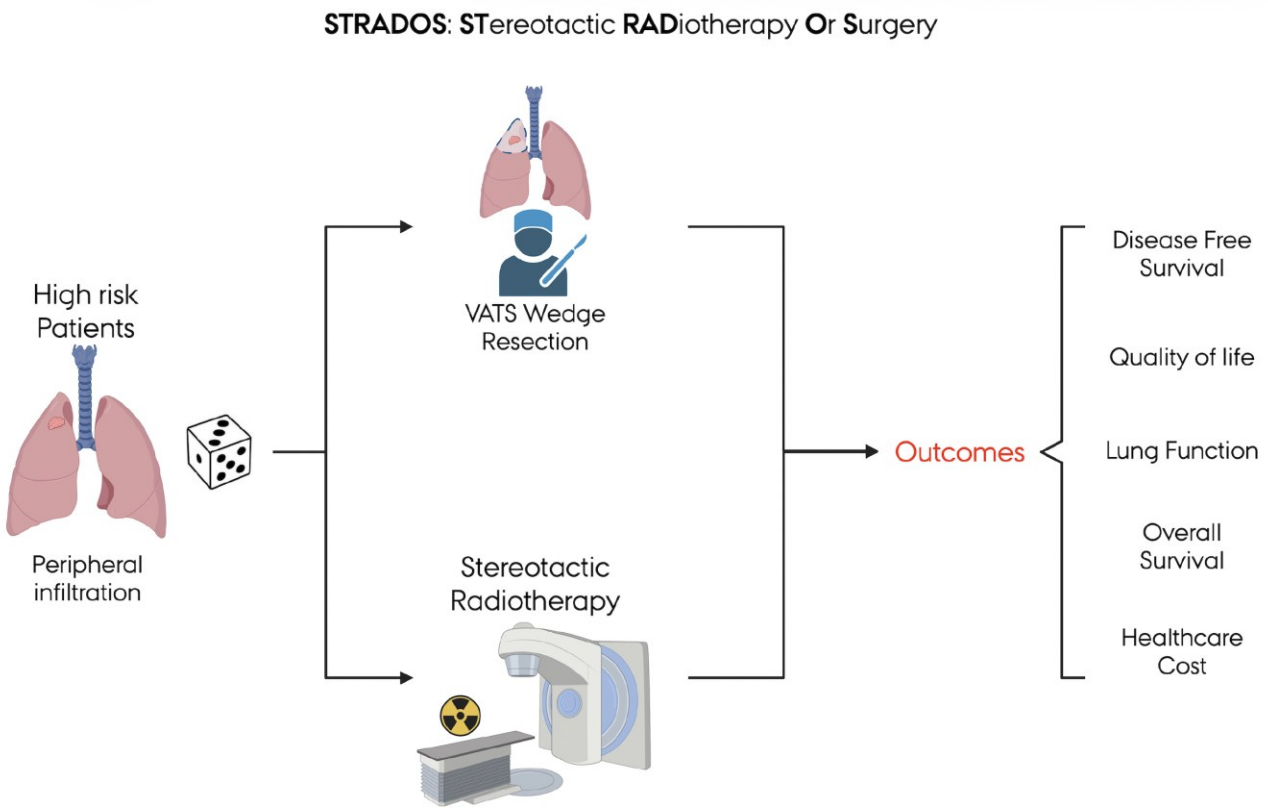
Baggrund (1)

- Clinical practice:
  - Low-risk patient:
    - Minimal invasive surgery with an anatomical resection (lobectomy or segmentectomy) and mediastinal lymph node sampling
  - High-risk patient:
    - Surgery with a wedge resection (SWR) and mediastinal lymph node sampling
  - Medically inoperable patients:
    - Stereotactic Body Radiation Therapy (SBRT)
- Systematic reviews and meta-analysis concluded that based on the non-randomized studies the outcome after SWR is probably better than after SBRT, but they all called for RCT
- Two RCT have been initiated but both terminated before inclusion of the number of planned patients were reached due to slow recruiting. In the two trials, merely 58 patients were included, and analysis indicated better outcome in the SBRT group

Baggrund (2)

- Three relevant studies at www.clinicaltrials.gov:
  - POSTILV study (NCT01753414) and VALOR study (NCT02984761):
    - investigate anatomical resections (segmentectomy and lobectomy) with SBRT in low-risk patients
  - STABLE-MATE study (NCT02468024):
    - Compares SWR to SBRT in high-risk patients with 3-year OS as primary outcome
    - Secondary endpoints are merely progression free survival and radiation toxicity.
    - US-based study
    - Informed consent obtained after patients are made aware of the randomized assignment, which entails attrition bias
    - Start July 2015, estimated finished enrollments of patients: December 2028
    - Despite the differences to our study, the results are very likely to complement each other

Grafisk abstract



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Overview

- Study objectives:
  - The overall purpose of this randomized, controlled trial is to investigate the 3-year DFS among high-risk patients with stage I NSCLC comparing SWR including lymph node sampling with SBRT (intervention)
- Design:
  - Randomized, controlled study (phase III trial)
  - Not blinded (open label)
  - National multicenter study including all thoracic surgical departments and relevant departments of oncology and pulmonology in Denmark
  - Endpoint are measured with the date of randomization as index
- 182 patients needs to be included

Interventions

SBRT:

– Planning target volume (PTV) is covered by 45 Gy ($V45Gy_{PTV}$ > 98%) over three fractions, 2-3 fractions / week

Surgery:

– Minimal invasive (VATS/RATS) sublobar wedge (SWR) resection with lymph node sampling

Endpoints

Primary endpoint

- DFS of patients treated with either surgery (SWR) or SBRT after 3 years

Secondary endpoint

- Quality of life after 1, 3, 6, 12 and 36 months

Tertiary endpoints

- Overall survival after 3 and 5 years.
- The 5-year DFS
- The 2-, 3- and 5-year loco-regional recurrence rate
- Re-admissions following treatment, adverse reactions and complications ranked by Clavien-Dindo classification, Comprehensive Complication Index (CCI) and Common Toxicity Criteria for Adverse Events (CTCAE) version 5 (32) grade 2 or more after 1, 3, 6, 12 and 36 months
- Cost-utility and healthcare related costs with 12 and 36 months of follow-up
- PRO data – other than quality of life (health condition, symptoms and functional level) after 1, 3, 6, 12 and 36 months
- Lung function test after 12 month

Inclusion criteria

- Age ≥ 18 years
- Biopsy-proven NSCLC
- Diagnostic codes: DC34, DC 34.1, DC 34.2, DC 34.3 or DC 34.9
- Clinical stage I NSCLC according to the 9th edition of TNM
- Performed diagnostic PET-CT and supplementary invasive procedures for staging purposes in accordance with the Danish national reference program for the staging and treatment of lung cancer 9th edition TNM staging: cT1aN0M0, cT1b-cN0M0, cT1cN0M0 and cT2aN0M0 (clinical stage I)
- Tumor is localized in the outer third of the lung and considered technically resectable by SWR, as well as treatable with peripheral SBRT when assessed during MDT conference
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) = 0-2.
- Preoperative pulmonary function test according to national guidelines performed within 6 weeks before the MDT conference
- Patient fulfills the “high-risk patient” criteria

Exclusion criteria

- Declared terminally ill or life expectancy shorter than one year.
- Multifocal disease
- PS ≥ 3
- Centrally located tumors not eligible to SBRT
- Previous ipsilateral lung surgery
- Pregnancy or breastfeeding.
- Inability to understand oral and written informed consent
- Intravenous substance abuse or severe alcohol abuse (> 25 units per week)
- Not amendable for surgery in general anesthetic
- Previous radiotherapy to the thorax, which may limit the feasibility or increase the risk of stereotactic reirradiation due to cumulative dose constraints and potential toxicity
- Diagnosed with Interstitial lung disease (ILD)

Definition of a high-risk patient

For the purpose of this study, the following criteria defining a “high-risk patient” have been chosen. These criteria are all cardiopulmonary comorbidities (apart from age) and are used for the rest of this study protocol. A high-risk patient is a patient that fulfills at minimum one of the main-risk criteria and/or two of the secondary criteria:

Main criteria:

- FEV-1 ≤ 50% and/or
- DLCO ≤ 50%

Secondary criteria:

- Age ≥ 80
- FEV-1 = 51-60% and/or DLCO = 51-60%
- Known pulmonary hypertension with PAP ≥40 mm Hg diagnosed < 6 months before inclusion
- Known LVEF ≤ 40% diagnosed < 6 months before inclusion

Er patienterne der så…?

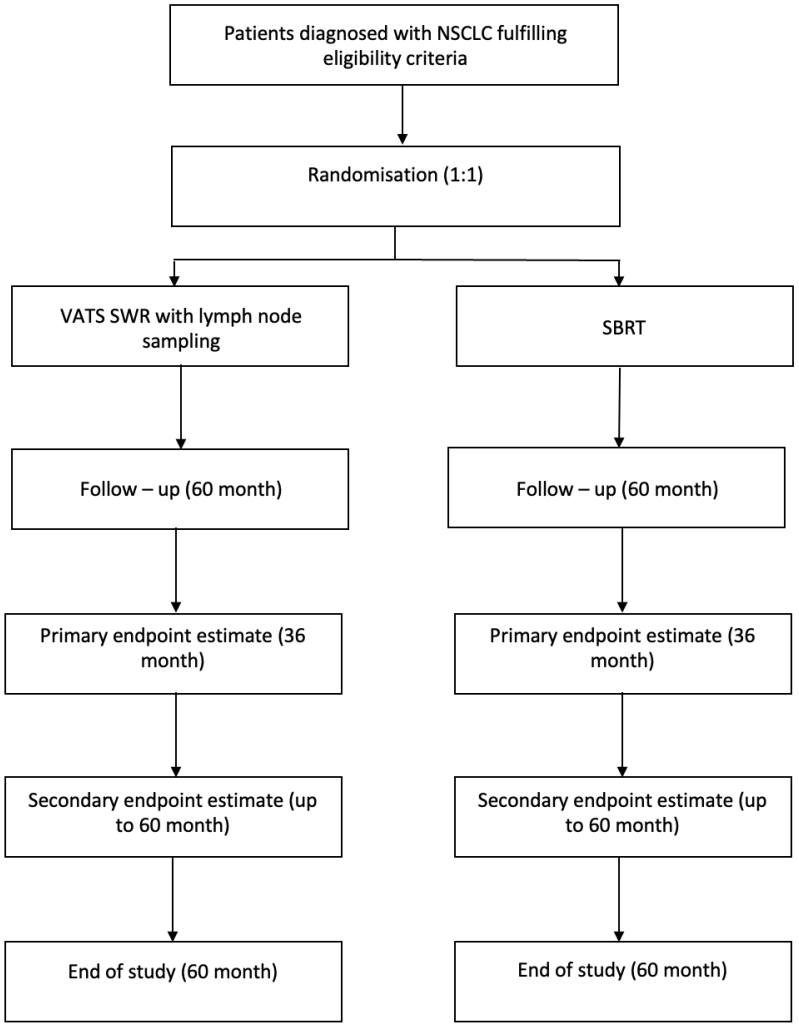
We have briefly estimated the potential fraction of patients who are candidates for inclusion using data from different centres (Vejle Hospital and Aarhus University Hospital) and using the Danish Lung Cancer Database[1] and found that the figure is 200 patients per year in Denmark and with a 75% acceptance to participate in the study approximately 150 patients can be included per year. However, based on experience, the inclusion rate is always lower that expected. A conservative estimate is accordingly 75 patients included per year, it will take approximately 3 years to include 200 patients and hereby accounting for the expected 10% drop-out rate resulting in the required 182 patients.

[1]*Data provided in 2025 by consultant Torben Riis Rasmussen, Aarhus University Hospital and consultant Morten Hornemann Borg, Vejle Hospital.*

Sample size and power calculation

- The sample size calculation is based on the primary endpoint: 3-year DFS.
- The standard/control treatment is SWR and the comparator/intervention is SBRT, and it set to be 70% and 50%, respectively.
- The sample size is calculated with the 2-sided significance level of 0.05 and 80% statistical power, and hence 182 patients needs to be included (91 patients in each of the two groups), and with an expected dropout of approximately 10%, a total of 200 patients will be included.

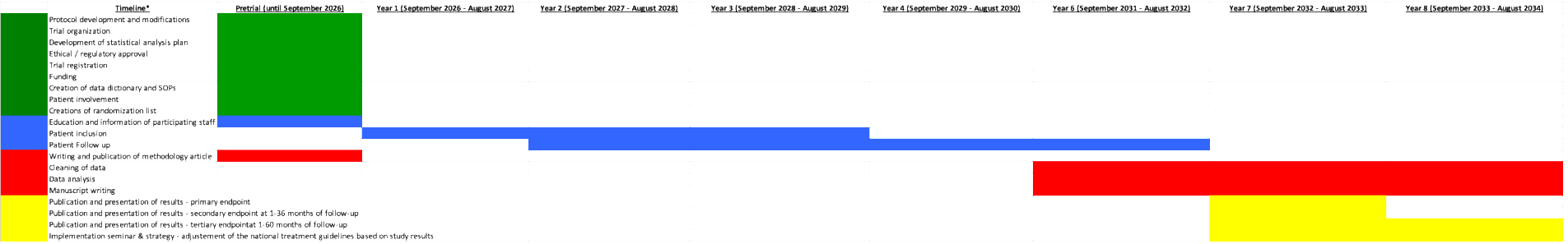
Flow diagram



Timeline with the interventions, controls etc.

	Screening (before and during MDT)	Baseline (at inclusion)	End of SBRT or at discharge after SWR	Follow-up at 1, 3, 6, 12, and 36 month
Informed consent		x		
Demographics[1]	x			
Prescribed medication	x		x	x
Comorbidity	x			
Physical examination and clinical control incl. PS	x		x	x[2]
Pulmonary function tests (FEV1, DLCO)	x	x		x[3]
ECG	x			
Adverse events			x	x
Contrast enhanced CT of the thorax and upper abdomen	x			x[4]
PET/CT	x			
Lung perfusion scintigraphy / SPECT	x			
pTNM			x[5]	
Quality of life assessment		x	x	x
PRO-data		x	x	x
Health-care related cost analysis and epidemiological data	At 12 and 36 months			
Decision regret	At 3 month, and each year			

Gantt diagram



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Praktik vedr. inklusion af patienter

- Patienter identificeres ved den enkelte MDT
  - Region Midt
  - Region Nord
  - Region Syddanmark
  - Region Hovedstaden
  - Region Sjælland (via MDT med Region Syddanmark eller Region Hovedstaden)

Logistik

Information og inklusion af patienter

- Videnskabsetisk komite har forlangt fysisk fremmøde mht. information og inklusion i projektet …..
- Hvorfor information ved udredende lungemediciner?
  - Giver logistisk mening
  - Lungemedicineren er den mindst biased mht. SBRT versus SWR

Inklusion af patienter (uddrag af SOP)

- Alle patienter diskuteres på lungekræft - MDT efter lokalt set-up
- Præ-MDT: Potentielle kandidater kan evt. identificeres som led i MDT-oplæg, hvor projektkoordinator og også gerne udredende lungemediciner screener oplæg i forbindelse med booking til MDT
- MDT: Identifikation af potentielle kandidater til STRADOS iht. flyer
- MDT – screeningslog: MDT-vurdering indgår som led i screeningslog
- Potentielle fundne kandidater til STRADOS indkaldes til fysisk samtale ved den lokale / udredende lungemediciner. Hvis MDT-svaret foregår telefonisk / virtuel indkaldes patienten til supplerende fysisk samtale
- Den lokale / udredende lungemediciner giver umiddelbart besked til den lokale projektkoordinator (initialt på AUH og OUH), som hurtigt randomisere patienten on-line via REDCap
- Den lokale / udredende lungemediciner henviser den randomiserede patient til den allokerede behandling

MDT

Definition af en højrisikopatient:
En højrisikopatient er en patient, der opfylder mindst et af hovedrisikokriterierne og/eller to af de sekundære kriterier:
Hovedkriterier:

- FEV-1 ≤ 50% og/eller
- DLCO ≤ 50%

Sekundære kriterier:

- Alder ≥ 80
- FEV-1 = 51-60% og/eller DLCO = 51-60%
- Kendt pulmonal hypertension med PAP ≥40 mm Hg diagnosticeret < 6 måneder før inklusion
- Kendt LVEF ≤ 40% diagnosticeret < 6 måneder før inklusion

Inklusionskriterier:

- Alder ≥ 18 år
- Biopsiverificeret NSCLC
- Diagnostiske koder: DC34, DC 34.1, DC 34.2, DC 34.3 eller DC 34.9
- Klinisk stadium I NSCLC i henhold til 9. udgave af TNM
- Udført diagnostisk PET-CT og supplerende invasive procedurer til stadieinddeling i overensstemmelse med det danske nationale referenceprogram for stadieinddeling og behandling af lungekræft
- 9. udgave af TNM-stadieinddeling: cT1aN0M0, cT1b-cN0M0, cT1cN0M0 og cT2aN0M0 (klinisk stadium I)
- Tumor er lokaliseret i den ydre tredjedel af lungen og anses for teknisk resektabel ved kileresektion, samt behandling med perifer SBRT ved vurdering under MDT-konference
- PS = 0-2
- Præoperativ lungefunktionstest i henhold til nationale retningslinjer udført inden for 6 uger før MDT-konferencen
- Patienten opfylder kriterierne for "højrisikopatient" som beskrevet ovenfor

Eksklusionskriterier:

- Erklæret uhelbredelig syg eller forventet levetid kortere end et år.
- Multifokal sygdom
- PS ≥ 3
- Centralt beliggende tumorer, der ikke er egnet til SBRT
- Tidligere ipsilateral lungekirurgi
- Graviditet eller amning.
- Manglende evne til at forstå og afgive mundtligt og skriftligt informeret samtykke
- Intravenøst stofmisbrug eller stort alkoholforbrug (> 25 enheder pr. uge)
- Kan tåle kirurgi i fuld narkose
- Tidligere strålebehandling af thorax, som kan begrænse muligheden for eller øge risikoen for stereotaktisk genbestråling på grund af kumulative dosisbegrænsninger og potentiel toksicitet
- Diagnostiseret med interstitiel lungesygdom (ILD)

Status (1)

- Alle relevante afdelinger og fagpersoner har sagt ja til at deltage.
- De internationale samarbejdspartnere har accepteret involvering i studiet.
- Endorsement/støtte fra de videnskabelige selskaber
- Studiet er godkendt af Videnskabsetisk komite (april 2026)
- Anmeldt på Clinicaltrials.gov
- Databehandleraftalen er godkendt
- Samarbejdsaftalerne er udarbejdet, udsendt og forventes at være underskrevet af alle medio 2026.
- Funding / økonomisk støtte:
  - Ansøgt støtte til Kræftens Bekæmpelse i januar 2026 – afslag maj 2026☹
  - Vil yderligere søge/har ansøgt medio 2026:
    - Danmarks Frie Forskningsfond (DFF), Alfred Benzon Fonden, Skibsreder Per Henriksen, R. og Hustrus Fond samt Novo Nordisk fonden

Status (2)

- Patientinvolveringsplanen er igangsat
- Vi er i gang med at teste REDCap databasen
- Det nationale samarbejde er etableret bl.a. ved gennemførelsen af det nationale, randomiserede studie om den bedste behandling af pleura empyem (infektion i lungehulen).
  - Vi anvender vores erfaring og samarbejde ml. bl.a. thoraxkirurger og lungemedicinere herfra til gennemførelsen af dette studie
- Vi planlægger at starte inklusion af patienter 1. september 2026

Mere info….

- Primær protokol (version 19) på i alt 32 sider
- Appendixer:

1. Participating departments and contact persons
2. Standard operating procedures (SOP)
3. Budget
4. Table displaying a timeline the with intervention, controls etc.
5. Declaration of consent
6. Patient information
7. CONSORT Flow Diagram
8. Protocol for the qualitative study
9. Study GANTT diagram
10. iDMC charter
11. Graphical abstract
12. Cooperation agreements
13. Data management agreements
14. Danish summary
15. Endorsements
16. Standard text for the epicrisis
17. Quality of life schemes
    a. EORTC QLQ-LC13
    b. EORTC QLQ-LC29
    c. EQ-5D-5L
18. RM oplysningspligt ifm. Forskningsprojekt
19. Projekt resume (lægmand til VEK)
20. Standard text when patients are identified at the MDT
21. Standard text when patients are included
22. Standard text when patients are randomized

1. artikel er næsten færdigskrevet..

Sublobar wedge resection or stereotactic radiotherapy treatment of high-risk patients with early-stage lung cancer - a randomized, controlled trial

The STRADOS trial

Thomas Decker Christensen,[1,2*] Rene H Petersen , Peter B Licht, T Schytt, WM Szejniuk, Asger R Pedersen, Tina B Nielsen, Søren H Skaarup, Niels L Christensen, Torben R Rasmussen, Niels L Christensen, Marianne Knap, Zaigham Saghir, Lone Hoffmann, Tine B Nielsen, Morten H Borg, O Hilberg, Gitte Persson, Kira S Simonsen, Rana Bibi, Mette Pøhl, Klaus R Larsen, Lars Møller, Anne O Ording, Flemming W Udsen, Uffe Bødtger, Amanda Dandanell Juul, Arman Ashad, Hiran Fernando, Yaron Shargall, Robert Timmermann, Matthias Guckenberger, Najib N Rahman, Christian B. Laursen, [16,17]

In preparation BMJOpen 2026

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Spørgsmål.....

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