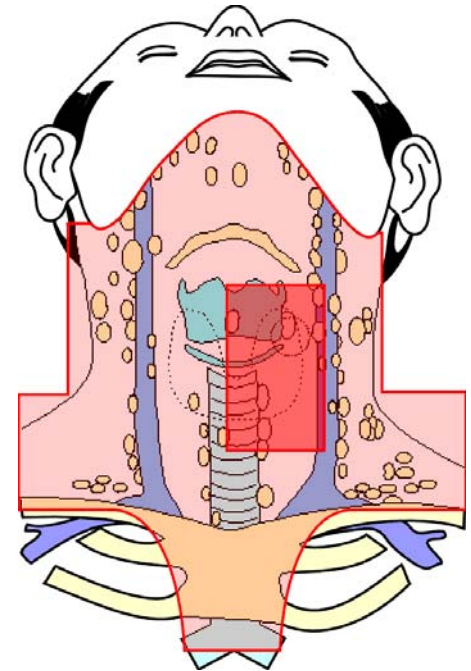


External beam radiotherapy for differentiated thyroid cancer

An ongoing debate (?)

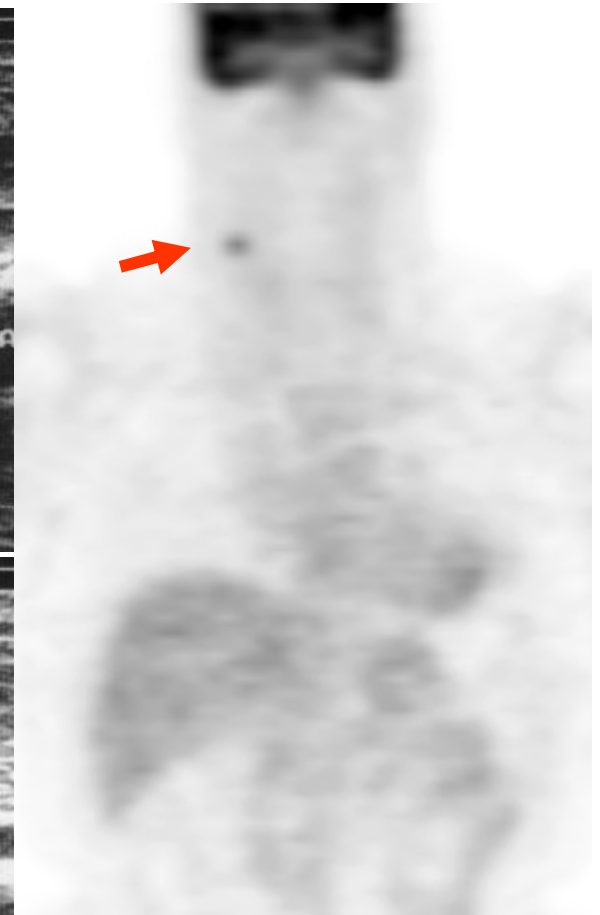
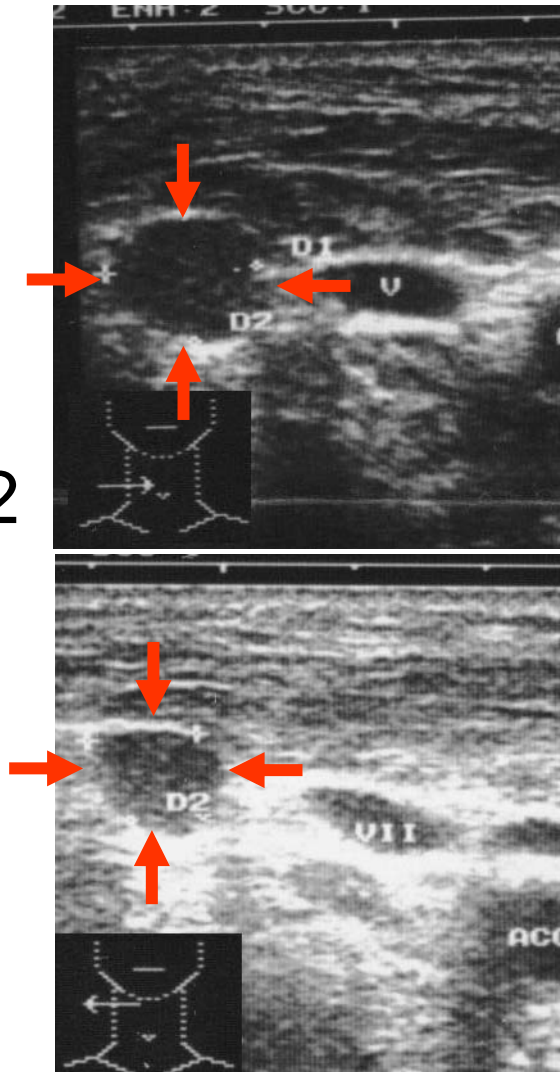
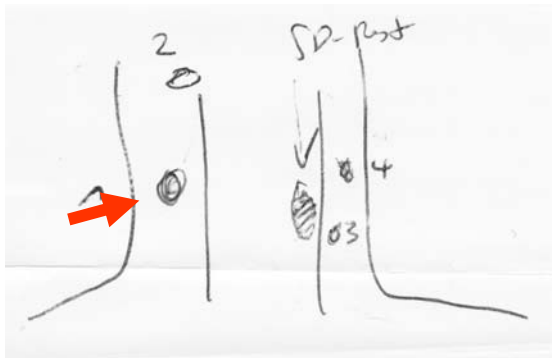
Martin Biermann

Consultant physician, Associate Professor
Specialist in Nuclear Medicine
Nuclear medicine/PET-centre
Haukeland University Hospital/
University of Bergen
Bergen, Norway



F18-FDG-PET f. 61 yrs., PTC pT4 pN1

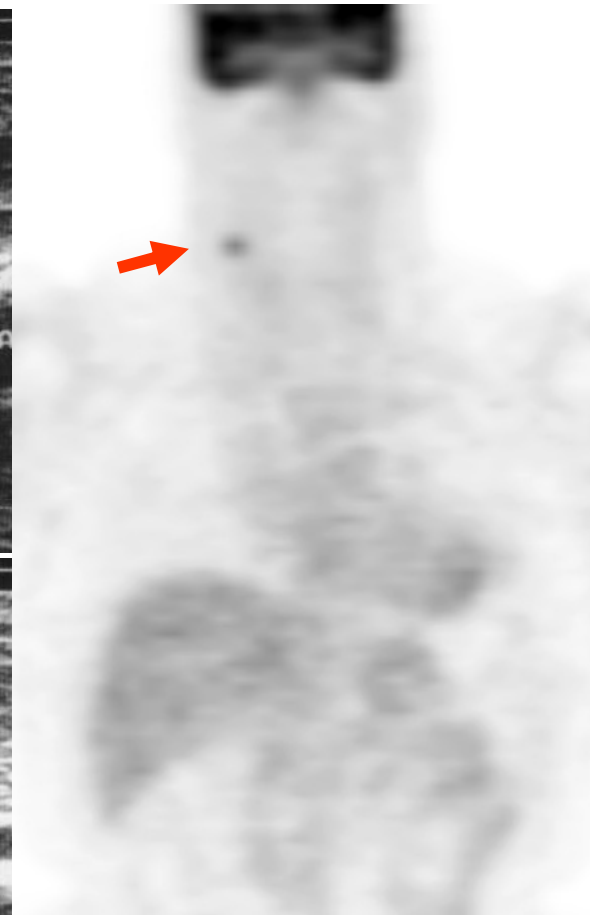
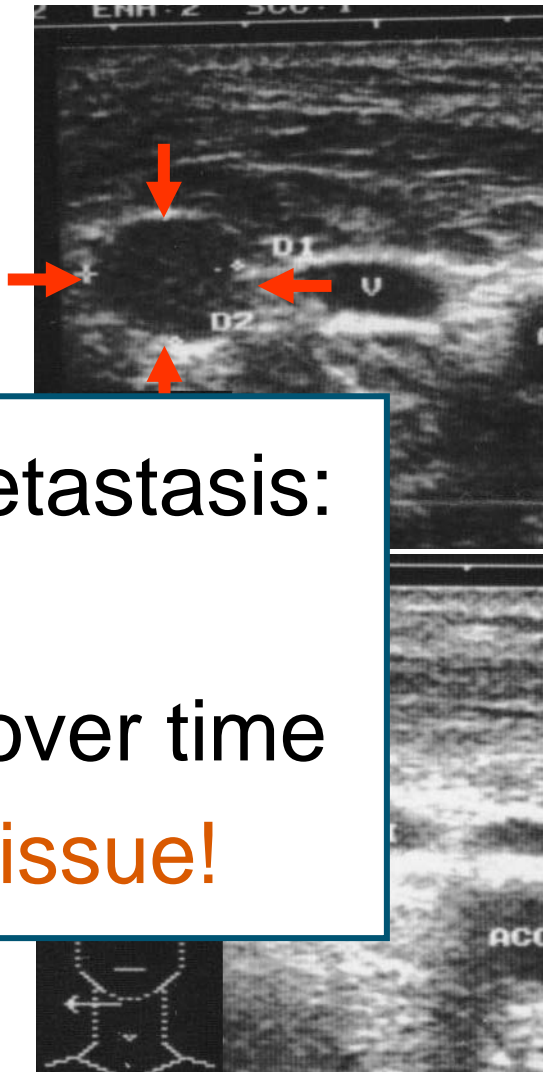
- female 61 yrs.
- DTC 2002
Right-sided PTC
pT4a (3.5 cm) pN1 Mx
- OP (3x) 5-6/2002
- I-131 (3 GBq) 6/02
- RTx (50 Gq) 7/02



FDG-PET

F18-FDG-PET f. 61 yrs., PTC pT4 pN1

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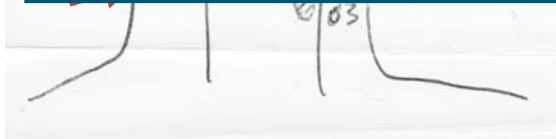


FDG-PET

lymph node metastasis:

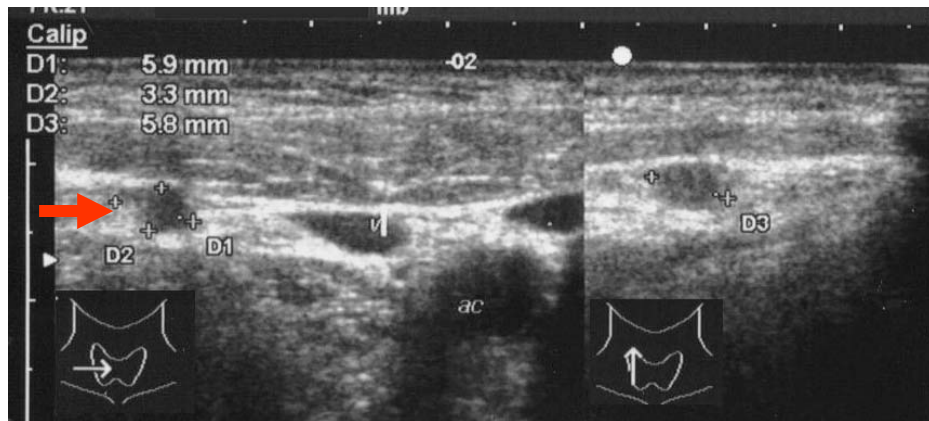
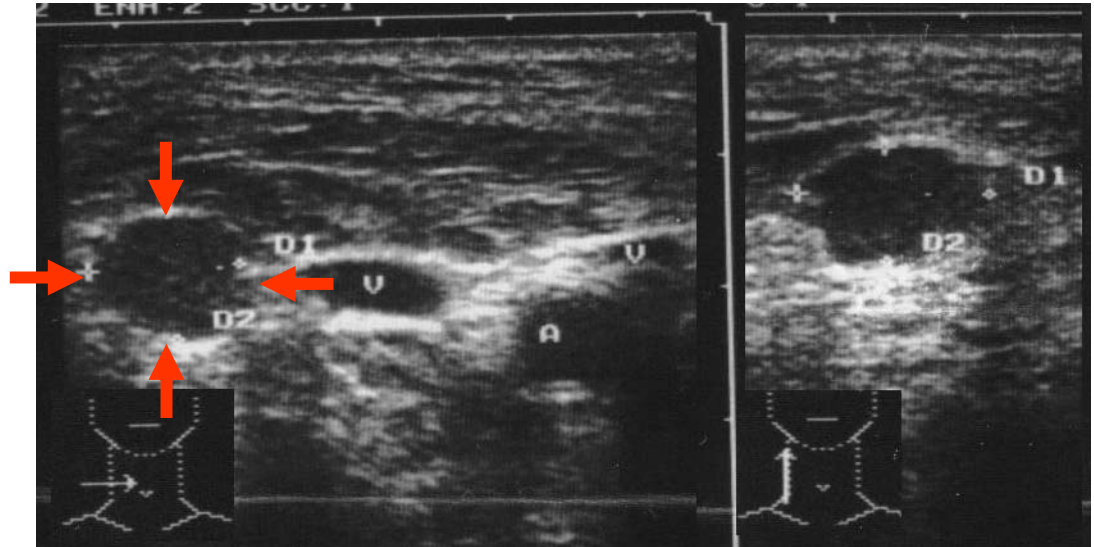
- FDG-pos.
- progresses over time

viable tumour tissue!

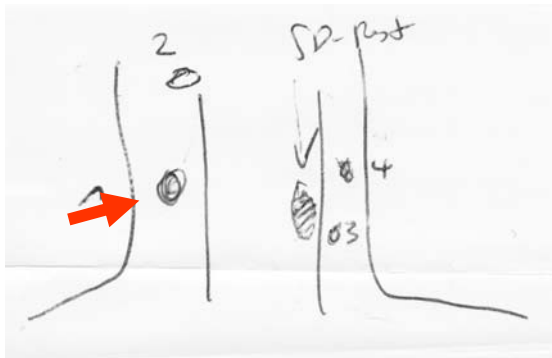


F18-FDG-PET f. 61 yrs., PTC pT4 pN1

- female 61 yrs.
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Right-sided PTC
pT4a (3.5 cm) pN1 Mx
- OP (3x) 5-6/2002
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- RTx (50 Gq) 7/02



2005



F18-FDG-PET f. 61 yrs., PTC pT4 pN1

- female 61 yrs.

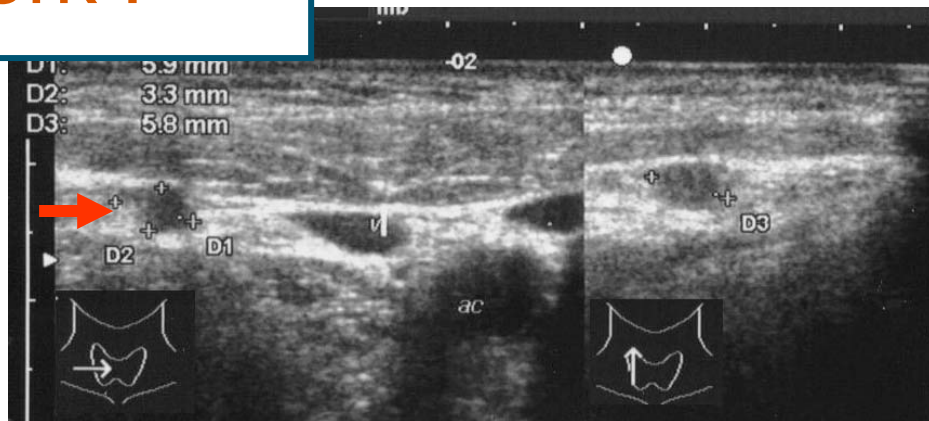
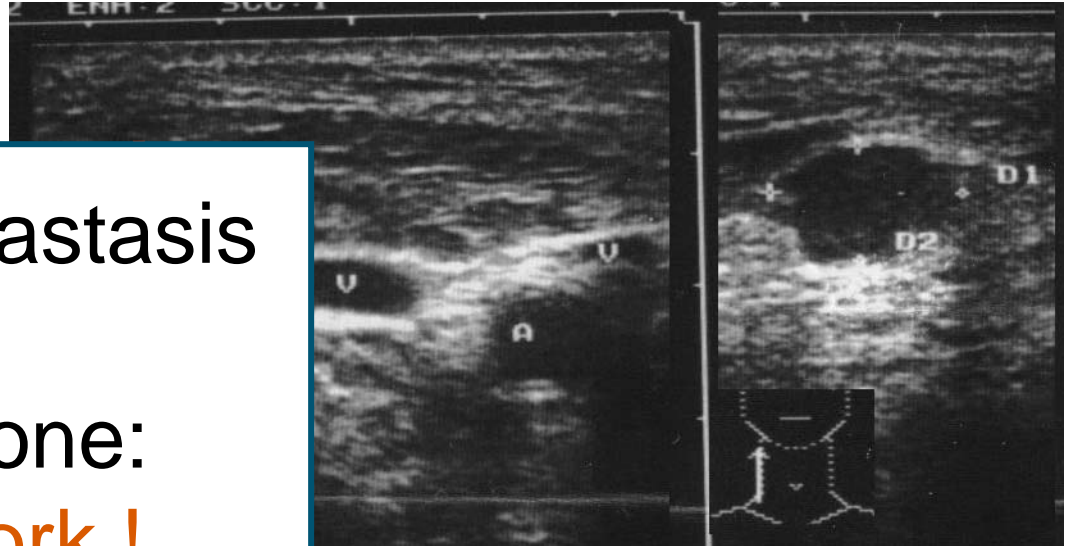
- DTC 2002

lymph node metastasis

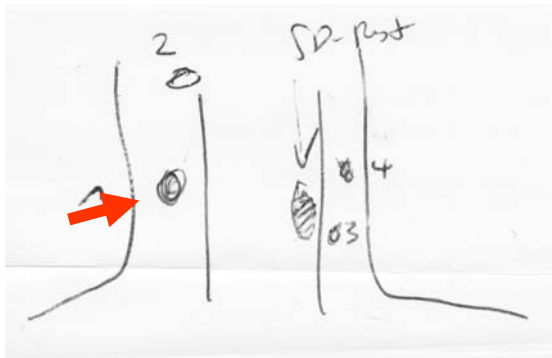
2002: FDG-pos.

2005: (nearly) gone:

RTx does work !

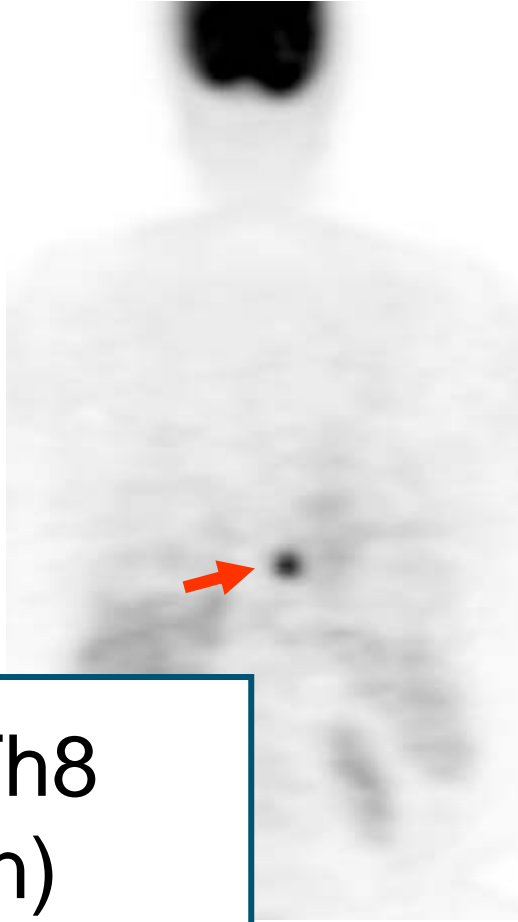


2005



F18-FDG-PET f. 61 yrs., PTC pT4 pN1

- female 61 yrs.
- DTC 2002
Right-sided PTC
pT4a (3.5 cm) pN1 Mx
- OP (3x) 5-6/2002
- I-131 (3 GBq) 6/02
- RTx (50 Gq) 7/02



metastasis to Th8
(biopsy-proven)
outside the field of RTx

-PET

FDG-PET

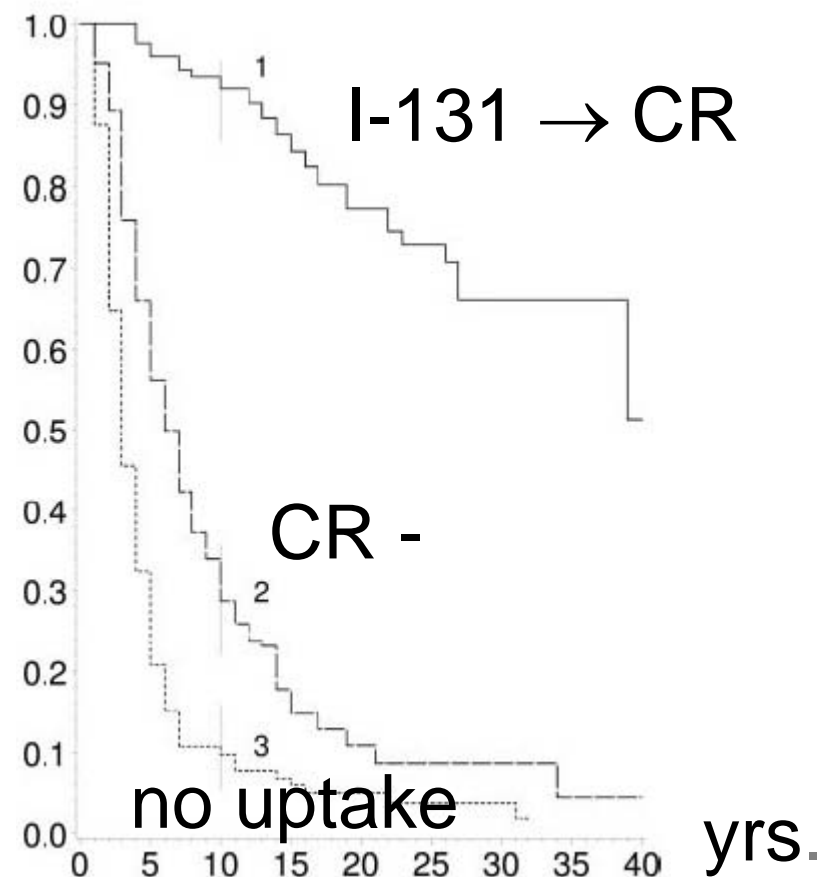
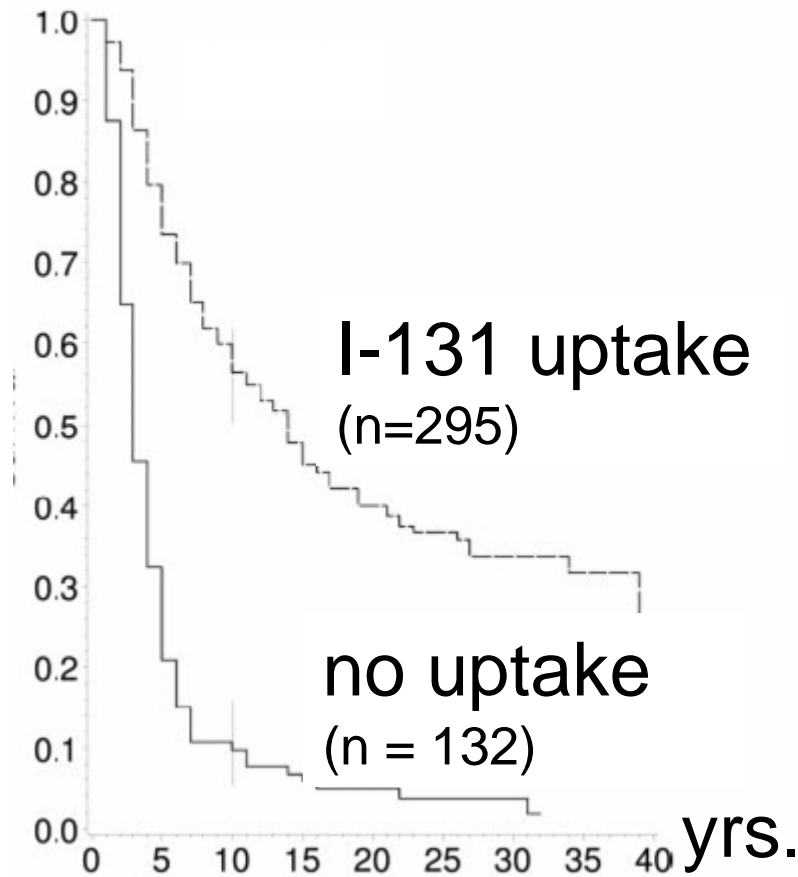


External beam radiotherapy (RTx)

- RTx for distant metastases
- RTx for recurrences in the thyroid bed
- adjuvant RTx:
 - for undifferentiated thyroid cancer
 - for differentiated thyroid cancer (DTC):
 - past and current guidelines
 - retrospective cohorts
 - MSDS-trial
 - metaanalysis
- conclusion



Survival with distant metastases



Good prognosis among responders

Durante (2006)
J Clin Endocrinol Metab
91:2892-9

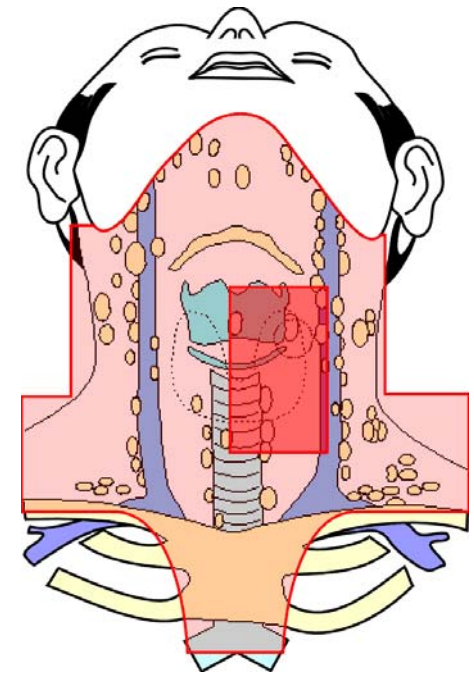


RTx for distant metastases

- generally palliative Schlumberger (1996) J Nucl Med 37:398-605
- indication:
not operable *and*
no I-131-uptake *and*
(risk of) complications:
 - pain
 - impending fracture
 - spinal compression (with or without surgery)
- 40 – 50 Gy (1.8 – 2 Gy/d)
- 30 Gy (3 Gy/d) Schuck (2005) Onkologe 11:87-92



Adjuvant RTx for DTC?



External beam RTx: Guidelines

- German Cancer Society (DKG; 1996 - 2002)
 - undifferentiated/anaplastic carcinoma
 - R1/2-resection *and* re-OP/I-131 therapy impossible

<http://awmf-online.de>
- German Soc. for Radiooncology (DEGRO; 1998)
 - pT4: RTx “indicated from a radiooncological perspective”
 - pN+: “individual risk-adapted decision”

<http://awmf-online.de>
- European Thyroid Association (2006)
 - unresectable tumours
 - local invasion with R1/2 resection

} + no I-131 uptake

Pacini, Schlumberger, Dralle... (2006) Eur J Endocrinol 154:787-803



Adjuvant RTx protocols

N. Am. DEGRO

- Margins

- thyroid bed

60 60-70 Gy

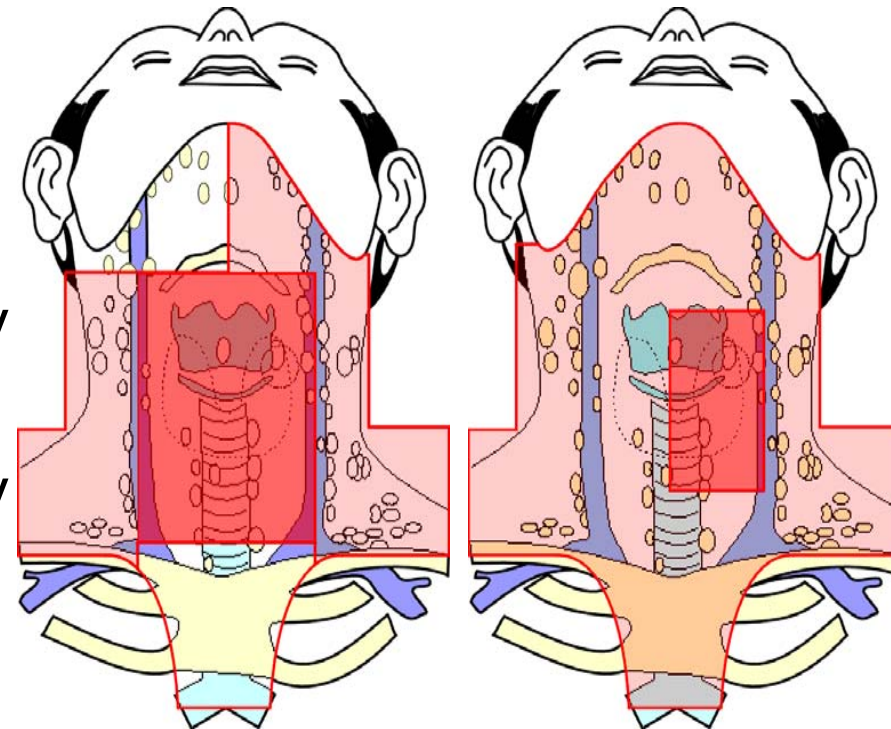
- lymph nodes

50 50-60 Gy

ipsilateral	(+)	+
contralateral	((+))	+
mediastinal	((+))	+
contra. submand.	-	+

- Timing

after 1st	after neg.
I-131 Tx	I-131 scan



North America

Germany

Simpson in: Cox (ed.):
Moss' radiation oncology,
1996, 280-304.

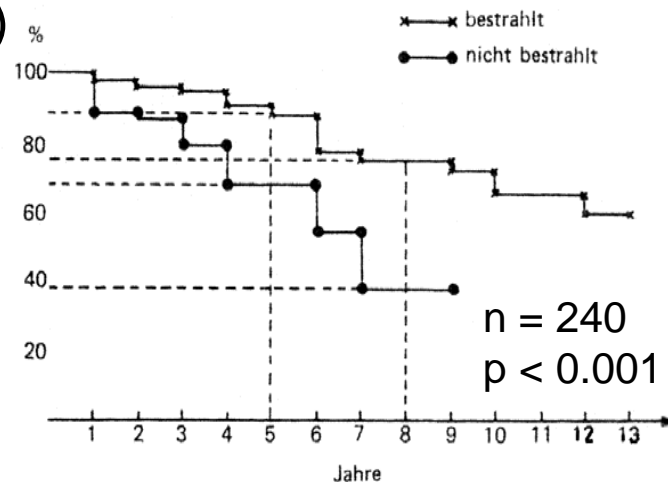
DEGRO
[http://www.
awmf-online.de](http://www.awmf-online.de)



Retrospective studies

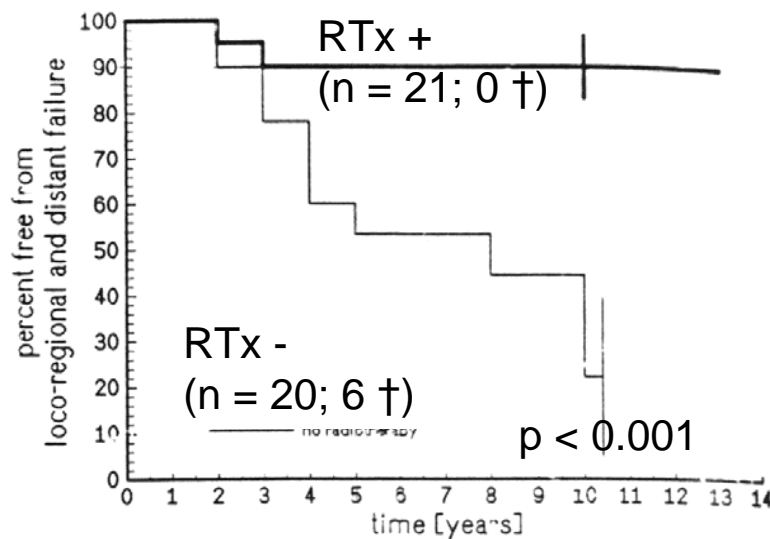
- Leisner 1982
 - pT4 N0/1/x M0
 - DMW 107:1702-7

survival (%)



- Farahati 1996
 - pap. pT4 N1 > 40 J.
 - Cancer 77:172-80

recurrence-free (%)



MSDS: external beam RTx

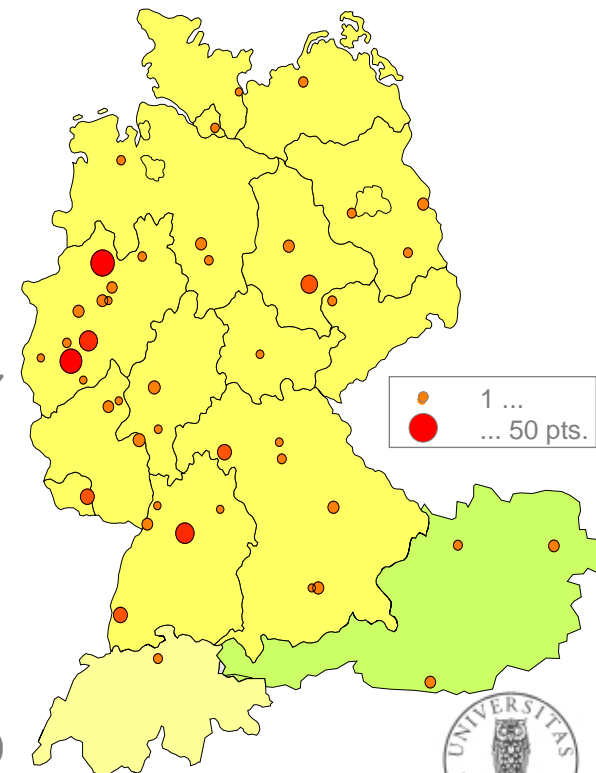
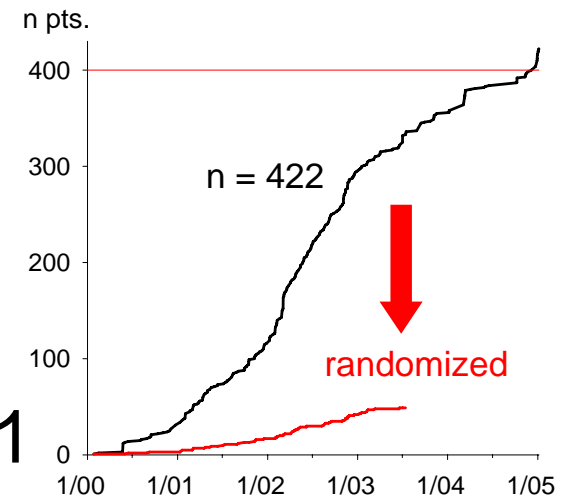
- prospective randomized trial: thyroidectomy + I-131 ± RTx
- locally invasive DTC pT3b M0 R0/1
- 46 centers in Germany, Austria & Switzerland
- n = 422 pts. Jan 2000 – Dec 2004
NATC cooperative study n = 385

Taylor (1998), Ann Int Med 129:622-7

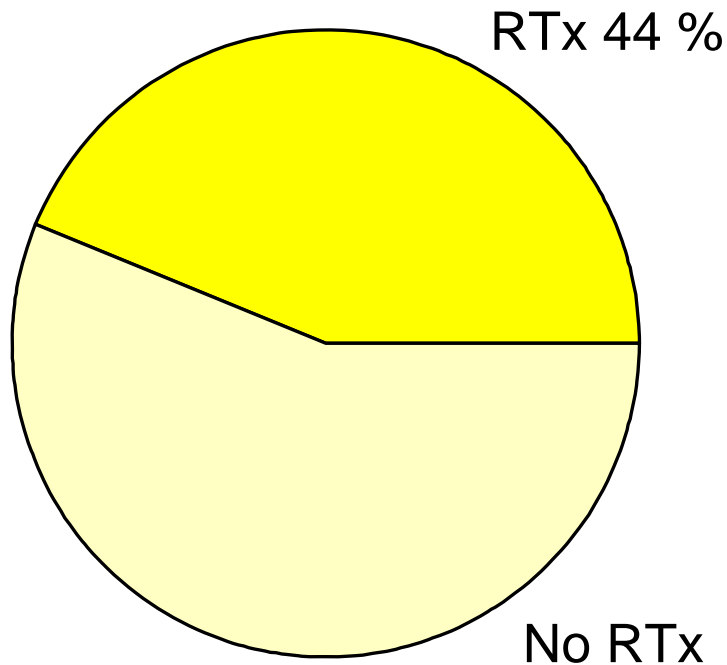
But:

- **too few randomized patients**
observational study from Apr 2003

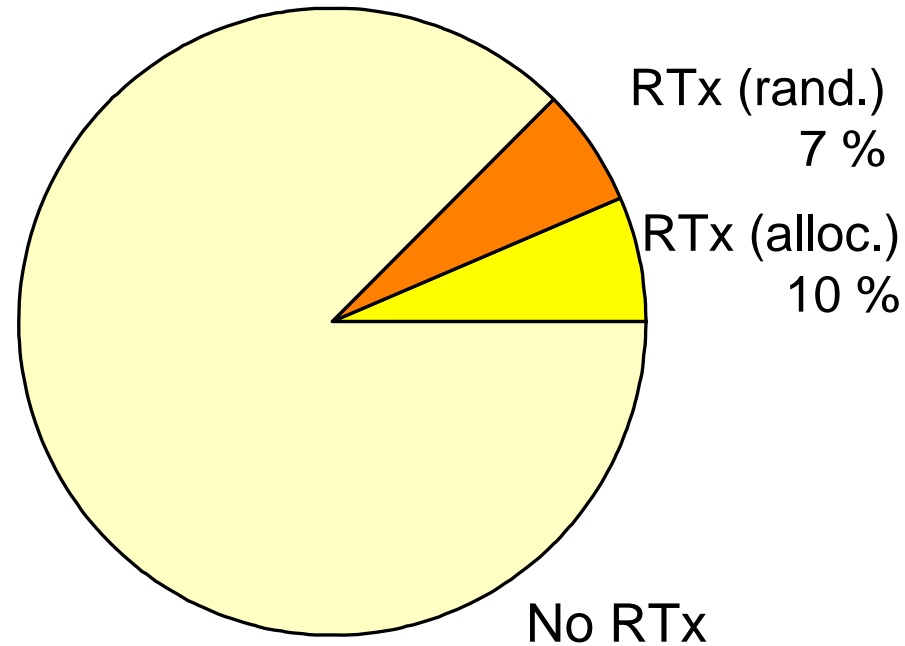
Biermann (2003) Nuklearmedizin 42:244-50



Adjuvant RTx for DTC pT3b/4



PCES 1996



MSDS 2000 ff.

Hölzer (2000) Eur J Nucl Med 27:1465-72 Biermann (2003) Nuklearmedizin 42:244-50



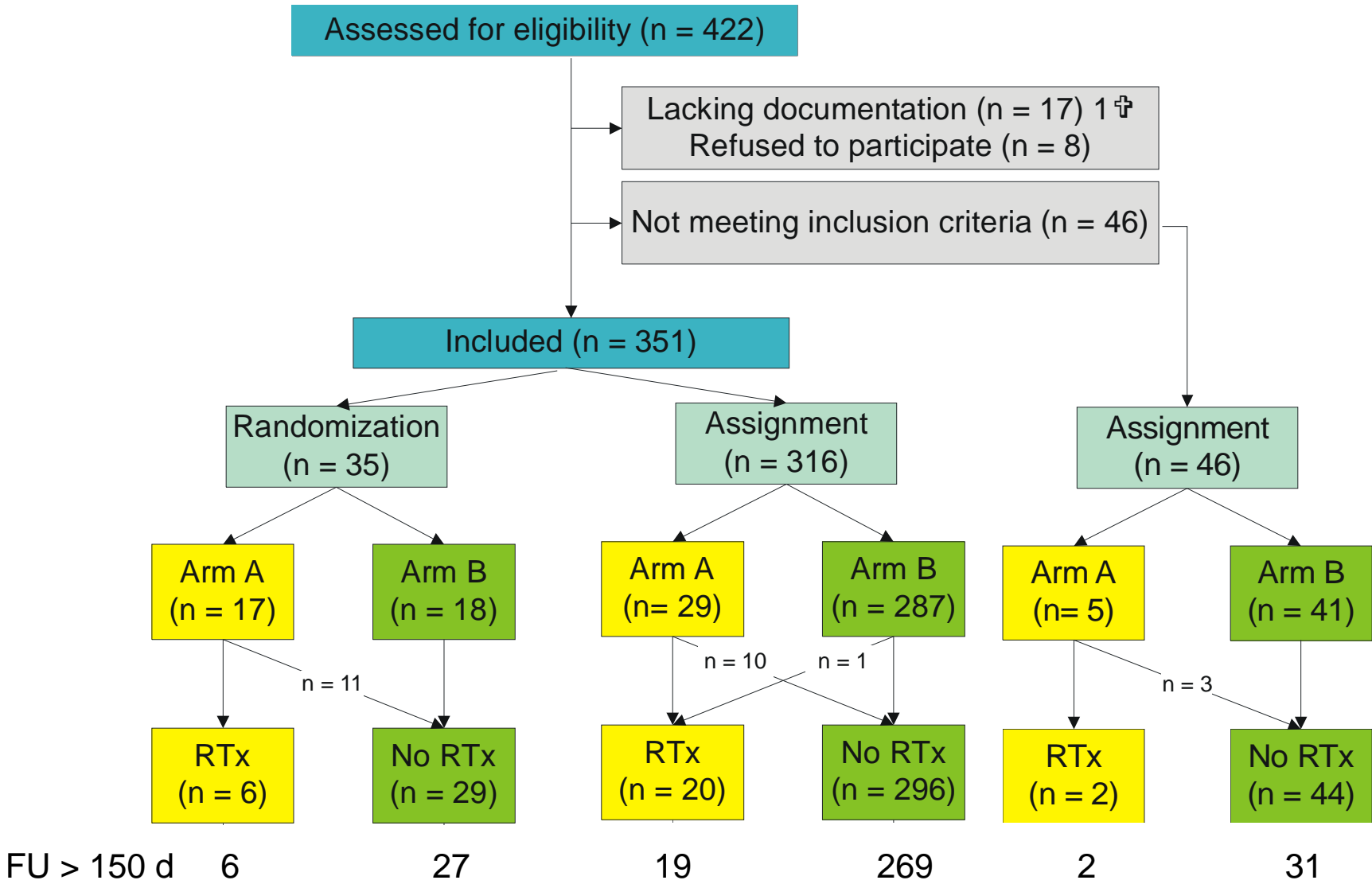
MSDS study cohort

- n = 351 pts.
follow-up 930 d (mean; 21 – 2045) = 930 pt.-yrs.
- age 48 ± 12 J. [20-69],
25 % males
- max. tumour diameter 2.0 ± 1.6 cm [0.3-9.5]
 ≤ 1 cm in 24 % of pts. (!)
- papillary cancer in 88 %
- Arm A (RTx+): 46 pts. (26 RTx+)
Arm B (RTx -): 305 pts. (1 RTx+)

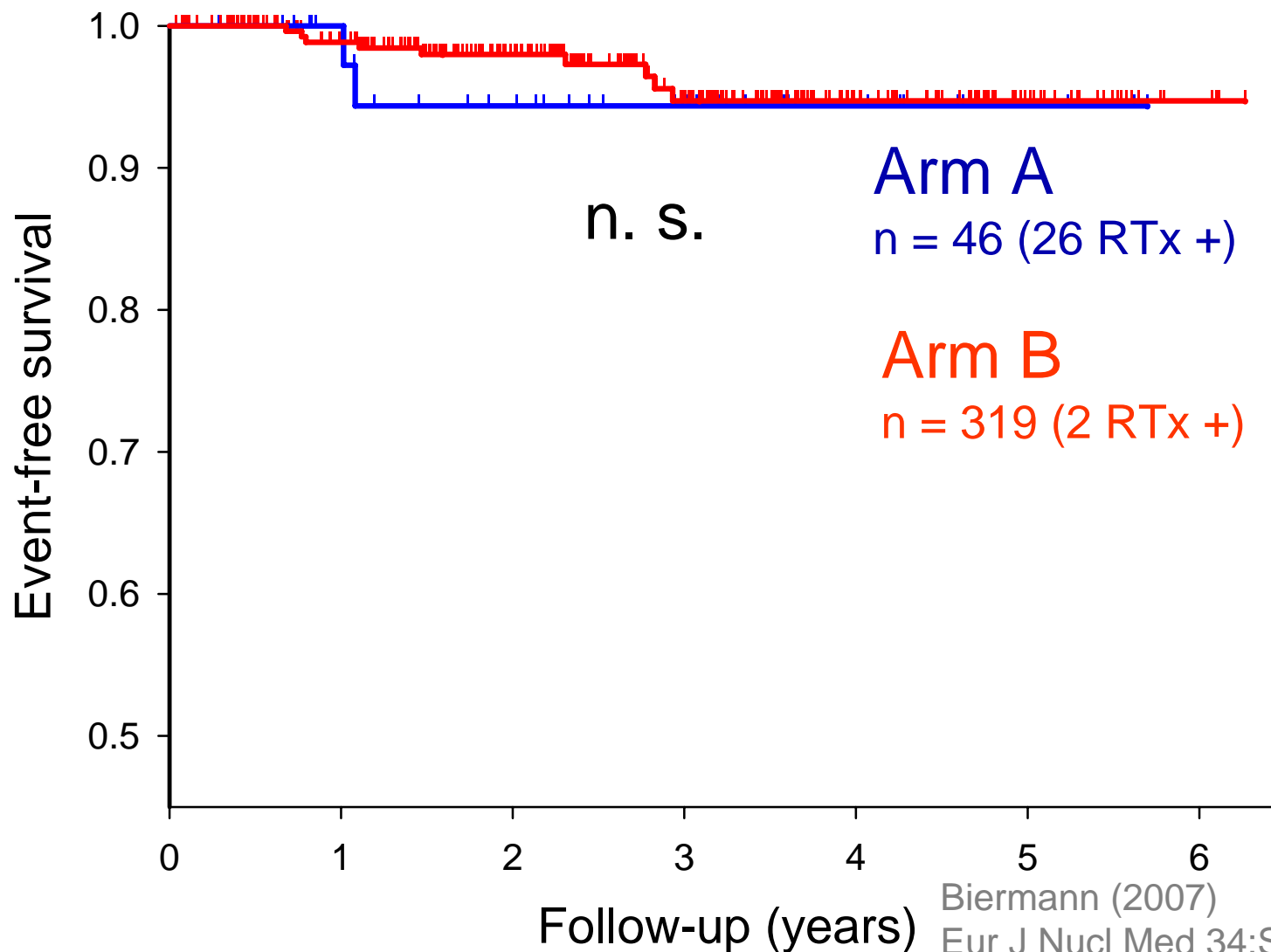
Biermann (2008)
Eur J Nucl Med (submitted)



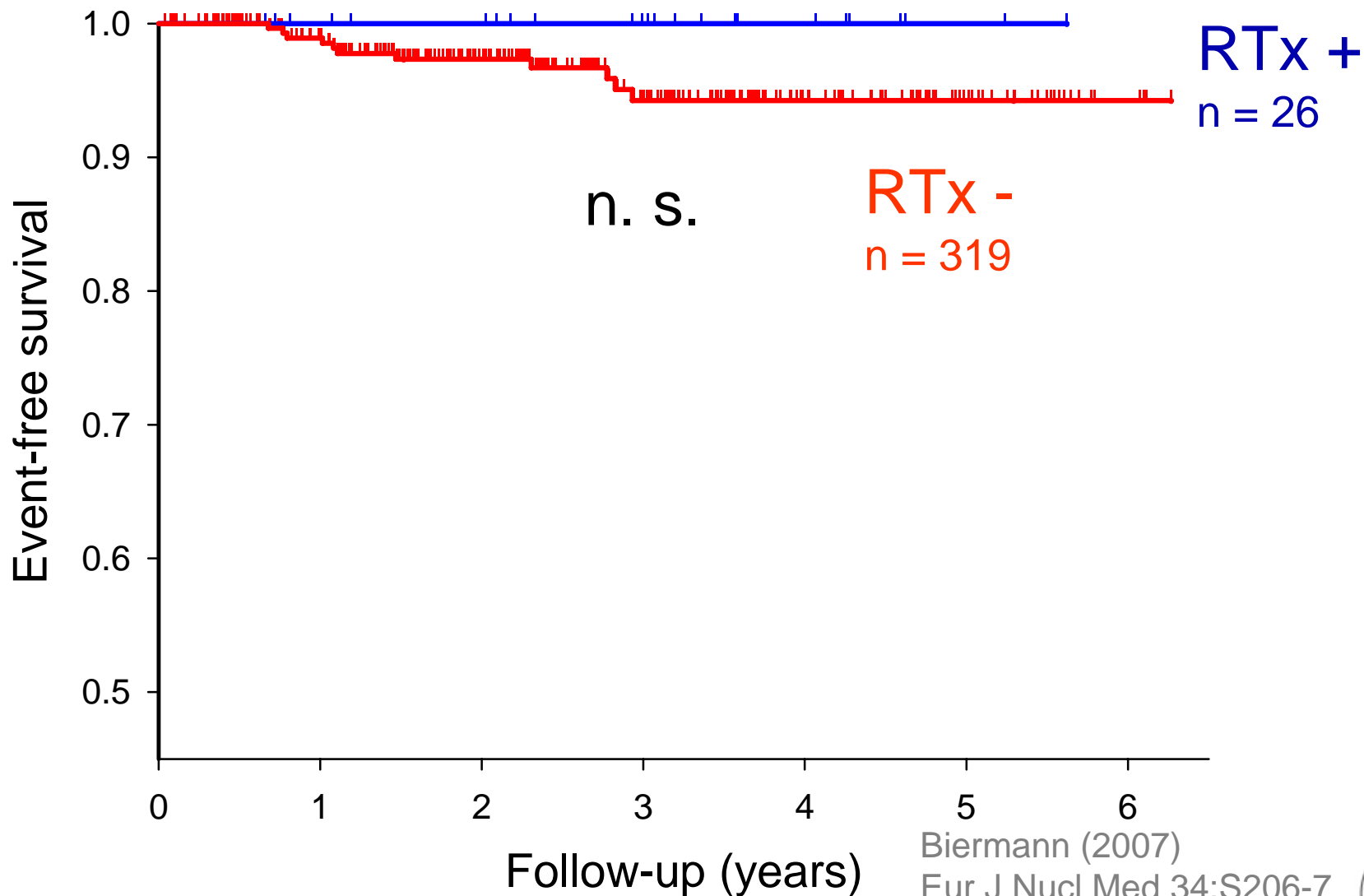
Patient flow



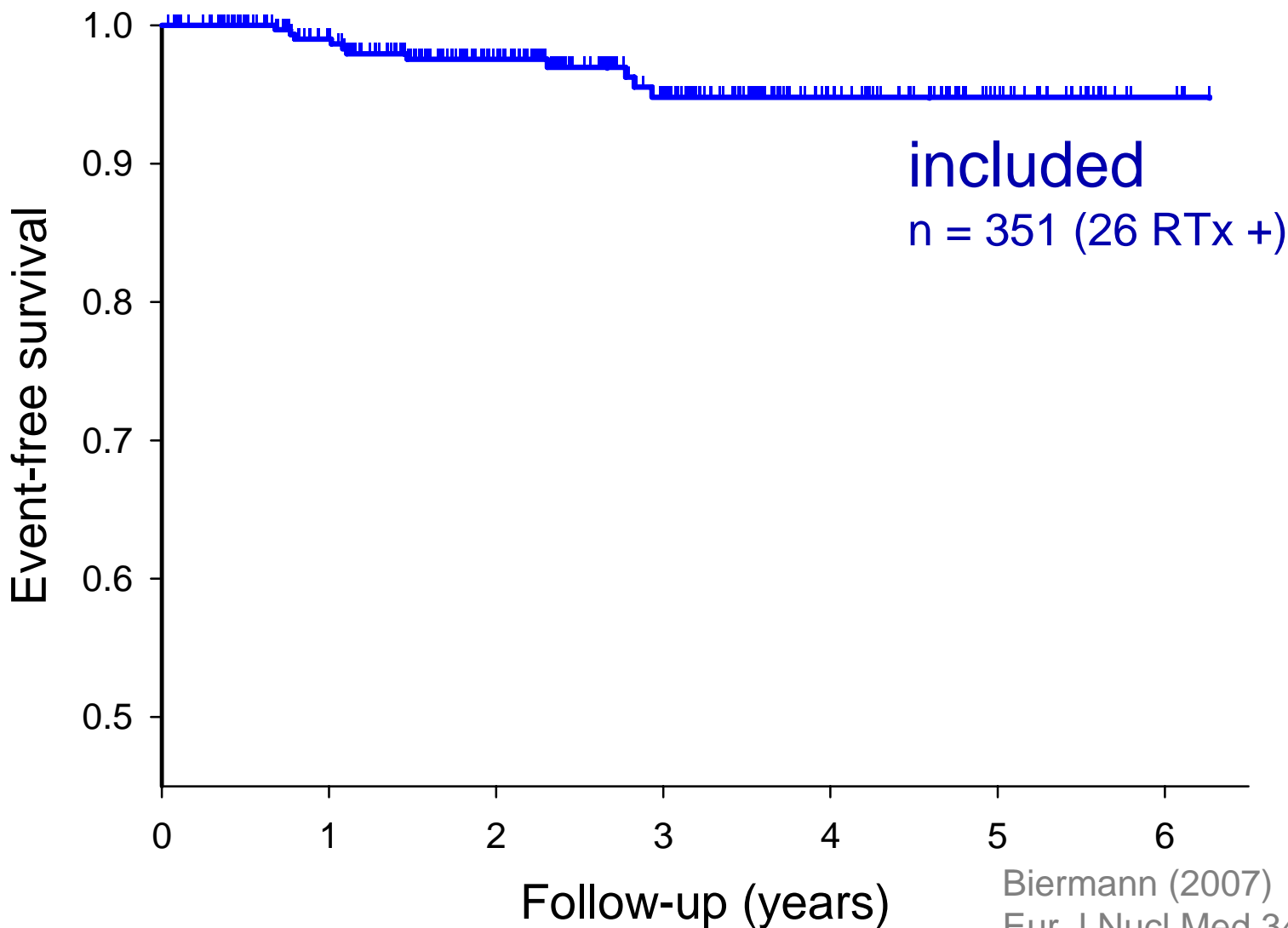
Event-free survival: intention to treat



Event-free survival: actual Tx



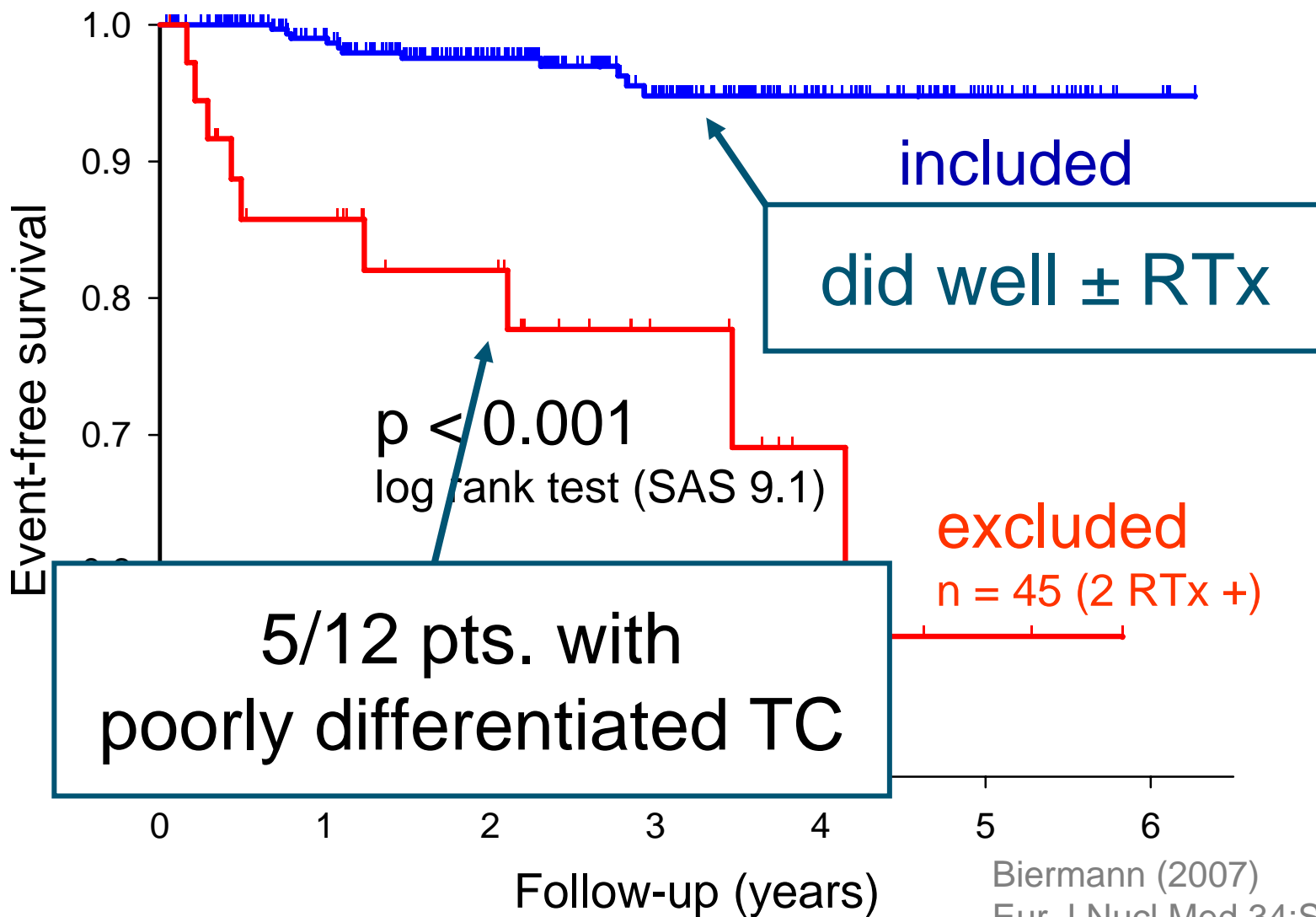
MSDS: event-free survival



Biermann (2007)
Eur J Nucl Med 34:S206-7



MSDS: event-free survival



Biermann (2007)
Eur J Nucl Med 34:S206-7



Events (included patients; n = 356)

#	Arm	Rnd.	RTx	CR	d	Event	Tx	Outcome
1	B	+	-	All RTx -		suicide (in CR)		†
2	A	-	-	-	370	Larynx	OP	Recurrence
3						metastases	OP	CR
4						metastases	OP	PR
5						of v. subclavia	OP	CR
6						metastasis	OP	CR
7						met. (I-131 pos.)	I-131	CR
8						metastases	OP	CR
9	B	-	-	+	842	Lymph node metastases	OP	CR
10	B	-	-	+	1013	Pulmonary metastases (I-131 negative)	-	Progression
11	B	-	-	+	1070	Paratracheal recurrence	OP	CR

11 events:
 1 unrelated to disease
 4 standard surgery
 4 advanced surgery/therapy
 2 potentially fatal (0.6 %)



Events (excluded patients; n = 41)

#	Arm	PDTC	RTx	CR	d	Event	Tx	Outcome
1	A	+	-			Local recurrence	Trach.	
2	B	+	-		1265	Pulmonary metastases (I-131 negative)	OP	
3	B	-	-		60	Locoregional progression	OP	
4	B	+	-		106	Local recurrence	Trach.	†
5	B	-	-				OP	†
6	B	-	-				OP	
7	B	-	-				I-131	CR
8	B	+	-				OP	CR
9	B	+	-					

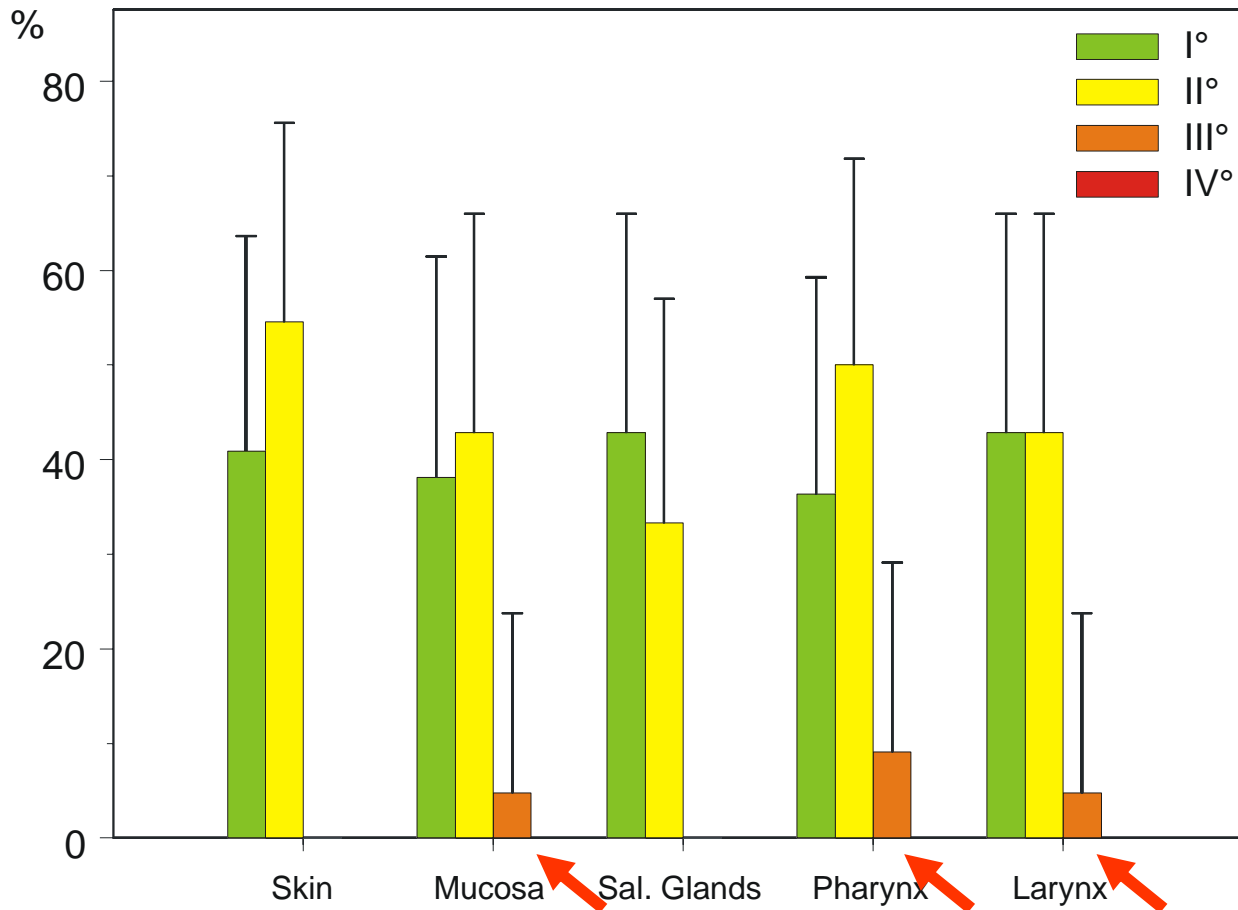
All RTx -

9 events:
 4 (potentially) fatal (10 %)
 Recurrences in 5/12 pts. with poorly differentiated TC

Poorly differentiated TC



Maximum acute RTx toxicity (RTOG)



RTOG III° toxicity:

- mucosa: confluent mucositis, central analgesics
- pharynx: ↑ dysphagia: dehydration or weight loss > 15 %
- larynx: whispering central analgesics

acute III° toxicity in 2 pts.

(2003) Strahlenther Onkol 179:821-7



RTx toxicity

- Acute:
2/22 pts. with RTOG III° toxicity (larynx, pharynx)
reversible

Schuck (2003) Strahlenther Onkol 179:821-7

- Chronic:
1/22 pts. (5 %) with RTOG III/IV° toxicity
(tracheostomy)
95 %-CI 0.1 – 22 % (Fisher's exact test)

13/252 (5 %) pts. with chronic IV° toxicity
after RTx of head & neck cancer

Lee (1995) Int J Radiat Oncol Biol Phys 32:567-76



RTx toxicity

- Acute:

2/22
revert

Serious chronic toxicity in the same order of magnitude as the (potential) treatment effect

, pharynx)

rahlenther Onkol 179:821-7

- Chronic.

1/22 pts. (5 %) with RTOG III/IV° toxicity (tracheostomy)

95 %-CI 0.1 – 22 % (Fisher's exact test)

13/252 (5 %) pts. with chronic IV° toxicity after RTx of head & neck cancer

Lee (1995) Int J Radiat Oncol Biol Phys 32:567-76



Adjuvant external beam RTx for DTC

- Systematic metaanalysis:
 - PubMed „thyroid neoplasms/radiotherapy [MH]“: n = 1697
 - 22 original papers since 1970 with ≥ 10 Pat. \pm RTx
- Statistically significant *benefit* of RTx:

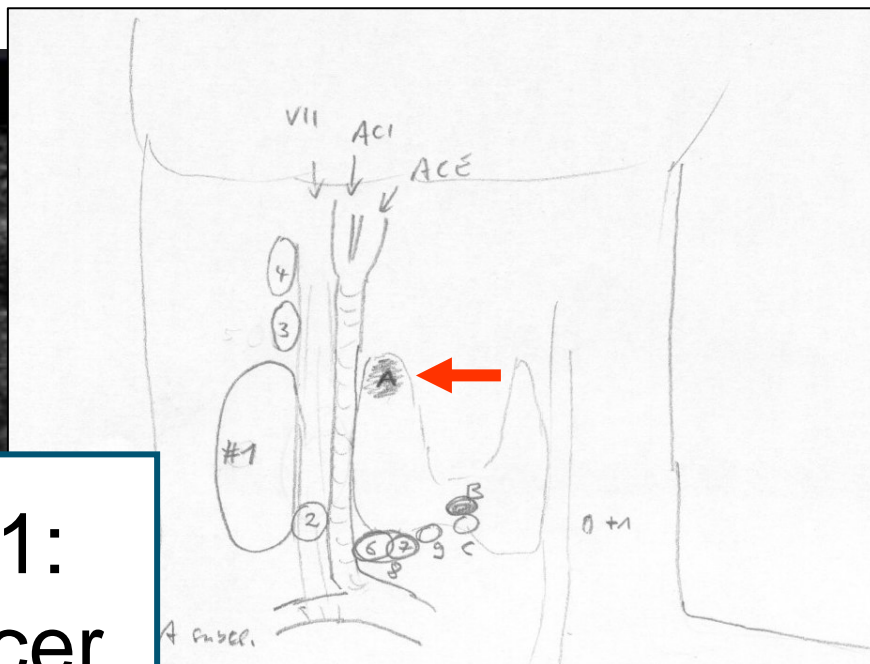
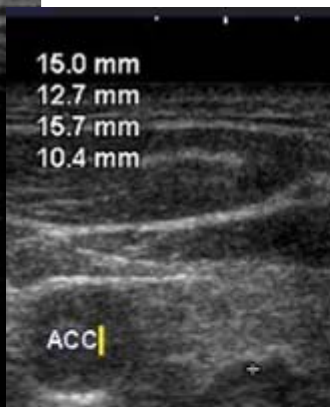
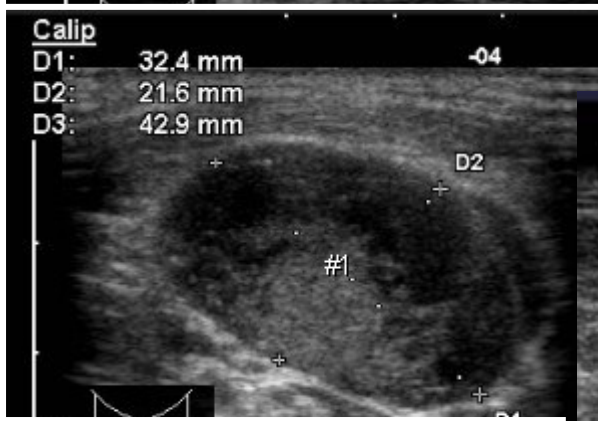
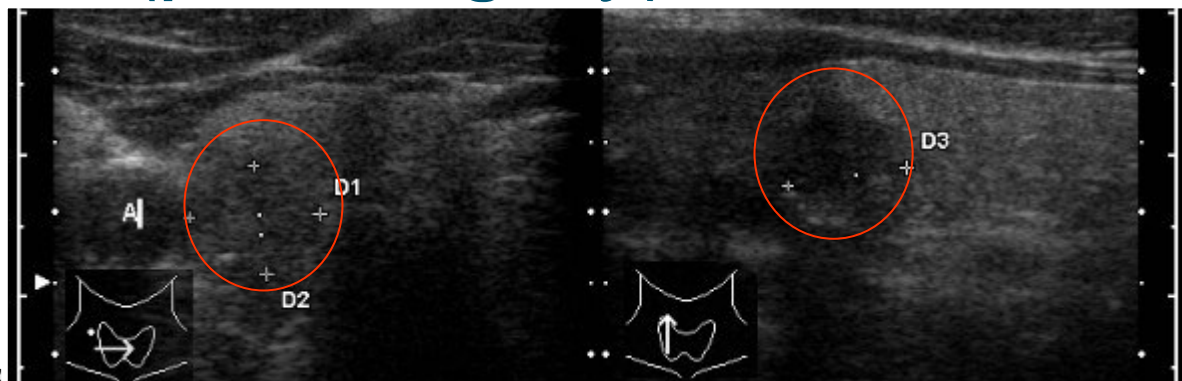
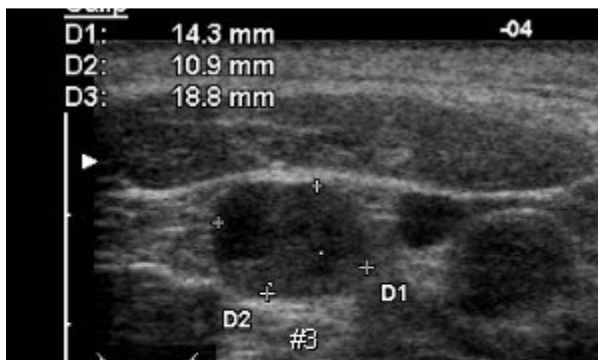
				I-131	local control	survival
1982	W Germany	Leisner	PTC pT4	yes		+
1987	China	Wu	TC R1/2	no		+
1988	Canada	Simpson	PTC R1	+/-	+	
1994	Hungary	Esik	PTC	no	+	+
1996	W Germany	Farahati	PTC pT4 N1 > 40 J.	yes	+	
1998	Canada	Tsang	PTC R1	+/-	+	+
2002*	Hong Kong	Chow	PTC R2	yes	+	+
2003*	S Korea	Kim	PTC pT4 or N1	yes	+	
					6/22	5/22

- Are these results applicable to *today's* state-of-the-art treatment in specialized centres in Europe?

Biermann (2005) In: Biersack, Thyroid Cancer, 2nd. ed, Springer, 139-61

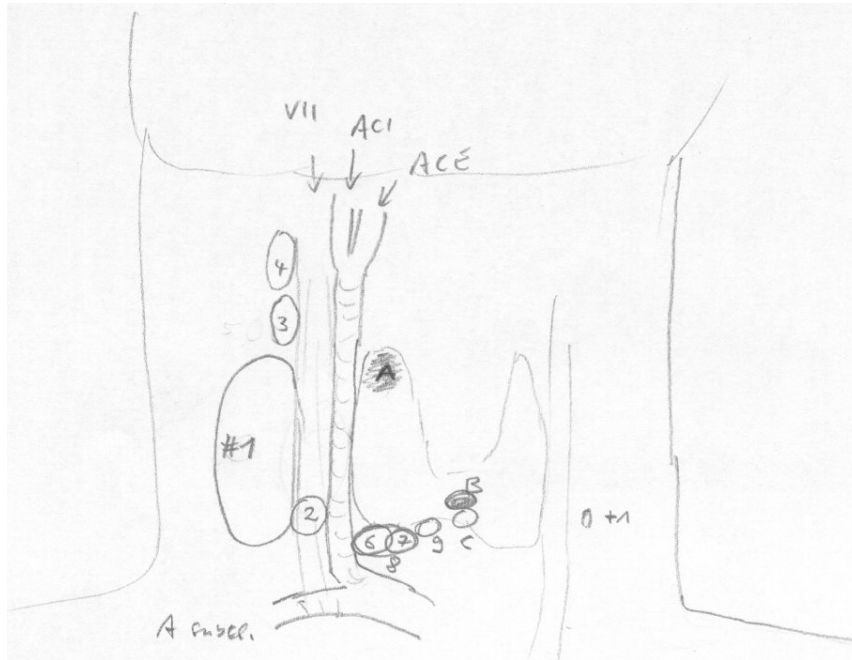


Ultrasound (pre surgery) m 42 yrs.



**FNAC lymph node #1:
papillary thyroid cancer**

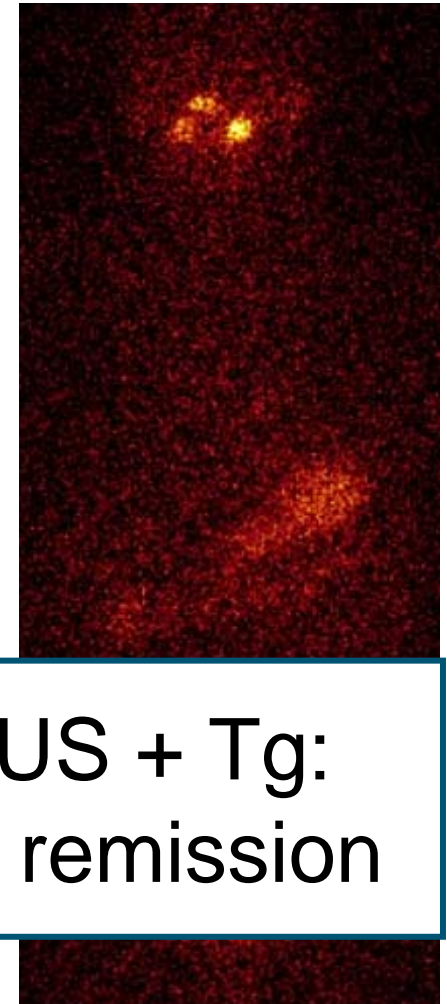
PTC pT3a (1 cm) pN1 (25/42 LK) m. 42 yrs.



1 operation 9/2006:
total thyroidectomy +
LN diss. central + R lat.
25/44 LK pos.



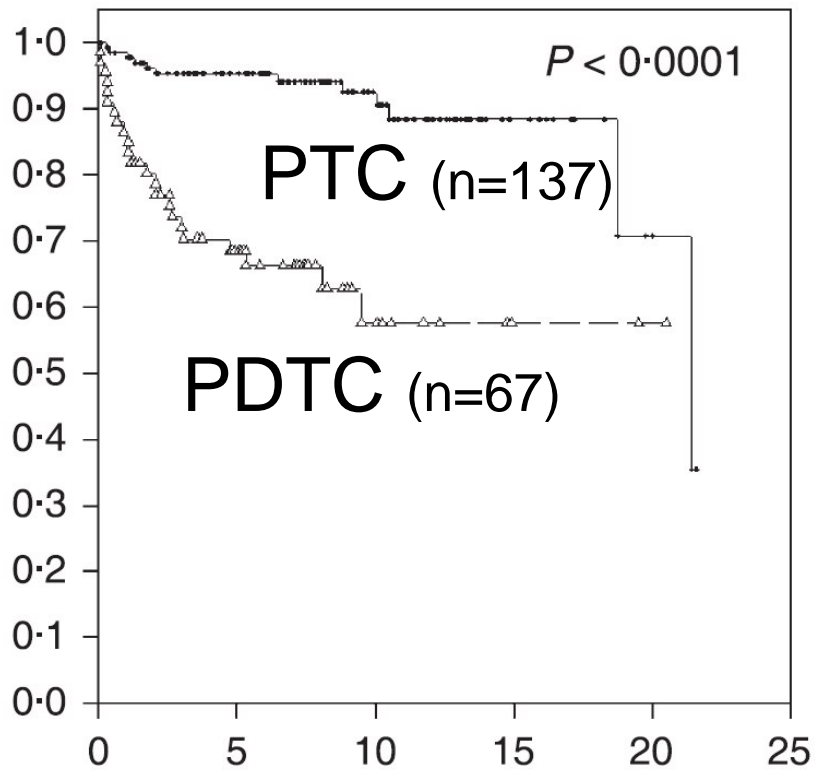
11/2006 (3 GBq)



11/2007 (200 MBq)

I-131 + US + Tg:
complete remission

Poorly differentiated TC: survival



Follow-up (yrs.) 1978 - 2005

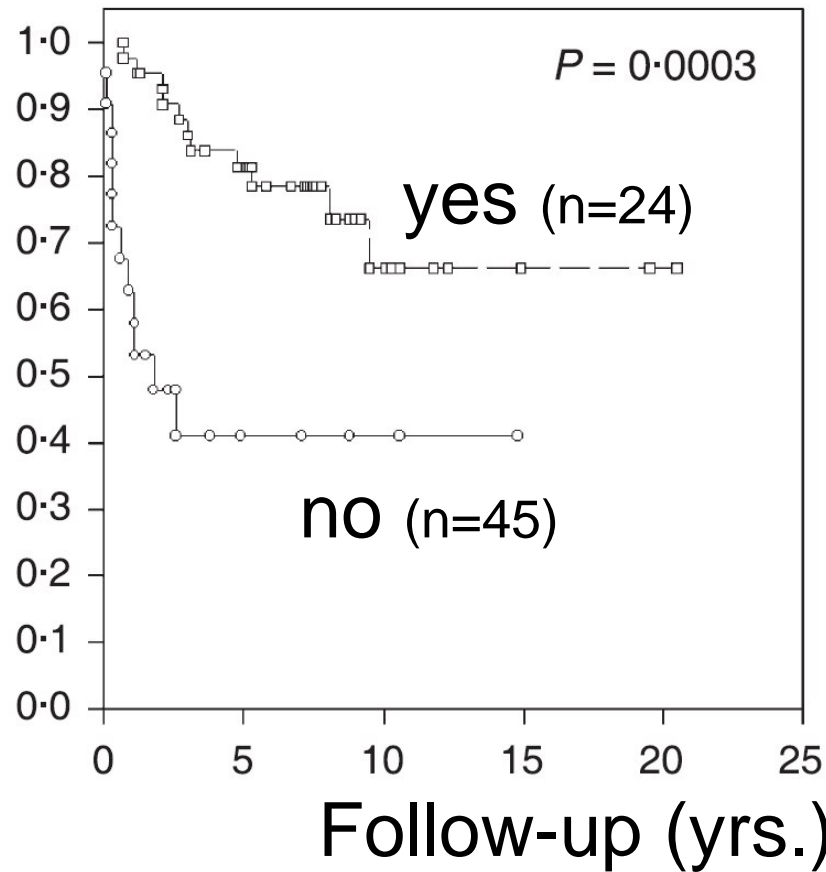
Chang Gang Mem. Hosp.
Taiwan

Lin (2007) Clin Endocrinol (Oxf) 66:224-8

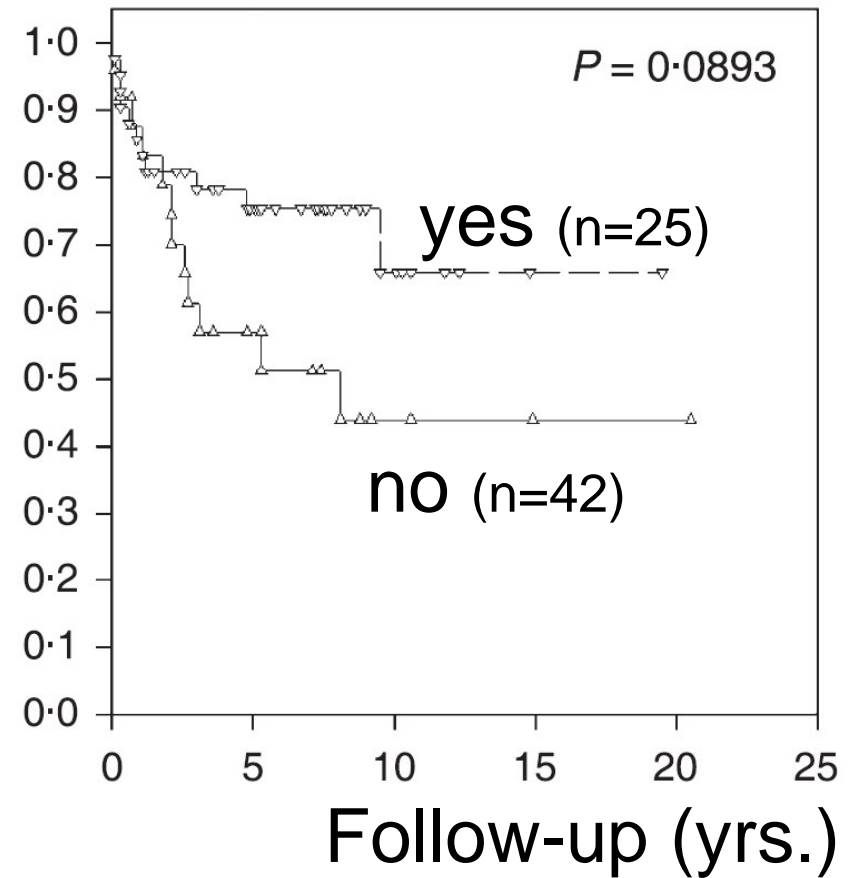


Poorly differentiated TC: survival

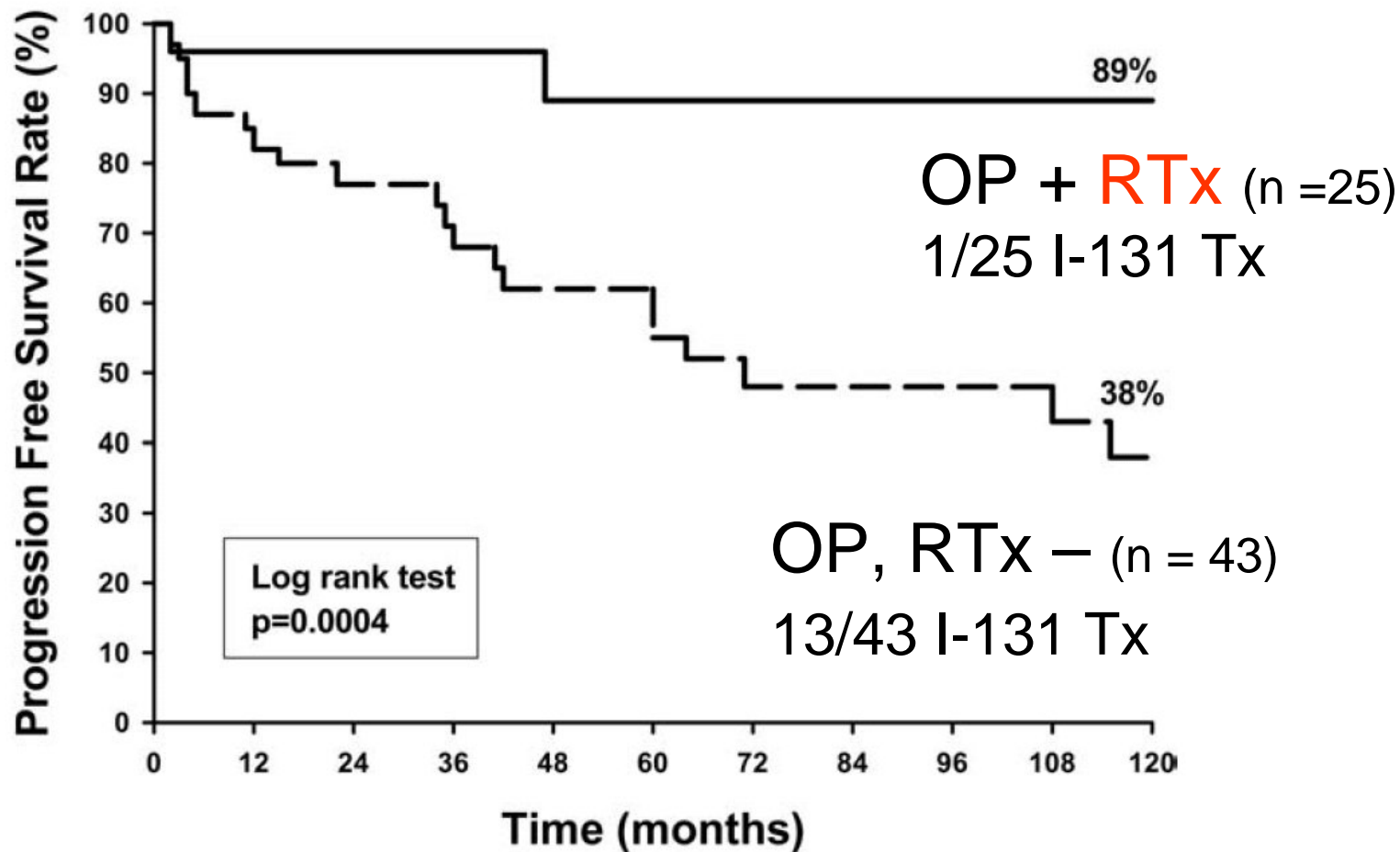
I-131 treatment



RTx



DTC invading the trachea



Summary

- Systematic metaanalysis:
only 4/22 studies showed a benefit of RTx in DTC

Biermann (2005) In: Biersack, Thyroid Cancer, 2nd. ed, Springer, 136-61

- MSDS-trial:
 - No statistically significant benefit of external beam RTx in addition to surgery, I-131-Tx and TSH-suppression in DTC pT3b pN0/1/x M0 (UICC 2002) 18 – 69 yrs.
 - Event rate of 3 % much lower than expected (18 %)
 - RTx toxicity in same order of magnitude:

Routine RTx in DTC pT3b/4 can no longer be recommended

- Recurrences in 5/11 pts. with poorly differentiated cancer !
Role for RTx ?

Funded by the Deutschen Krebshilfe e. V.