Surgery for Early-Stage NSCLC

MA03.07, MA03.11, M15.03

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Outcomes of Older Patients in CALGB 140503 (Alliance): Lobar vs Sublobar Resection for Peripheral Stage IA Non-Small Cell Lung Cancer

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Lobar or Sublobar Resection for Peripheral Stage IA Non–Small-Cell Lung Cancer

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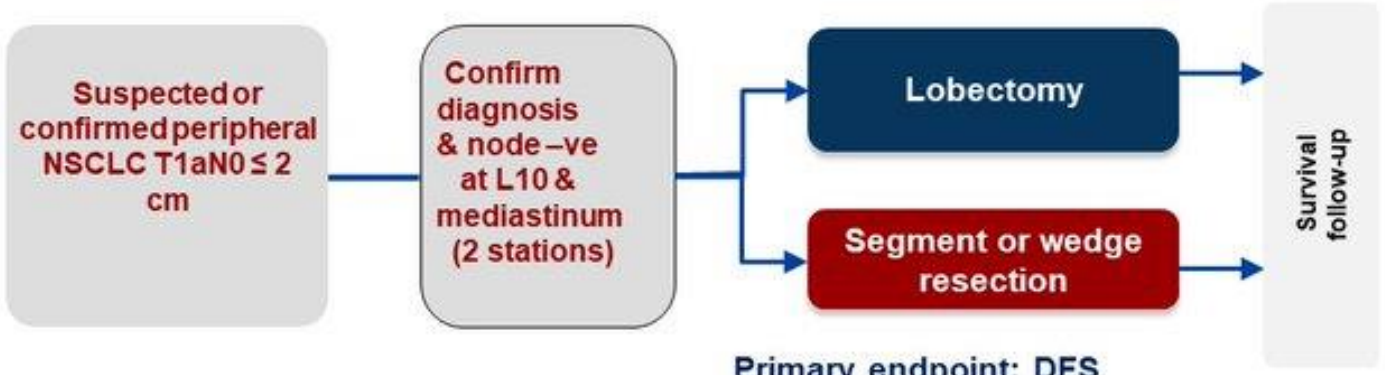
https://acknowledgments.alliancefound.org

ClinicalTrials.gov number: NCT00499330

Introduction

CALGB 140503: Phase III randomized trial comparing lobectomy and sublobar resection for small-sized carcinoma



Stratification factors
- tumor size (<1,1-15,1.6-2)
- Ever/never smokers
- Squamous/adenocarcinoma

Primary endpoint: DFS

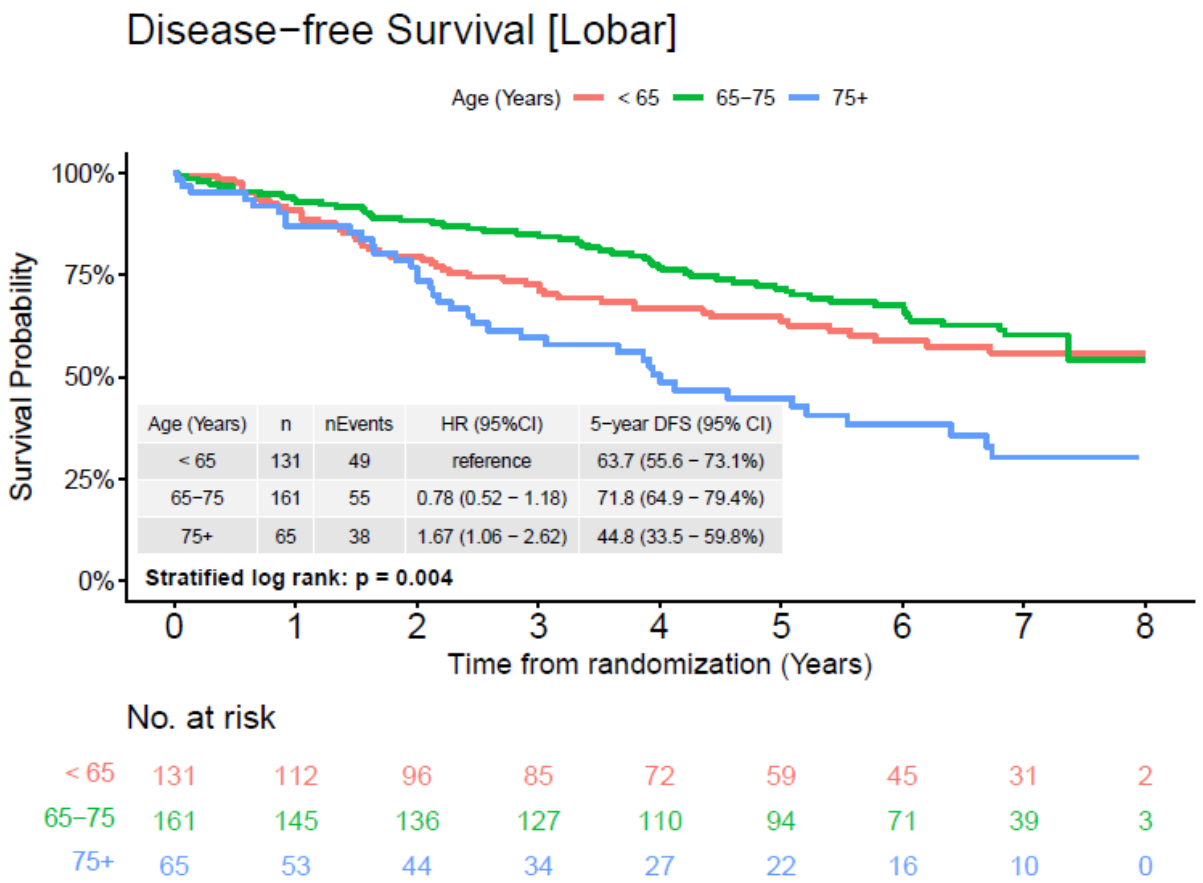
secondary endpoints
- OS
- PFTs at 6 months
- Rates of loco-regional and systemic recurrence

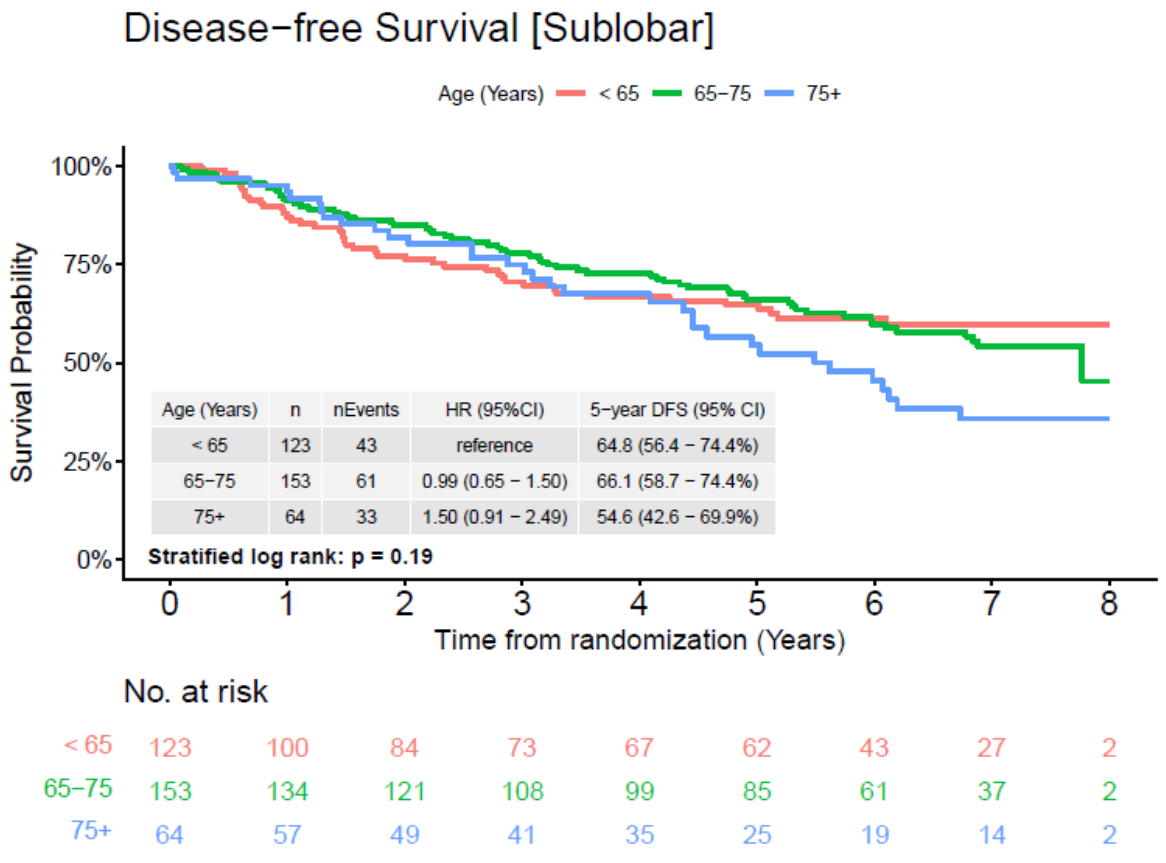
Conclusion: Sub-lobar resection not inferior to lobar resection for NSCLC patients with small peripheral tumors

Patients and Methods

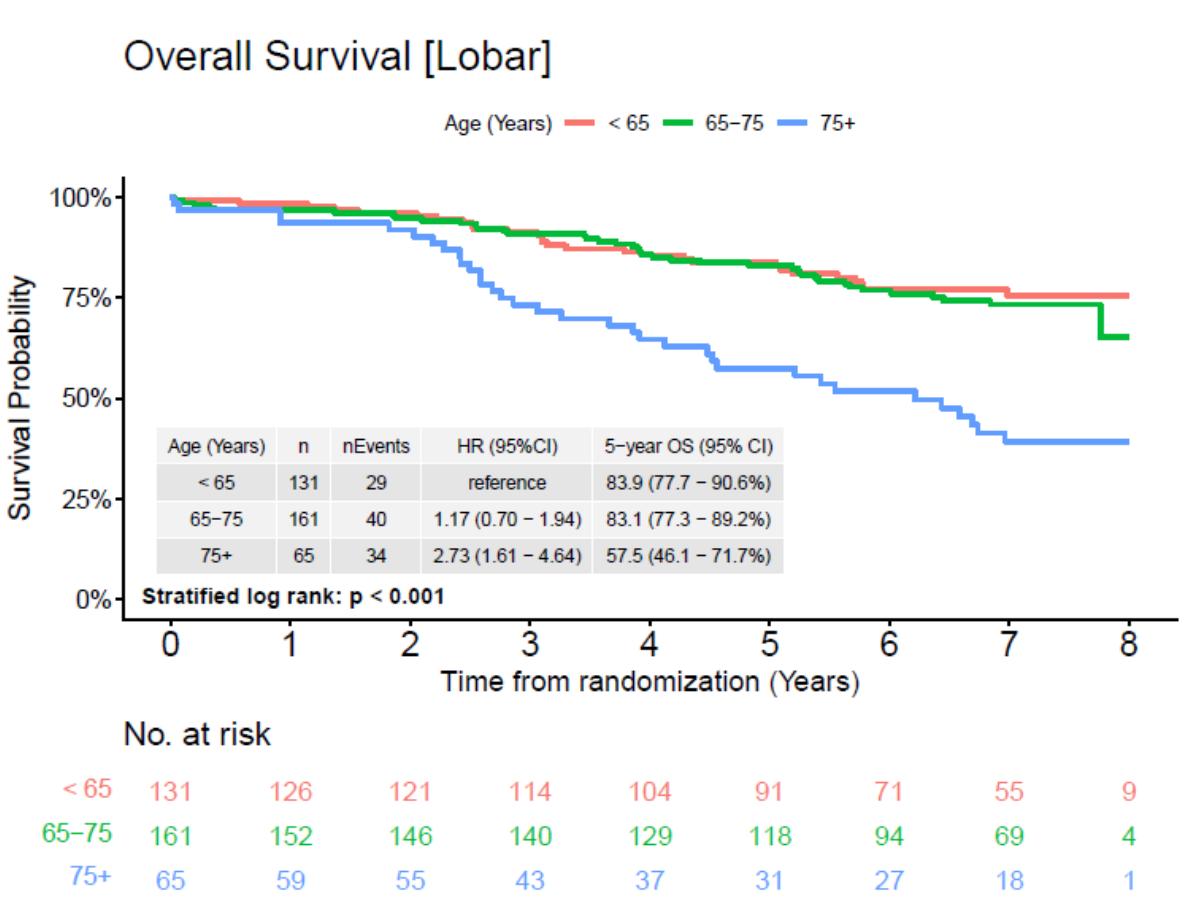
- Patients enrolled on CALGB 140503 were categorized into 3 groups based on age: <65 years, 65-75 years and >75 years.
- Baseline characteristics, surgical approaches, pathological findings, DFS, overall survival OS, ≥grade 3 AEs and 90-day mortality were compared
- Comparison of continuous variables - Kruskal-Wallis test; discrete variables - chi-square or Fisher's exact test
- Survival outcomes - stratified log-rank test

Results - DFS

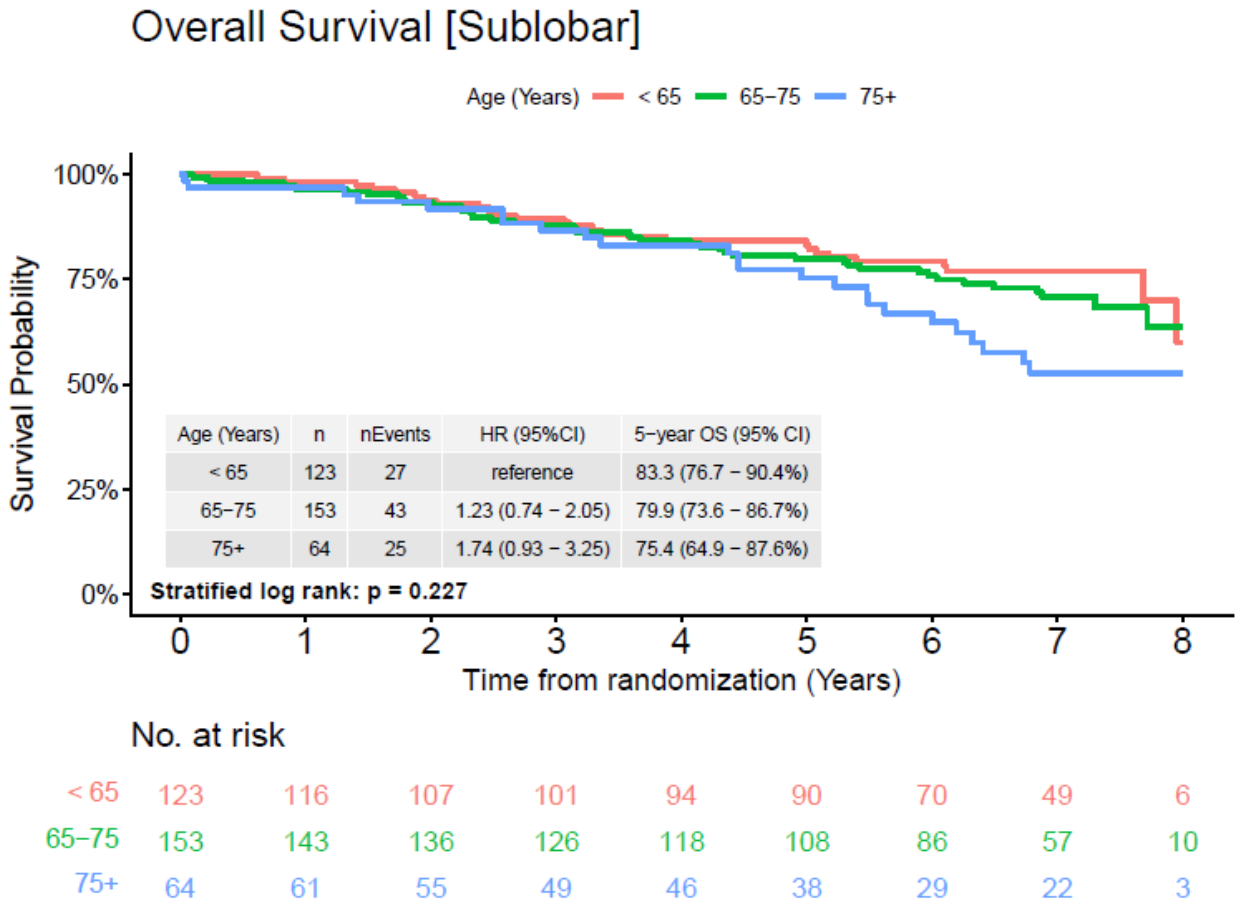

Disease−free Survival [Lobar]
Age (Years) < 65 65−75 75+
Survival Probability
100%
75%
50%
25%
0%
0 1 2 3 4 5 6 7 8
Time from randomization (Years)
Age (Years) | n | nEvents | HR (95%CI) | 5−year DFS (95% CI)
< 65 | 131 | 49 | reference | 63.7 (55.6 − 73.1%)
65−75 | 161 | 55 | 0.78 (0.52 − 1.18) | 71.8 (64.9 − 79.4%)
75+ | 65 | 38 | 1.67 (1.06 − 2.62) | 44.8 (33.5 − 59.8%)
Stratified log rank: p = 0.004
No. at risk
< 65 131 112 96 85 72 59 45 31 2
65−75 161 145 136 127 110 94 71 39 3
75+ 65 53 44 34 27 22 16 10 0


Disease−free Survival [Sublobar]
Age (Years) < 65 65−75 75+
Survival Probability
100%
75%
50%
25%
0%
0 1 2 3 4 5 6 7 8
Time from randomization (Years)
Age (Years) | n | nEvents | HR (95%CI) | 5−year DFS (95% CI)
< 65 | 123 | 43 | reference | 64.8 (56.4 − 74.4%)
65−75 | 153 | 61 | 0.99 (0.65 − 1.50) | 66.1 (58.7 − 74.4%)
75+ | 64 | 33 | 1.50 (0.91 − 2.49) | 54.6 (42.6 − 69.9%)
Stratified log rank: p = 0.19
No. at risk
< 65 123 100 84 73 67 62 43 27 2
65−75 153 134 121 108 99 85 61 37 2
75+ 64 57 49 41 35 25 19 14 2

Results - OS



Age (Years)	n	nEvents	HR (95%CI)	5−year OS (95% CI)
< 65	131	29	reference	83.9 (77.7 − 90.6%)
65−75	161	40	1.17 (0.70 − 1.94)	83.1 (77.3 − 89.2%)
75+	65	34	2.73 (1.61 − 4.64)	57.5 (46.1 − 71.7%)



Age (Years)	n	nEvents	HR (95%CI)	5−year OS (95% CI)
< 65	123	27	reference	83.3 (76.7 − 90.4%)
65−75	153	43	1.23 (0.74 − 2.05)	79.9 (73.6 − 86.7%)
75+	64	25	1.74 (0.93 − 3.25)	75.4 (64.9 − 87.6%)

Results – Outcomes based on age groups

		<65 years	65-75 years	>75 years	P-value
5-yr DFS % (95% CI)	Lobar	63.7 (55.6 – 73.1)	71.8 (64.9 – 79.4)	44.8 (33.5 – 59.8)	0.004
	Sublobar	64.8 (56.4 – 74.4)	66.1 (58.7 – 74.4)	54.6 (42.6 – 69.9)	0.19
5-yr OS % (95% CI)	Lobar	83.9 (77.7 – 90.6)	83.1 (77.3 – 89.2)	57.5 (46.1 – 71.7)	<0.001
	Sublobar	83.3 (76.7 – 90.4)	79.9 (73.6 – 86.7)	75.4 (64.9 – 87.6)	0.23
≥grade 3 AE n (%)	Lobar	17 (13%)	27 (16.8%)	11 (16.9%)	0.63
	Sublobar	12 (9.8%)	22 (14.4%)	13 (20.3%)	0.14
90-day mortality n (%)		1 (0.4%)	5 (1.6%)	4 (3.1%)	0.09

Conclusions

- Older patients tolerated surgical resection in CALGB 140503 well,
  - Similar adverse events and 90-day mortality as younger patients
- The reasons for a lower DFS and OS in patients >75 who underwent a lobectomy need to be studied further
- Surgical resection for early-stage NSCLC should be offered to all appropriate patients regardless of age

Postoperative Complications Compromised Disease-Free and Recurrence-Free Survival in CALGB 140503 (Alliance) Trial Patients

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Perioperative mortality and Morbidity after Lobar versus Sublobar Resection for early stage lung cancer: A post-hoc analysis of an international randomized phase III trial (CALGB/ Alliance 140503)

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Perioperative mortality was defined as death from any cause within 30 and 90 days of surgical intervention and was calculated on all randomized patients.

Morbidity was graded using the Common Terminology Criteria for Adverse Events (CTCAE v4.0). All analyses were done on an intention to treat basis.

	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)	Grade 5 (fatal)
Cardiovascular					
Atrioventricular heart block					
Lobar resection	1 (<1%)	0	0	0	0
Sublobar resection	0	0	0	0	0
Cardiac ischaemia or infarction					
Lobar resection	0	0	3 (1%)	2 (1%)	0
Sublobar resection	0	0	0	0	1 (<1%)
Hypertension					
Lobar resection	4	2	1 (<1%)	0	0
Sublobar resection	0	2	0	0	0
Hypotension					
Lobar resection	3 (1%)	10 (3%)	1 (1%)	0	0
Sublobar resection	2 (1%)	6 (2%)	4 (1%)	0	0
Left-ventricular diastolic dysfunction					
Lobar resection	0	0	0	0	0
Sublobar resection	1	0	0	0	0
Pulmonary hypertension					
Lobar resection	1 (<1%)	0	0	0	0
Sublobar resection	0	0	0	0	0

- Cardiovascular (AV block, ischemia, HTN, HYPOTN, arrhythmia, etc.)
- Hemorrhage (local or CVA)
- Infection (PNA, wound infection, UTI, sepsis, etc.)
- Neurological (confusion, pain)
- Pulmonary (ARDS, aspiration, air leak, PTX, etc.)
- Surgical (intra-op injury)
- Vascular (thrombus or embolism)

Lancet Respir Med. 2018 December ; 6(12): 915–924. doi:10.1016/S2213-2600(18)30411-9.

CALGB 140503

Adverse Events (30 Days of Surgery)

	Lobar resection (n=355)*	Sublobar resection (n=337)*	Difference (95% CI)
Grade 1 event	64 (18%)	75(22%)	−4.2% (−10.2 to 1.8)
Grade 2 event	75(21%)	49 (15%)	6.6% (0.9 to 12.3)
Grade 3 event	37 (10%)	41(12%)	−1.7% (−6.6 to 30)
Grade 4 event	13 (4%)	5(1%)	2.2% (−0.2 to 4.9)
Grade 5 event	4 (1%)	2(1%)	0.5% (−1.1 to 2.3)

*

No complications in 47% of patients (LR 46%, SLR 49%)
Grade 3/4/5 AEs occurred in 15.2% (LR) and 14.2% (SLR)
Grade 3 hemorrhage (transfusion) in 1.6% (LR) and in 2.3% (SLR)
Prolonged air leak 2.5% (LR) and in 0.6% (SLR)
No statistical difference between treatment arms

Methods

- Between 6/2007 and 3/2017, 697 patients were randomized to LR (357) or SLR (340)
  - **80.2% of the resections were via VATS approach. No RATS procedures.**
- Adverse events (1-5) were graded using the AEs version 4.0 and were grouped
  - Low-Grade group (AEs ≤ 2) and a High-Grade group (AEs ≥ 3).
  - Grade 5 AE (Death) was excluded from survival analyses.
- **Survival endpoints were estimated by the Kaplan–Meier estimator and tested by stratified Log-rank test.** The Chi-square test was used to compare the distribution of LG AEs vs HG AEs among various groups. Overall, Disease-free, Recurrence-free, Locoregional recurrence-free and Distant recurrence-free survivals were calculated.

Association between High Grade AE and Type of Surgical Treatment

	Lobar(n = 357)	Sublobar(n = 340)
No/Low Grade AE	302 (84.6%)	293 (86.2%)
High Grade AE	55 (15.4%)	47 (13.8%)

P-value: 0.555

Association between High Grade AE and Surgical Procedure

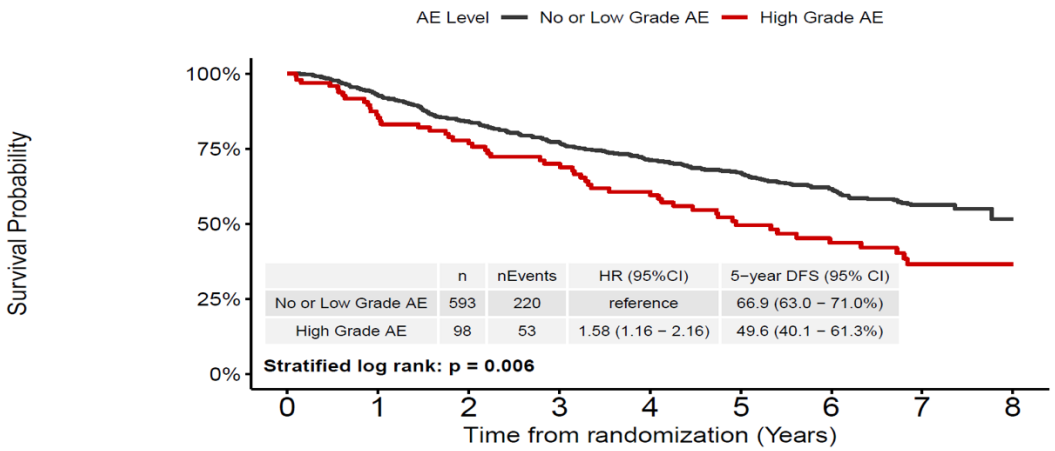
	Lobectomy(n = 362)	Segment(n = 131)	Wedge(n = 204)
No/Low Grade AE	305 (84.3%)	108 (82.4%)	182 (89.2%)
High Grade AE	57 (15.7%)	23 (17.6%)	22 (10.8%)

P-value: 0.159

Association between High Grade AE and Site Volume

	Low(n = 210)	Medium(n = 257)	High(n = 230)
No/Low Grade AE	180 (85.7%)	211 (82.1%)	204 (88.7%)
High Grade AE	30 (14.3%)	46 (17.9%)	26 (11.3%)

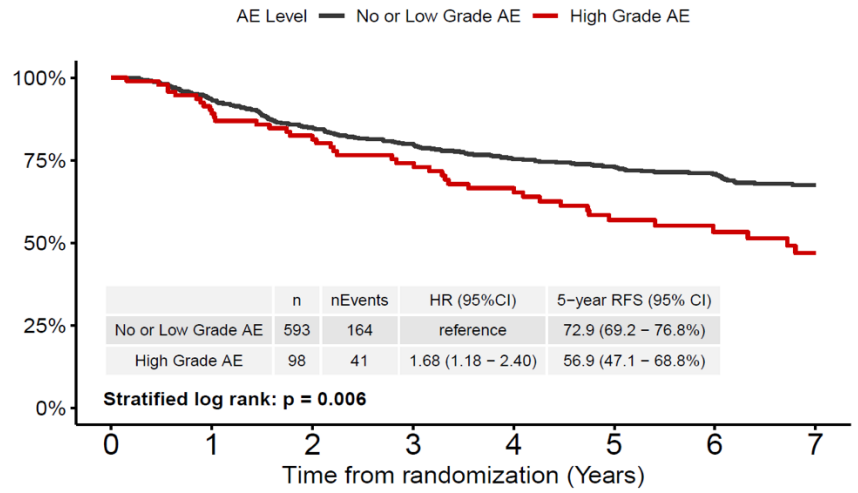
Disease-free Survival



	n	nEvents	HR (95%CI)	5-year DFS (95% CI)
No or Low Grade AE	593	220	reference	66.9 (63.0 – 71.0%)
High Grade AE	98	53	1.58 (1.16 – 2.16)	49.6 (40.1 – 61.3%)

Stratified log rank: p = 0.006

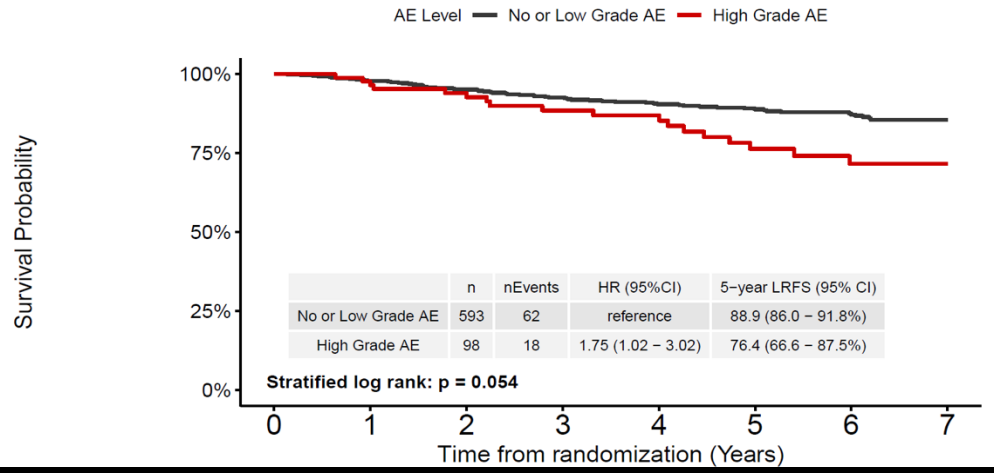
Recurrence-free Survival



	n	nEvents	HR (95%CI)	5-year RFS (95% CI)
No or Low Grade AE	593	164	reference	72.9 (69.2 – 76.8%)
High Grade AE	98	41	1.68 (1.18 – 2.40)	56.9 (47.1 – 68.8%)

Stratified log rank: p = 0.006

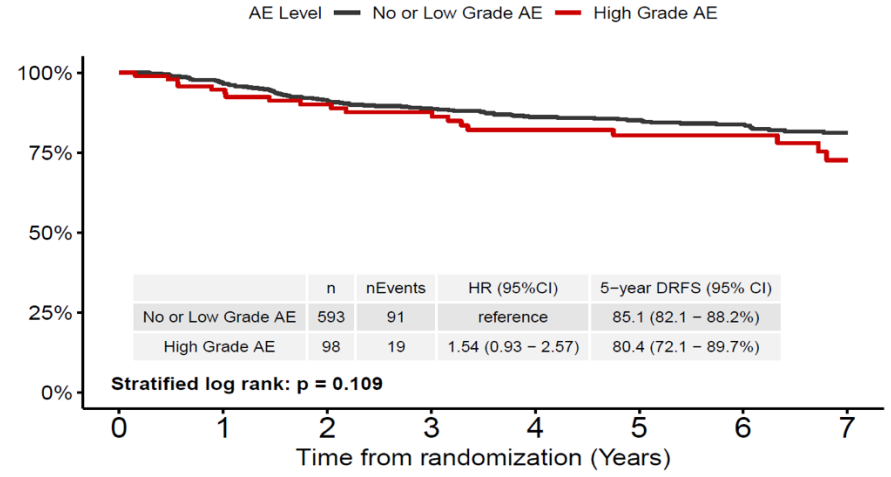
Locoregional Recurrence-free Survival



	n	nEvents	HR (95%CI)	5-year LRFS (95% CI)
No or Low Grade AE	593	62	reference	88.9 (86.0 – 91.8%)
High Grade AE	98	18	1.75 (1.02 – 3.02)	76.4 (66.6 – 87.5%)

Stratified log rank: p = 0.054

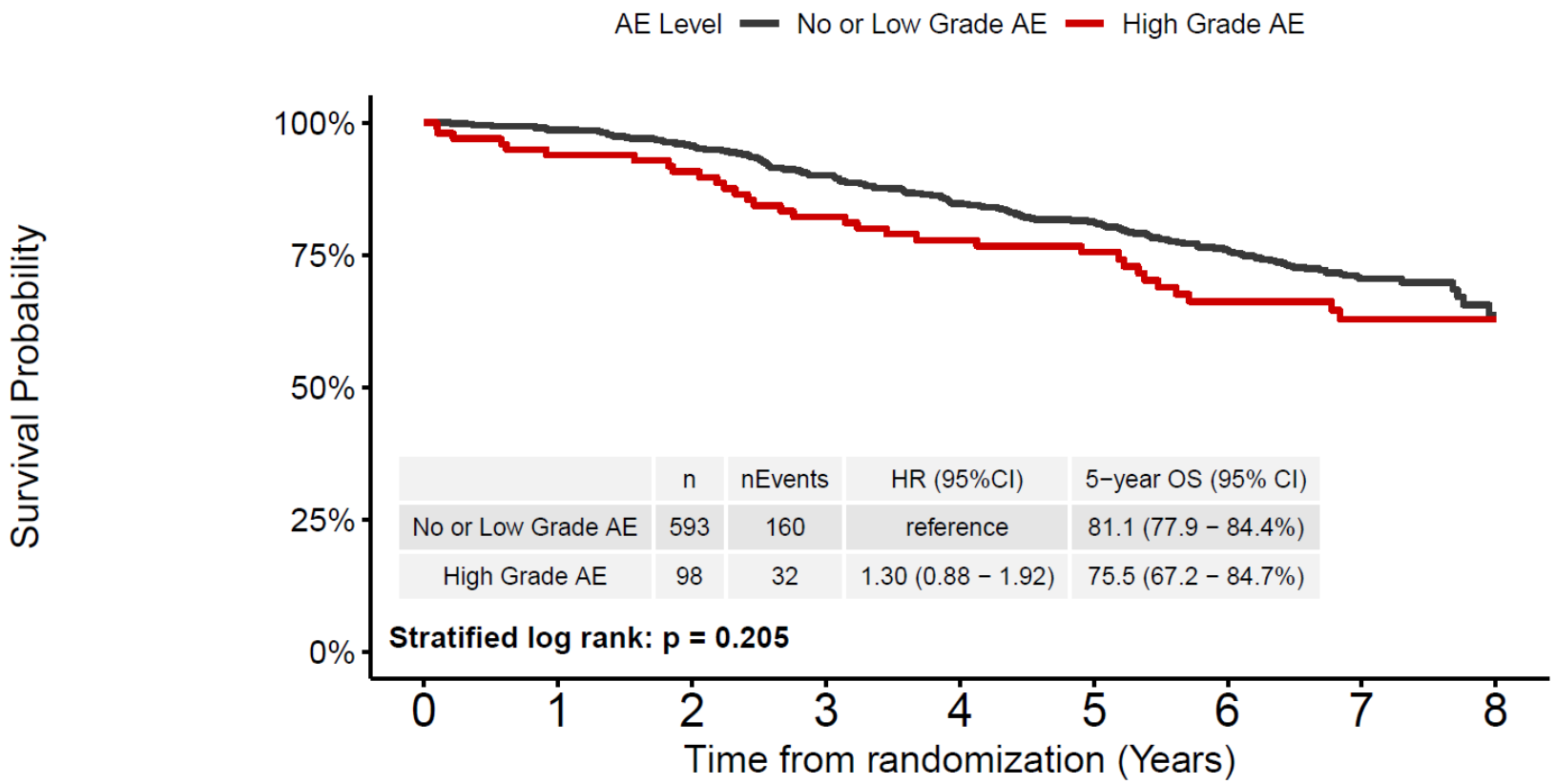
Distant Recurrence-free Survival



	n	nEvents	HR (95%CI)	5-year DRFS (95% CI)
No or Low Grade AE	593	91	reference	85.1 (82.1 – 88.2%)
High Grade AE	98	19	1.54 (0.93 – 2.57)	80.4 (72.1 – 89.7%)

Stratified log rank: p = 0.109

Overall Survival



	n	nEvents	HR (95%CI)	5−year OS (95% CI)
No or Low Grade AE	593	160	reference	81.1 (77.9 − 84.4%)
High Grade AE	98	32	1.30 (0.88 − 1.92)	75.5 (67.2 − 84.7%)

Survival	Low Grade AEs	High Grade AEs	P Value
Overall	81.1%	75.5%	0.205
Disease-free	66.9%	49.6%	0.006*
Recurrence- free	72.9%	56.9%	0.006*
Locoregional Recurrence-free	88.9%	76.4%	0.054
Distant Recurrence-free	85.1%	80.4%	0.109

Conclusions

In this large, prospective randomized trial, **High Grade AEs negatively influenced Disease-Free and Recurrence-Free survival, but not overall survival**. LRR and DR survivals were also affected, but not significantly.

This analysis shows that **even in patients who undergo resection for the smallest (< 2 cm) of NSCLCs**, postoperative High-Grade AEs can decrease cancer-specific survivals.

Prevention (ERAS protocols) of postoperative High-Grade AEs is mandatory in patients undergoing surgical treatment for early-stage NSCLC to reduce recurrence and maximize survival. **Less than 10% of sites had Fast track or ERAS protocols during trial time period.**

Surveillance with [^{18}F]FDG PET/CT of Lung Cancer after Curative Therapy; First Results of a Randomized Trial (SUPE_R)

On behalf of the SUPE_R study group,

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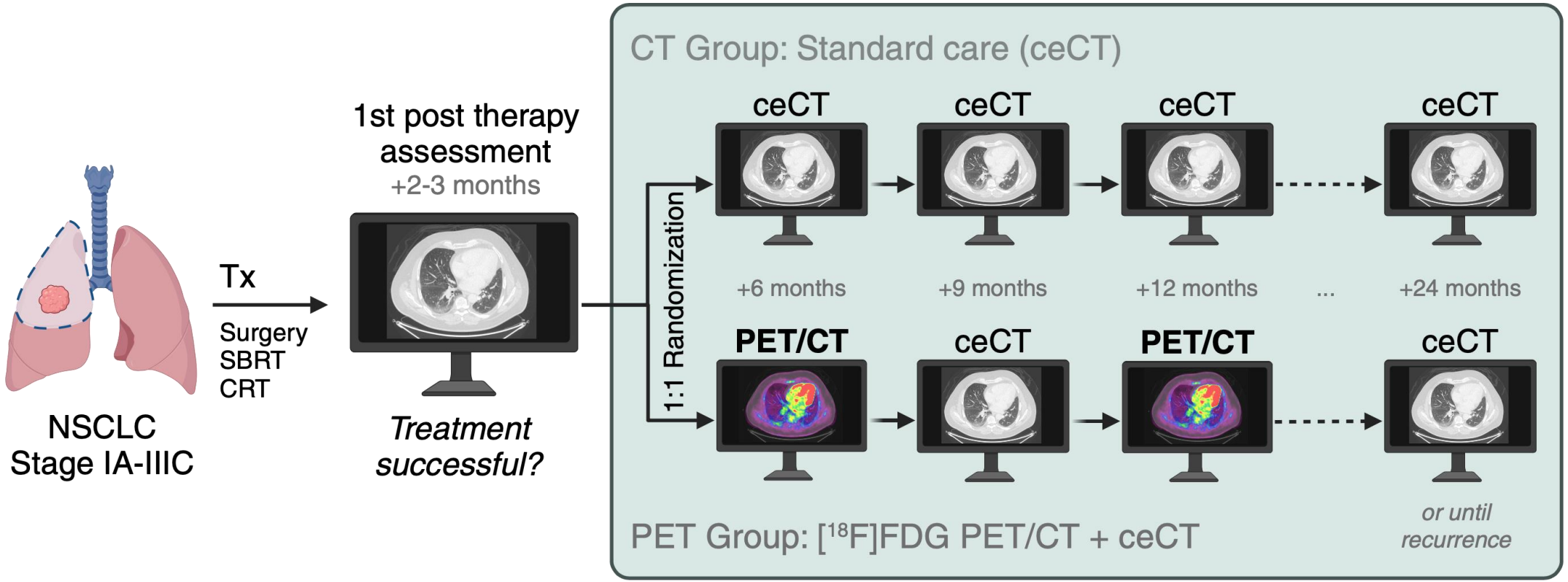
Denmark

Surveillance of Lung Cancer

- High risk of recurrence (20-60%) in NSCLC patients after curative therapy, which is why surveillance with CT is recommended
- Up to 40% of recurrences are diagnosed because of symptoms, despite CT surveillance[1]
- [^{18}F]FDG PET/CT shows promising diagnostic performance and can detect recurrences that are not detectable by CT[2]
- SUPE_R Trial: Evaluate if [^{18}F]FDG PET/CT improves NSCLC recurrence detection and patient outcomes compared to CT surveillance

[1]**Lou F**, et al. Ann Thorac Surg. **2014**;98(5):1755-60 [2]**Choi** S, et al. Ann Thorac Surg. **2011**;92(5):1826-32

SUPE_R Trial: Design



Quality of Life questionnaire and blood samples for ctDNA analysis at each assessment

Results: Recruitment and Recurrences

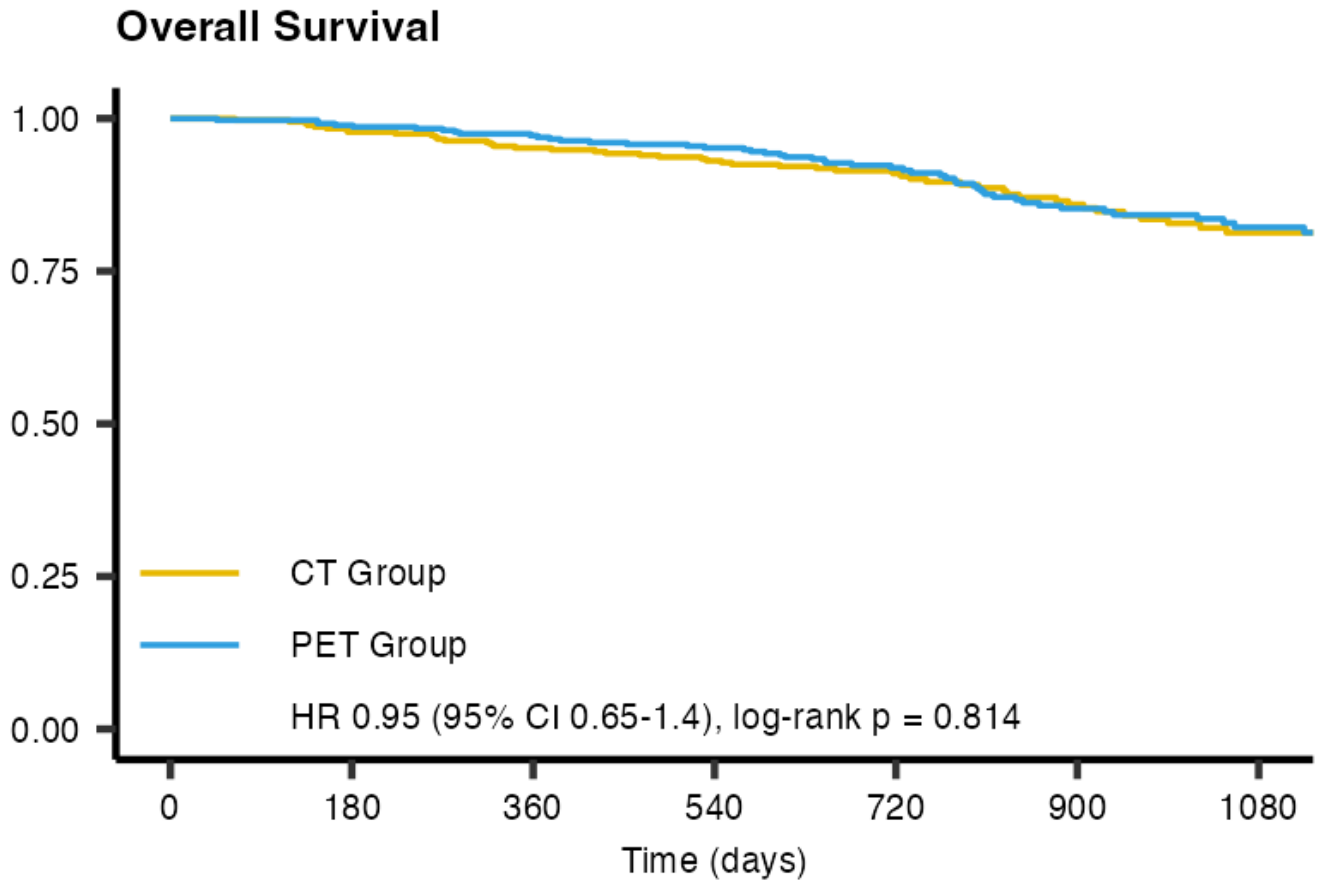
- 750 patients were recruited from 10 hospitals in Denmark and randomized to PET (n=373) or CT (n=377).
- The majority had adenocarcinomas (73%), stage I disease (71%), and received surgery (79%).
- More patients with suspected recurrence in the PET group ($p < 0.01$).
- More surveillance-detected recurrences in the PET group ($p = 0.02$).
- No difference in the number of confirmed recurrences, extent of recurrence, or curative treatment rate.

Table 1. Recurrence Characteristics

	PET Group	CT Group	P-value
Suspected recurrence	166/373 (45)	132/377 (35)	<0.01
Confirmed recurrence	87/373 (23)	77/377 (20)	0.34
Surveillance detected	78/87 (90)	59/77 (77)	0.02
Recurrence extent			
Local only	48/87 (55)	47/77 (61)	0.45
Distant only	19/87 (22)	14/77 (18)	0.56
Both	18/87 (21)	13/77 (17)	0.53
Recurrence treatment			
Curative intent	**42/86 (49)**	**37/75 (49)**	**0.95**
Palliative	41/86 (48)	34/75 (45)	0.77

Results: Time to Recurrence and OS

- No difference in overall survival
  - HR 0.95, 95% CI 0.65-1.40, p = 0.81
- No difference in time to recurrence
  - HR 1.12, 95% CI 0.83-1.53, p = 0.46
- More invasive diagnostic procedures in PET group
  - 147 vs 88, p < 0.01
- Increased costs and radiation exposure
  - +8-16 mSv per year



Take Home Message

- [^{18}F]FDG PET/CT is not recommended for routine surveillance due to lack of benefit, increased costs and radiation exposure
- Alignment with recent evidence:
  - Gambazzi et al. (2019)[1]: RCT in 96 patients, no difference rate of curative treatment or diagnostic performance of [^{18}F]FDG PET/CT vs CT
  - Westeel et al. (IFCT-0302, 2022)[2]: RCT in 1775 patients, no survival benefit of CT vs. chest X-ray, median follow-up 7.2 years
  - Galjart et al. (meta-analysis, 2022)[3]: No survival benefit for intensive follow-up in multiple cancer types, including lung cancer
- Perhaps we should reconsider our approach to surveillance - "Less is more?"

[1]**Gambazzi**, et al. Ann Thorac Surg. **2019**;107(2):430-435 [2]**Westeel**, et al. Lancet Oncol. 2022;23(9):1180-1188.**2011**;92(5):1826-32 [3]**Galjart**, et al. Eur J Cancer. **2022**;174:185-199.