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Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung
Groupe Suisse de Recherche Clinique sur le Cancer
Swiss Group for Clinical Cancer Research
Gruppo Svizzero di Ricerca Clinica sul Cancro

Final results of SAKK 16/00: A randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer (NSCLC)

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The Swiss Oncology Research Network

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Conflict of interest

- Advisory Board Sanofi-Aventis

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Stage IIIA/N2 NSCLC

- **Role of systemic treatment**
  - **Neoadjuvant chemotherapy improves survival compared to surgery**

    (Rosell NEJM 1994/Roth JNCI 1994, Song JTO 2010, Meta-Analysis Lancet 2014)
  - **Adjuvant chemotherapy improves survival compared to surgery**

    (Winton NEJM 2005, Arriagada NEJM 2004, Douillard Lancet Oncol 2006, Arriagada Lancet 2010)
- **Role of local therapy unclear**
  - **Adjuvant radiotherapy**

    (Cochrane 2005, Lally JCO 2006, Douillard IJROBP 2008)
  - **Surgery after chemo-radiotherapy**

    (Albain Lancet 2009, van Meerbeeck JNCI 2007)

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Neoadjuvant Chemotherapy: Lessons from Phase II trials

Local relapse occurred in 22% of patients (Betticher JCO 2003)

The two strongest predictors of favorable survival were

- Complete resection (R0)
- Pathological downstaging of N2 -> N0/1
- These factors also found in other trials (Albain, JCO 1995)

Hypothesis:

Neoadjuvant chemo-radiotherapy could increase nodal downstaging and R0 resection rate, resulting in an improved local control, event-free survival and overall survival

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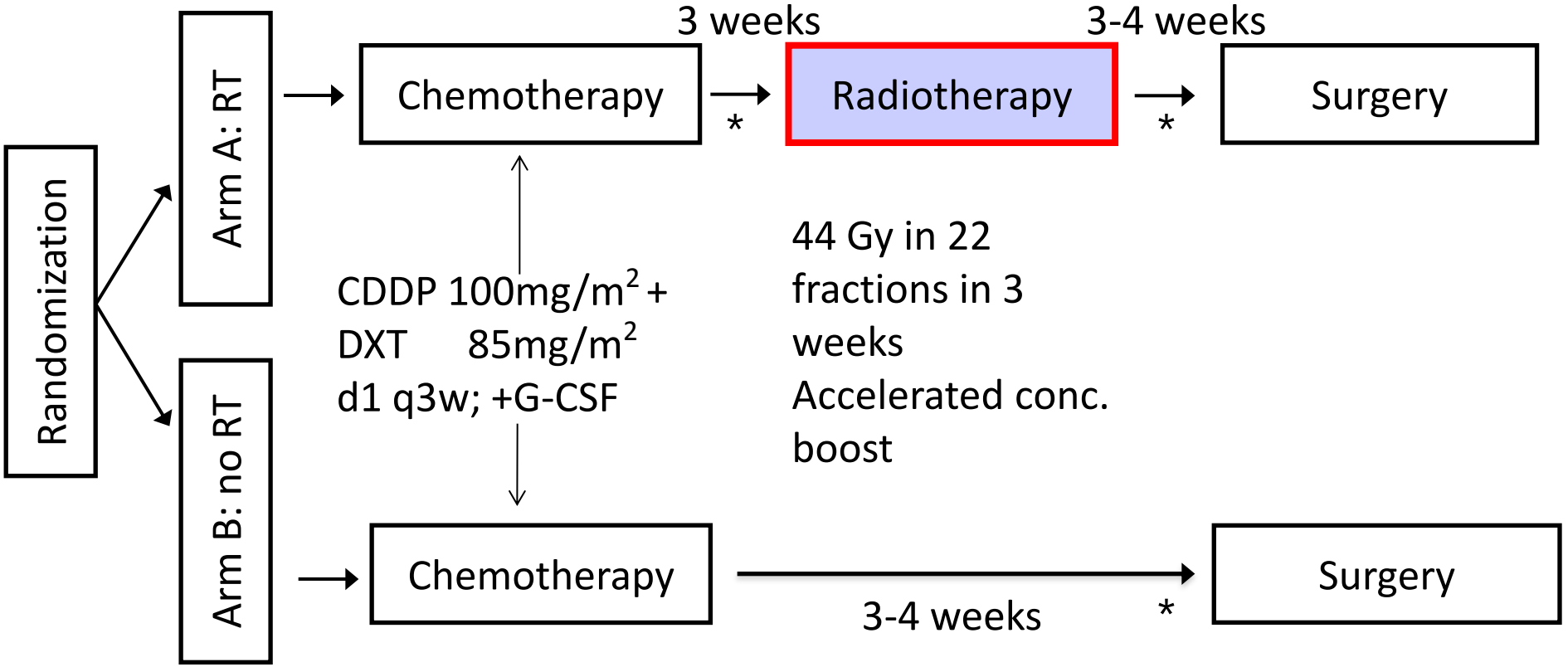
SAKK 16/00 (IIIA/pN2 NSCLC): Trial design

Stratification factors: Mediastinal bulk (≥5cm vs. <5cm), weight loss (≥5% vs. <5% in past 6 months), center



* Staging: (PET-) CT: PD went off study

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Main Eligibility Criteria

- Age 18-75
- PS 0-1
- Pathologically proven stage IIIA/**N2** NSCLC
  - Mediastinoscopy
  - EBUS + PET-CT
  - PET-CT only for position 5/6
- Resectable tumor, operable patient (pulmonary and cardiac function)
- Adequate renal (Cl ≥ 60 ml/min), hepatic and bone marrow function
- No uncontrolled infection, diabetes, cardiac disease, relevant neuropathy or gastric ulcer

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Study Endpoints

- **Primary endpoint:** **Event-free survival**

  from randomization to either relapse, progression, second tumor or death

- Secondary endpoints:
  - Overall survival
  - Postoperative 30-day mortality
  - Objective response rate
  - Failure pattern
  - Rate of complete resection
  - Operability

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Statistical Considerations

Goal: Improvement of median EFS from 12 to 18 months

- 3 planned interim analyses (50, 100, 150 events)
- Early stopping rules for futility and efficacy

- Two-sided log-rank test with 5% type I error and 80% power:

-> 208 events or 240 patients required

Initially 120 patients planned: EFS improvement of 10 months (Fleck, ASCO 1993): after ANITA analysis amended to 240 (before first interim analysis!)

- At 3rd interim analysis (134 events) the futility boundary was crossed: trial stopped with 232 patients included)

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Patients' Characteristics

From April 2001 to December 2012, 232 patients in 23 centers included, median follow up 52 months

		RT (N=117)	no RT (N=115)
Age (years), median (range)		60.0 (37-76)	59.3 (30-75)
Sex:	Male/Female	78/39	77/38
Stage:	T1	14%	17%
	T2	50%	53%
	T3	35%	28%
WHO PS	0	71%	69%
	1	29%	31%
Smoking	No	9%	4%
	Yes	91%	96%
Histology	Adenocarcinoma	44%	43%
	Squamous Cell Carcinoma	36%	31%
	Large Cell Carcinoma	6%	7%
	Poorly differentiated	15%	18%

Chemo- and Radiotherapy

	RT	No RT
Chemotherapy not completed:	7%	11%)
Toxicity	6 (1 death)	7 (1 death)
PD	0	3
Other	1	1

Received Radiotherapy as planned	**84%**	**98/117**
Did not receive RT	16%	4x toxicity 6x PD 2x refusal 7x other
Median time last chemo to start RT	25 days	
Median duration of radiotherapy	20 days (17-36)	
Radiotherapy stopped early	0%	
Radiotherapy interrupted	0%	

Surgery

		RT (N=99)	no RT (N=94)
Resected		99/117 (85%)	94/115 (82%)
Surgery	Lobectomy	59%	63%
	Bilobectomy	13%	10%
	Pneumonectomy	25%	20%
Resection	R0	91%	81%
	R1	6%	12%*
	R2	3%	8%*
			* PORT

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Chemotherapy: Hematological Toxicity

	RT			no RT		
AE	**Grade**			**Grade**		
	1/2	3	4	1/2	3	4
Anemia	100%	-	–	99%	1%	–
Leukopenia	67%	30%	3%	71%	19%	10%
Neutropenia	57%	19%	24%	50%	22%	28%
Thrombocytopenia	100%	-	–	97%	3%	1%

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Adverse events during Chemotherapy

	RT N=117			no RT N=115		
AE						
Grade	1/2	3	4	1/2	3	4
Diarrhea	38%	9%	1 %	40%	12%	1%
Nausea/Vomiting	65%	6%	–	55%	10%	1%
Febrile Neutropenia	–	12%	–	–	16%	–
Fever	10%	–	–	13%	–	–
Neurotoxicity	34%	1%	–	31%	3%	–
Stomatitis	25%	1%	–	17%	4%	–
Hypersensitivity	3%	2%	–	4%	–	–
Skin toxicity	22%	–	–	17%	–	–
Fluid retention	20%	–	–	12%	–	

Radiotherapy Toxicity (N=98)

AE	Grade 1/2	Grade 3	Grade 4
Esophagitis/Dysphagia	71%	7%	–
Skin Toxicity	25%	–	–
Fatigue	37%	1%	–
Anorexia	12%	–	–
Cough	25%	–	–
Nausea/Vomiting	20%	–	–
Dyspnea	14%	–	–

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Postoperative Complications/Mortality

	RT (N=99)	no RT (N=94)
Infection	14%	12%
Bronchial Stump Fistula	4%	0%
Reoperation	6%	6%
Other complications	25%	28%
Death within 30 days postop	**0%**	**3%**

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Response Rate & Local Control

		RT		no RT
		After Chemotherapy (N=117)	**After Radiotherapy (N=117)**	**After Chemotherapy (N=115)**
WHO response	CR	0%	3%	2%
	PR	51%	57%	42%
	ORR	**51%**	**61%**	**44%**
	NC	30%	15%	39%
	PD	9%	3%	14%
Not known/assessable		9%	3%	4%
Missing (no RT)			17%	
First relapse:	**Local**		**15%**	**28%**
	Both		9%	7%
	Distant		37%	33%

Pathological Response after Induction Therapy

	RT	no RT
ypN0/1	**64%**	**53%**
ypN2	33%	44%
missing	3%	3%
pCR	**16%**	**12%**
PORT after R1/2 resection		13%
PORT with R0 resection		6%

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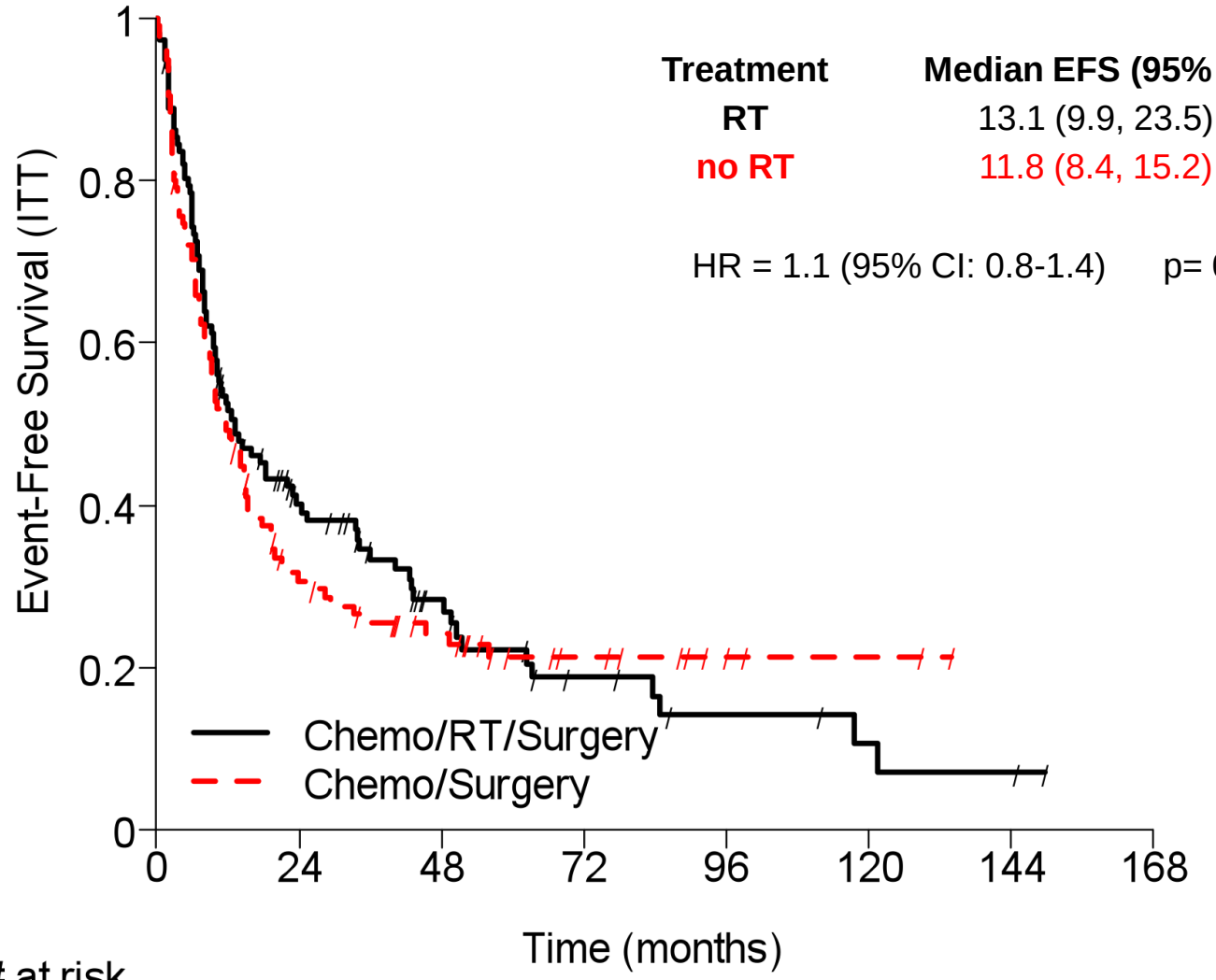
Event Free Survival



Treatment	Median EFS (95% CI)
RT	13.1 (9.9, 23.5)
no RT	11.8 (8.4, 15.2)

HR = 1.1 (95% CI: 0.8-1.4) p= 0.665

# at risk								
RT	117	38	19	9	5	3	2	0
no RT	115	31	19	9	3	2	0	0

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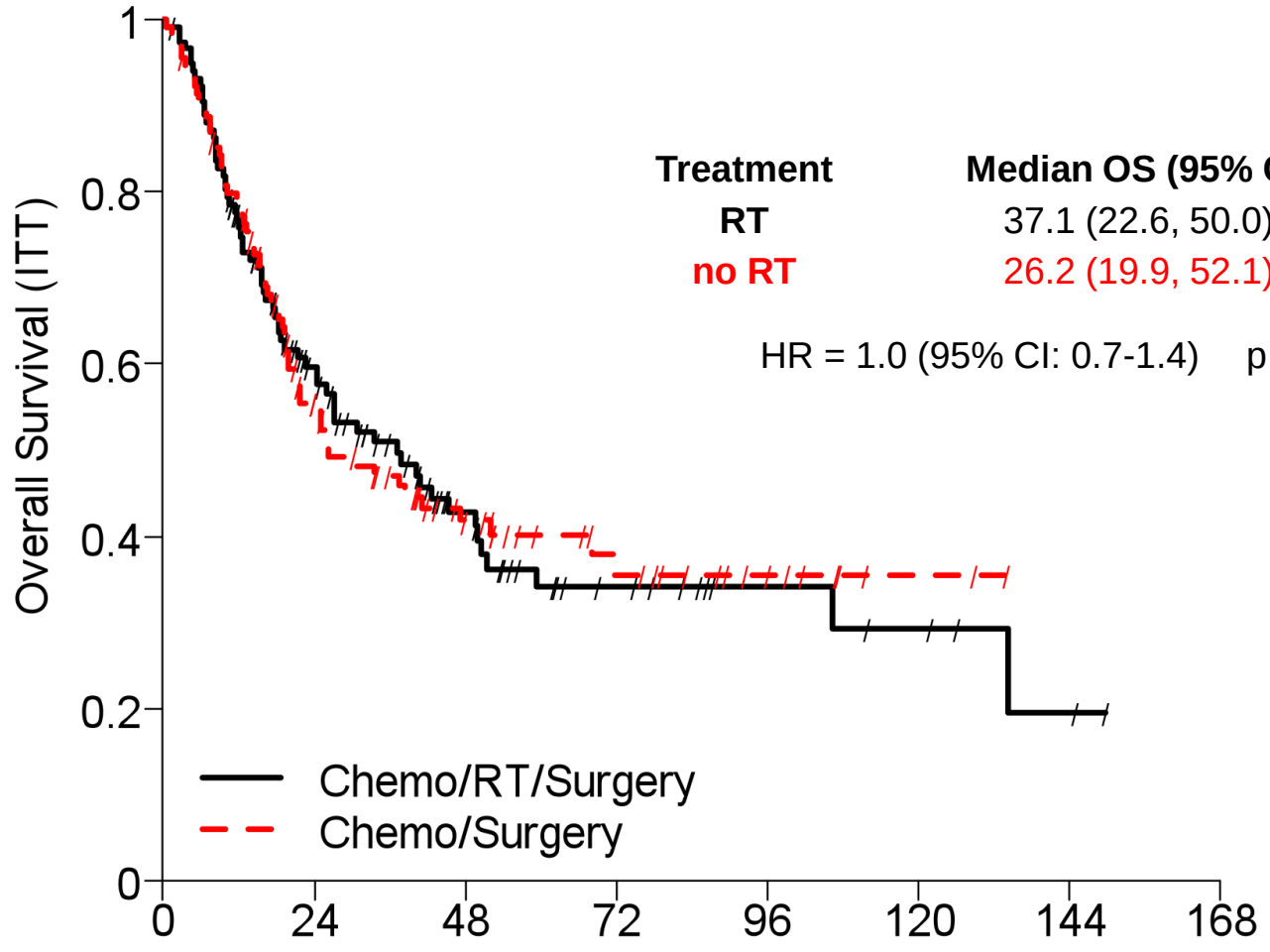
Overall Survival



Treatment	Median OS (95% CI)
RT	37.1 (22.6, 50.0)
no RT	26.2 (19.9, 52.1)

HR = 1.0 (95% CI: 0.7-1.4) p 0.938

# at risk								
RT	117	57	27	13	7	5	2	0
no RT	115	53	28	15	7	2	0	0

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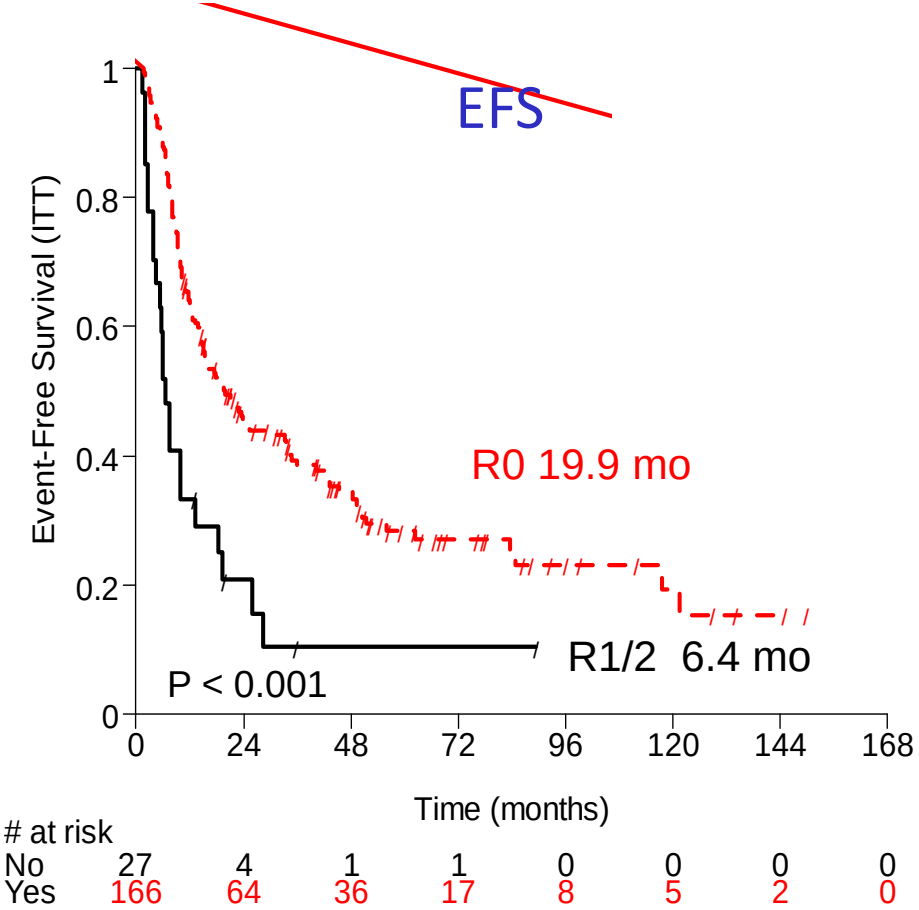
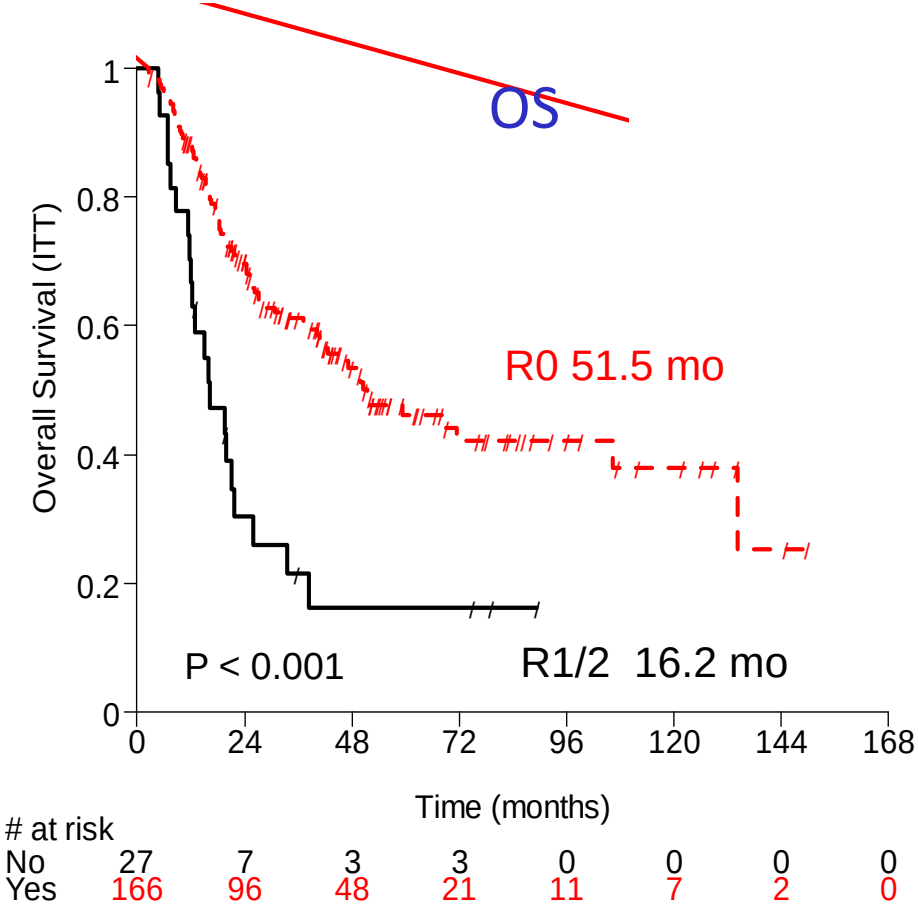
Prognostic effect of R0 resection





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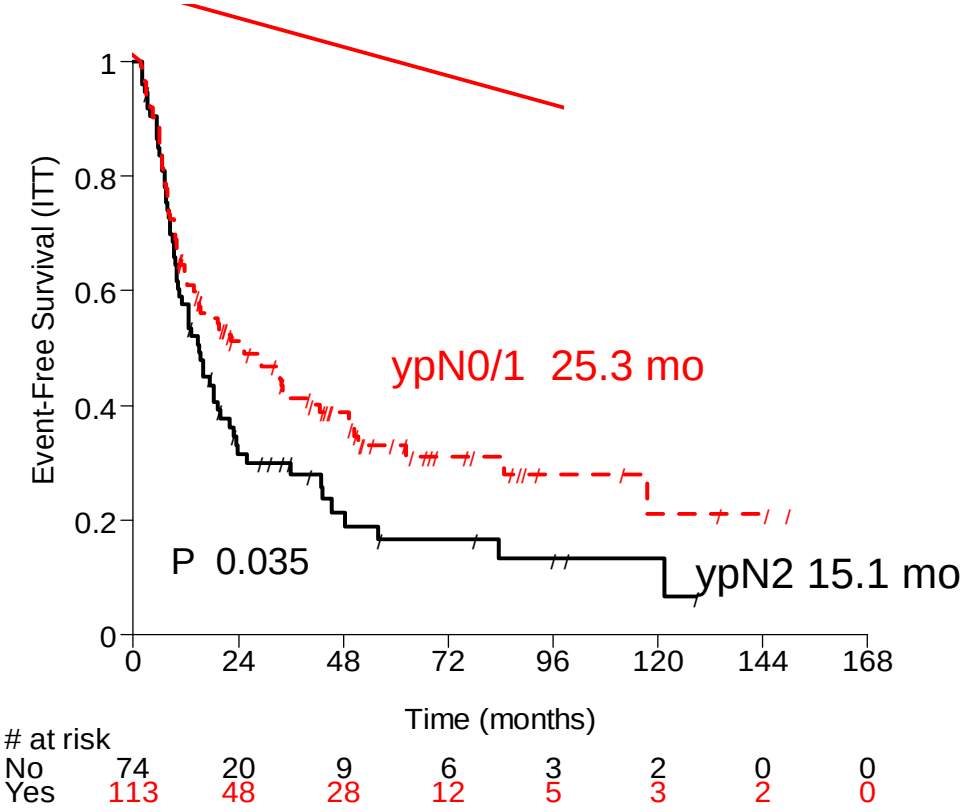
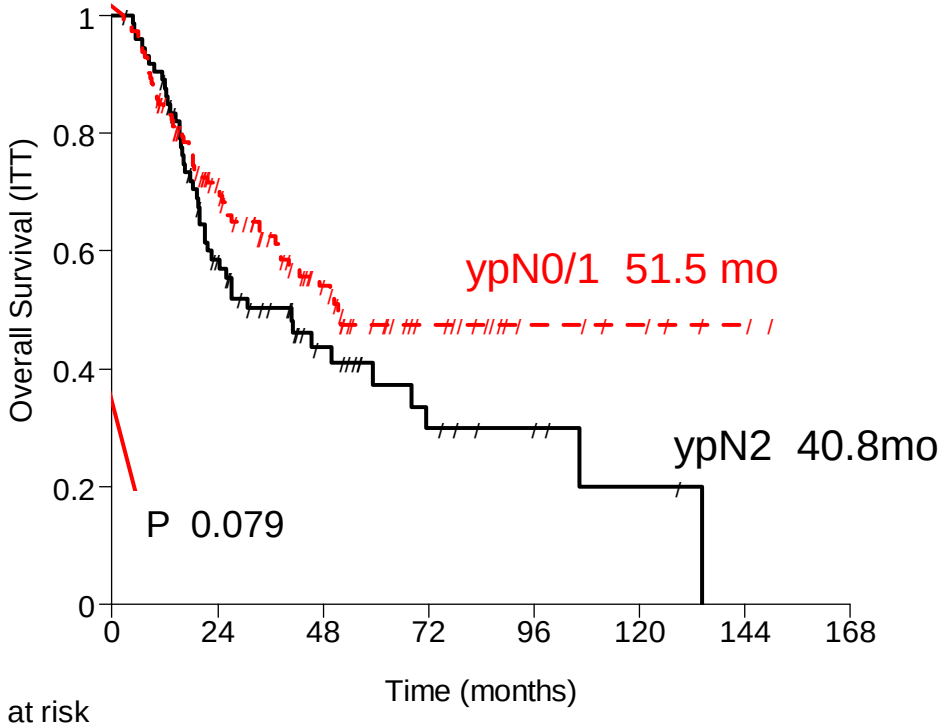
Prognostic effect of mediastinal clearing

EFS



# at risk								
No	74	20	9	6	3	2	0	0
Yes	113	48	28	12	5	3	2	0

OS



# at risk								
No	74	37	17	8	4	2	0	0
Yes	113	65	34	16	7	5	2	0

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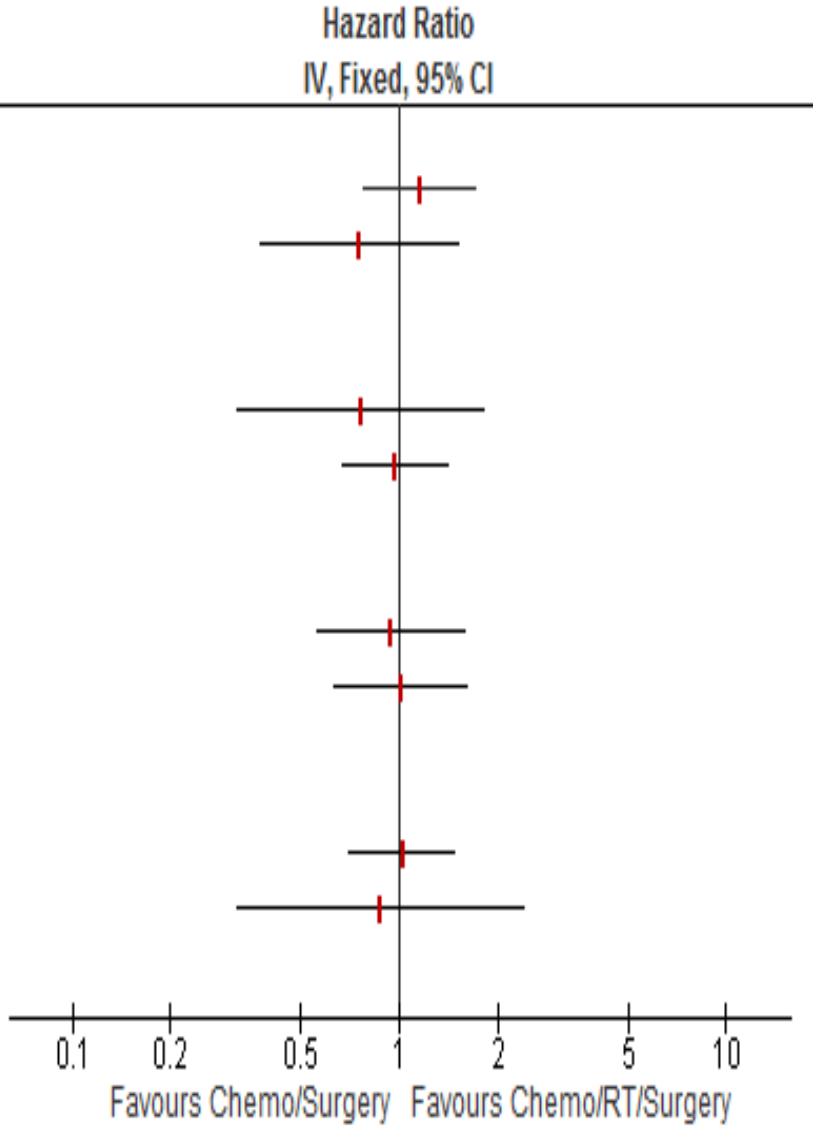
Exploratory subgroup analyses: EFS

Study or Subgroup	log[Hazard Ratio]	SE	Chemo/RT/Surgery Total	Chemo/Surgery Total	Hazard Ratio IV, Fixed, 95% CI
1.1.1 Pneumonectomy subgroups					
No pneumonectomy	0.145	0.199	74	75	1.16 [0.78, 1.71]
Pneumonectomy	-0.278	0.357	25	19	0.76 [0.38, 1.52]
1.1.2 R0 subgroups					
No R0	-0.275	0.441	9	18	0.76 [0.32, 1.80]
R0	-0.035	0.19	90	76	0.97 [0.67, 1.40]
1.1.3 ypN0/1 subgroups					
No ypN0/1	-0.059	0.264	33	41	0.94 [0.56, 1.58]
ypN0/1	0.014	0.238	63	50	1.01 [0.64, 1.62]
1.1.4 pCR subgroups					
No pCR	0.022	0.189	80	80	1.02 [0.71, 1.48]
pCR	-0.138	0.515	16	11	0.87 [0.32, 2.39]



Summary & Conclusions

- First completed randomized trial for this question

- The addition of neoadjuvant radiotherapy to chemotherapy

    - did impact on ORR, mediastinal downstaging, R0 rate and local control

    - did not improve **EFS or OS**

- Overall results encouraging!

    - bulky N2 included

    - 5 year OS: 40%

- Pneumonectomy after induction treatment was safe

•**Chemotherapy plus *one* local treatment remains the standard**

•**At this time no indication for neoadjuvant RT outside of a clinical trial**

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Acknowledgments

- The patients and their families
- The SAKK Coordinating Center
- All the investigators and their teams

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Thank You!

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Back Up

Survival summary

Survival		RT N=117	no RT N=115
EFS	1-year	52%	49%
	2-year	40%	31%
	3-year	33%	26%
	5-year	22%	21%
OS	1-year	76%	79%
	2-year	60%	55%
	3-year	51%	47%
	5-year	34%	40%

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