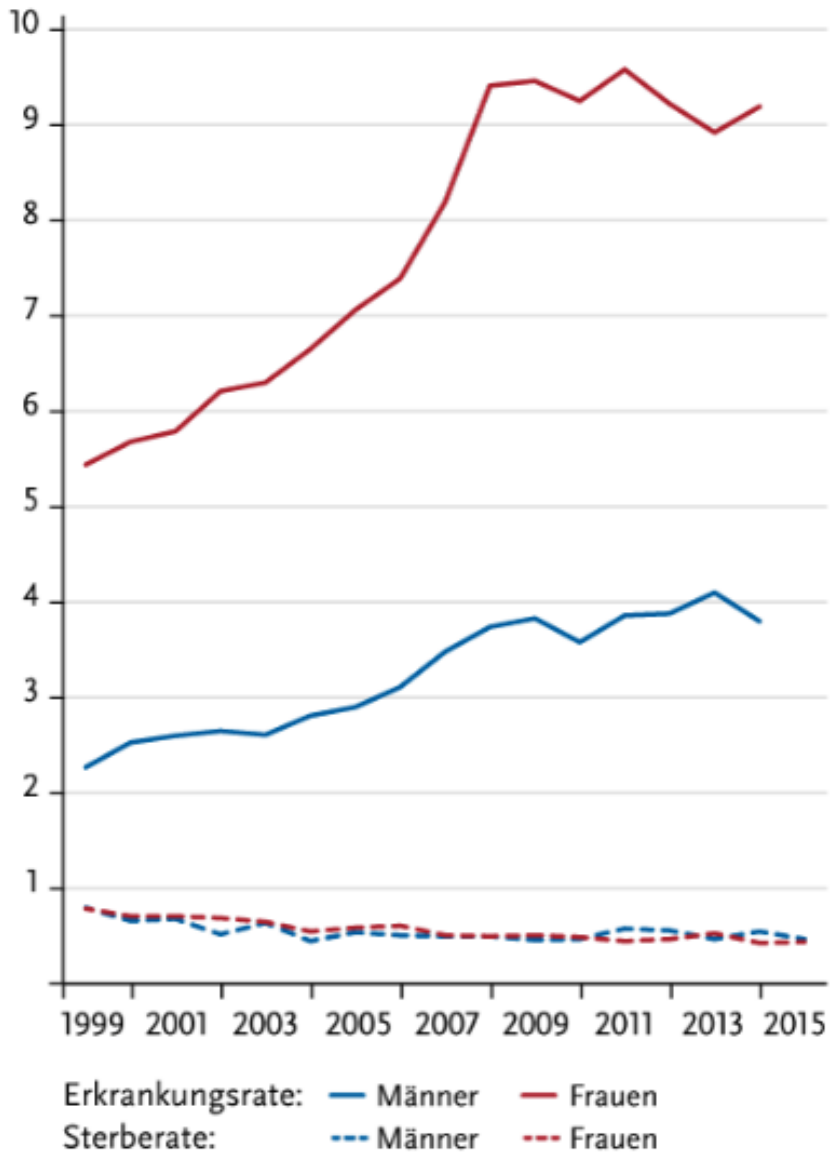
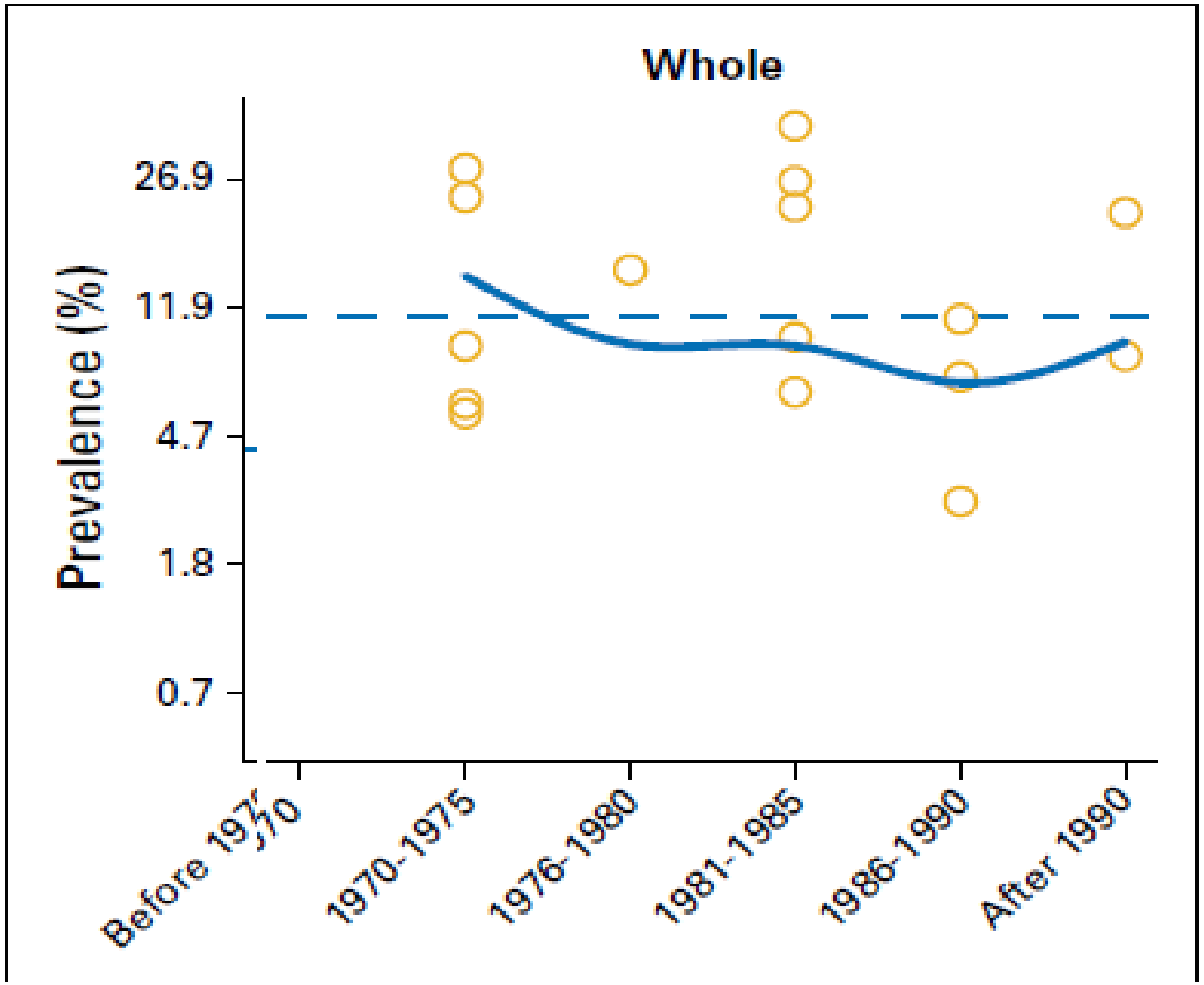
Welcher Patient benötigt eine hochdosierte Radiojodtherapie?

GEMEINSAME JAHRESTAGUNG
ÖGES und OSDG

Assoc.-Prof. PD Dr. med. Alexander Haug



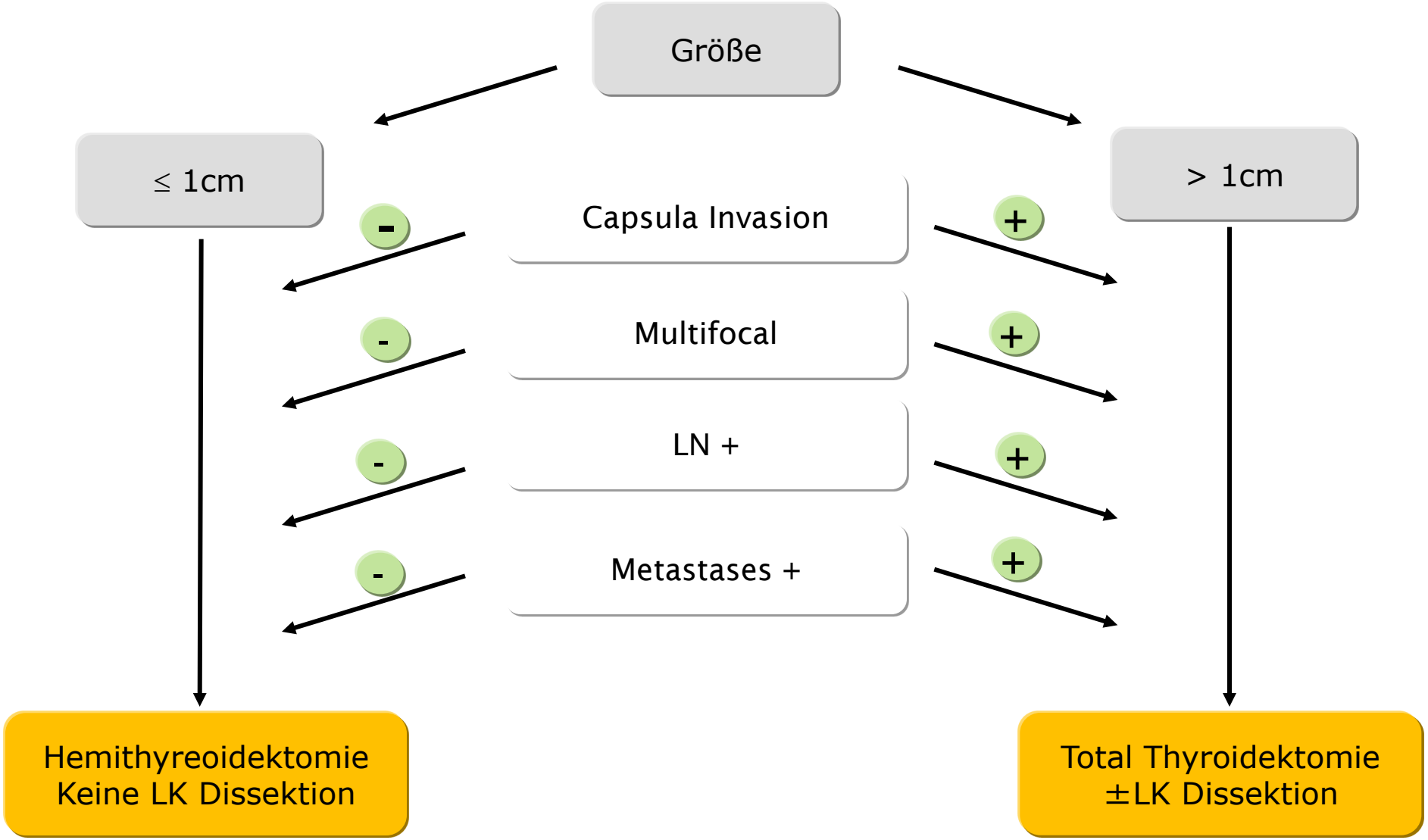


Furuya-Kanamori et al, JCO 2016

Radiojodtherapie

- Jod-131
  - Kombinierte beta- und gamma-Strahlung
    - Therapeutische Wirkung durch beta-Strahlung
    - Möglichkeit der Bildgebung und Dosimetrie durch gamma-Strahlung
  - Reichweite der beta-Strahlung im Gewebe ca. 0,3 mm
  - Halbwertszeit von 8 Tagen
  - Wird wie „normales“ Jod von Schilddrüsenzellen aufgenommen und verstoffwechselt
  - Wird über den Urin ausgeschieden

Status quo Chirurgie



ATA Guideline Chirurgie

- **RECOMMENDATION 35**

(A) For patients with thyroid cancer >4 cm, or with gross extrathyroidal extension (clinical T4), or clinically apparent metastatic disease to nodes (clinical N1) or distant sites (clinical M1), the initial surgical procedure should include a near-total or total thyroidectomy and gross removal of all primary tumor unless there are contraindications to this procedure.

(Strong recommendation, Moderate-quality evidence)

(B) For patients with thyroid cancer >1 cm and <4 cm without extrathyroidal extension, and without clinical evidence of any lymph node metastases (cN0), the initial surgical procedure can be either a bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy alone may be sufficient initial treatment for low-risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable RAI therapy or to enhance follow-up based upon disease features and/or patient preferences.

(Strong recommendation, Moderate-quality evidence)

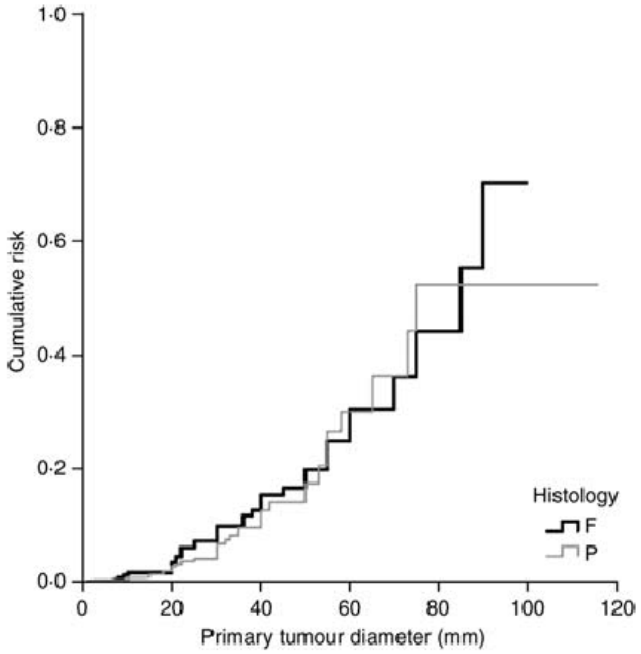


Fig. 2 Cumulative risk of distant metastasis by primary tumour diameter in patients with follicular (F) or papillary (P) thyroid cancer.

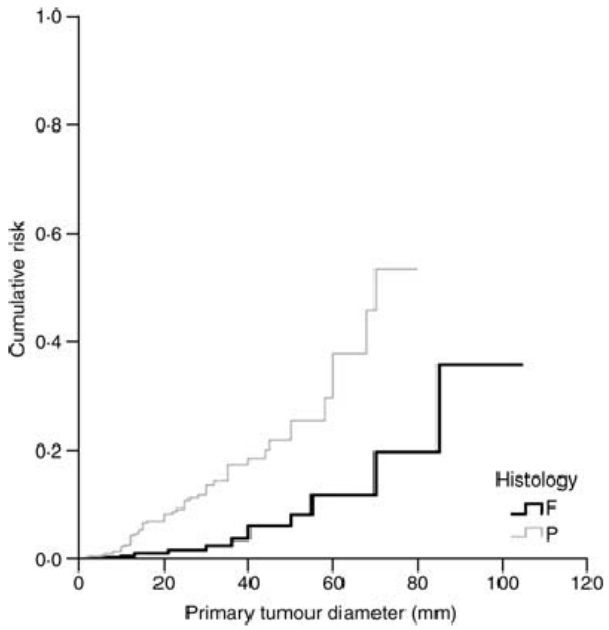
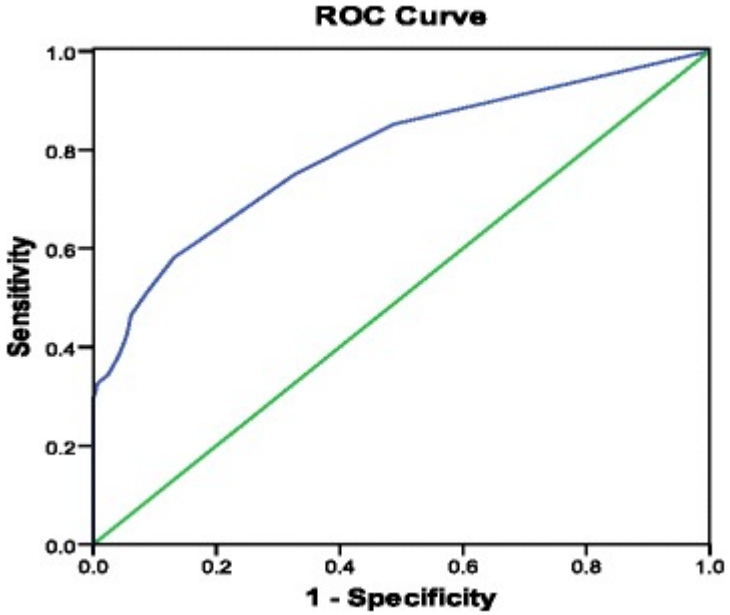


Fig. 4 Cumulative risk of lymph-node metastasis by primary tumour diameter in papillary (P) and follicular (F) thyroid carcinoma.

Verburg et al., Clinical Endocrinology 2009

Diagnostische Genauigkeit Sonographie



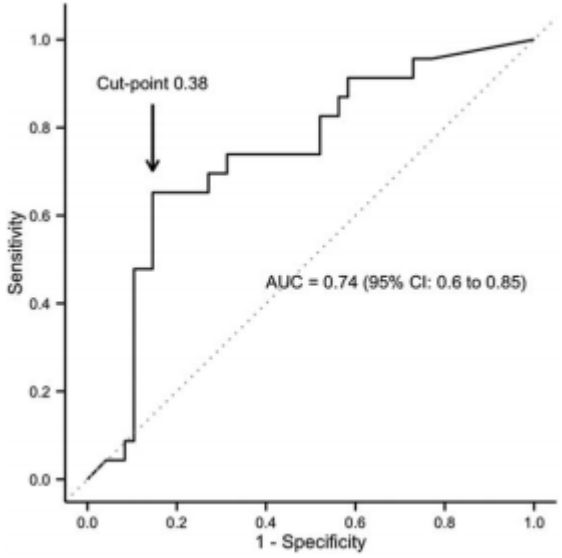


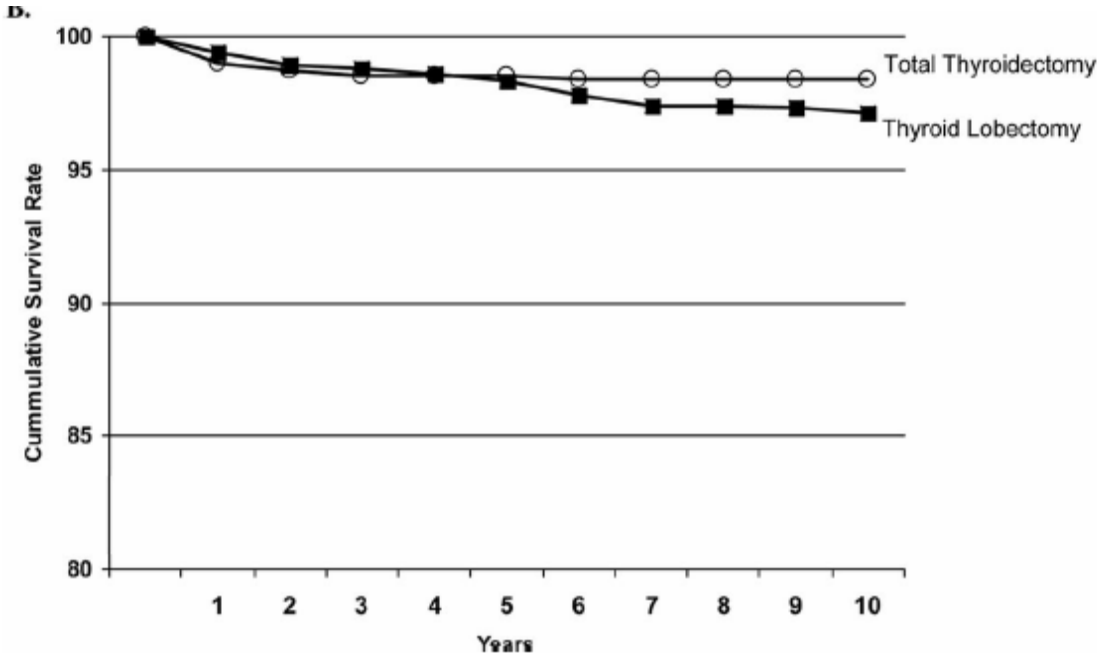
TABLE 4. HUS FOR THE ASSESSMENT OF MCLN

	MCLN positive	*MCLN negative*	*Total*
HUS positive	39	12	51
HUS negative	65	111	176
Total	104	123	227

Liu et al., World J Surg Oncol 2017
Khokhar et al., Thyroid 2015
Patel et al., J Clin Ultrasound 2015

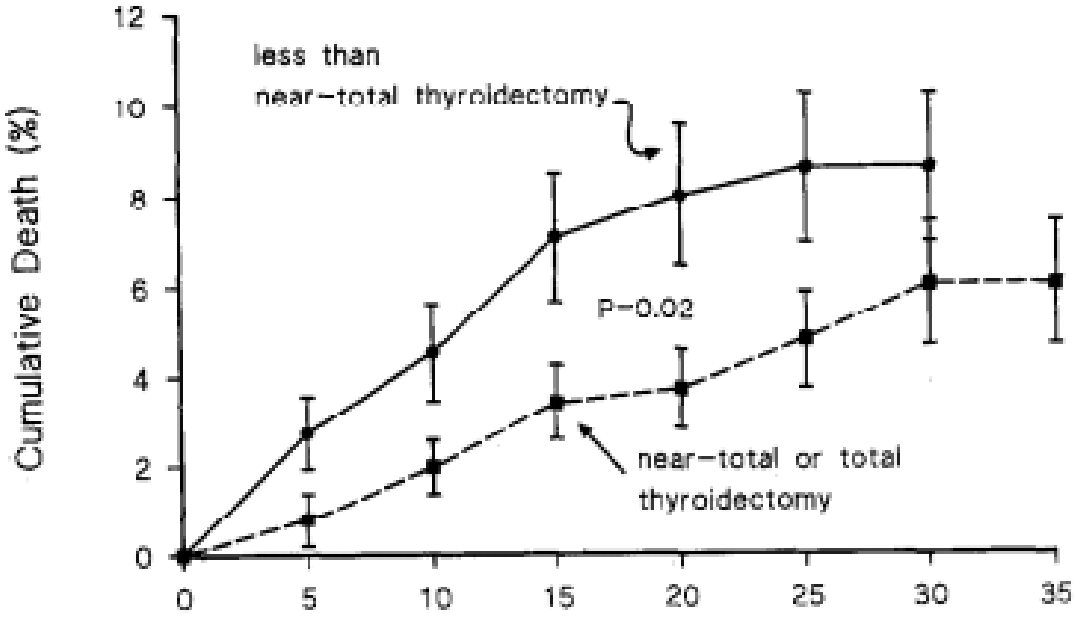
Chirurgie: Prognose

42.952 Pat. – pap. SD-CA (National Cancer Database)
82.9 % Thyroidektomie, 17.1 % Lobektomie



	Hazard Ratio (95% Confidence Interval)				
	All Patients	< 1.0 cm	≥ 1.0 cm	1.0–2.0 cm	2.1–4.0 cm
No. patients	42,952	10,247	32,705	12,778	16,365
Survival					
Total thyroidectomy	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Lobectomy	1.21 (1.02–1.44) $P = 0.027$	1.02 (0.74–1.41) $P = 0.83$	1.31 (1.07–1.60) $P = 0.009$	1.49 (1.02–2.17) $P = 0.04$	1.31 (1.01–1.69) $P = 0.04$

Barczynski et al. Ann Surg 2011

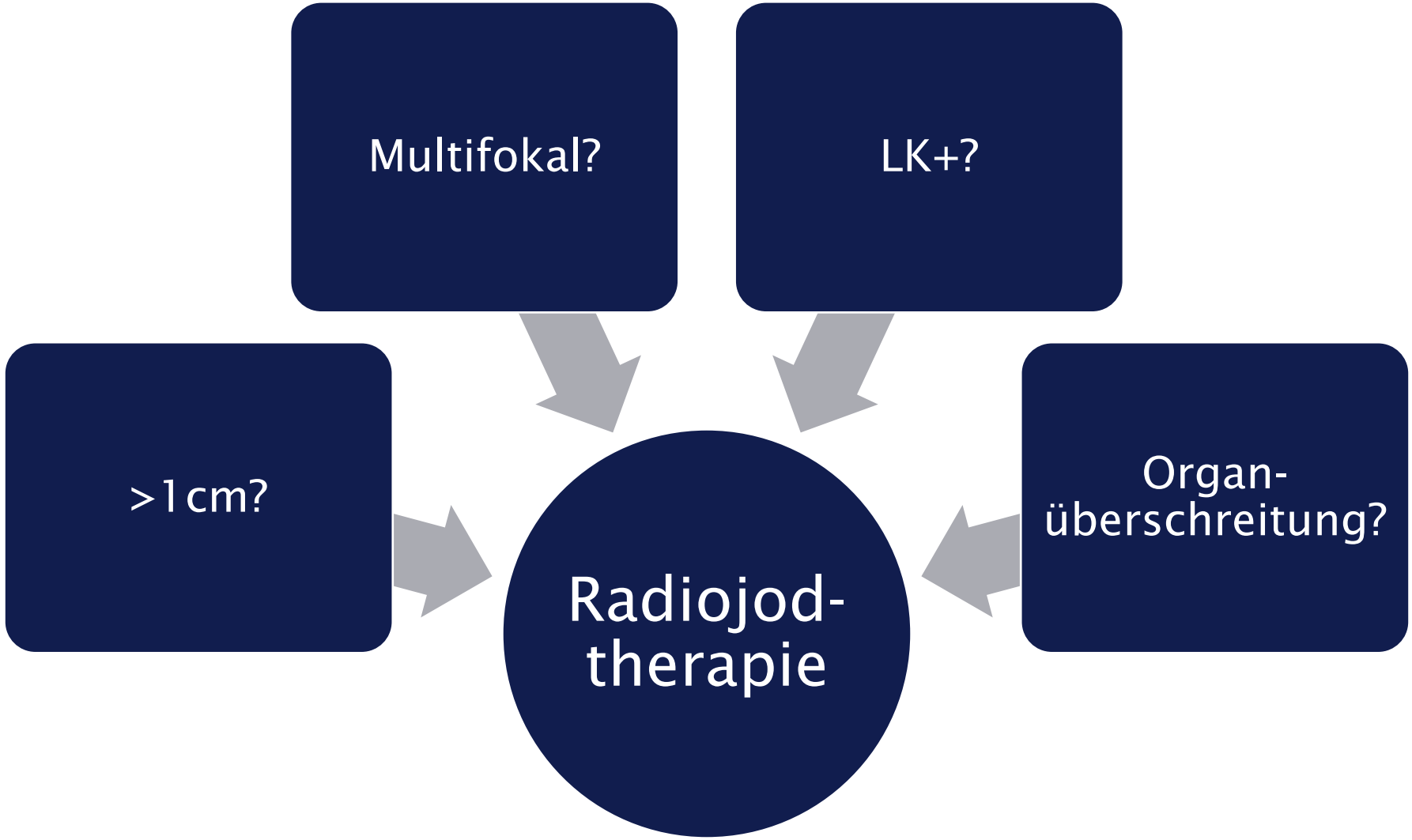


Mazzaferri et al, Am J Medicine 1994

ATA Guideline

- Lässt viel Spielraum für subjektive Entscheidungen (kann-Empfehlungen)
- Teils nur bedingt durch Evidenz gedeckt (Lobektomie, moderate-quality evidence)
- Erschwert follow-up
  - Lobektomie → TG
  - Sonographische Verlaufskontrollen des verbliebenen Lappens (was tun bei Auftreten von Knoten?)
- Radiojodtherapie?

Status quo Radiojodtherapie



ATA Guideline

- **RECOMMENDATION 51 (details in Table 14)**

(A) RAI remnant ablation is not routinely recommended after thyroidectomy for ATA low-risk DTC patients. Consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preferences are relevant to RAI decision-making.

(Weak recommendation, Low-quality evidence)

(B) RAI remnant ablation is not routinely recommended after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in the absence of other adverse features.

(Strong recommendation, Moderate-quality evidence)

(C) RAI remnant ablation is not routinely recommended after thyroidectomy for patients with multifocal papillary microcarcinoma in absence of other adverse features. Consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preferences are relevant to RAI decision-making.

(Weak recommendation, Low-quality evidence)

(D) RAI adjuvant therapy should be considered after total thyroidectomy in ATA intermediate-risk level DTC patients.

(Weak recommendation, Low-quality evidence)

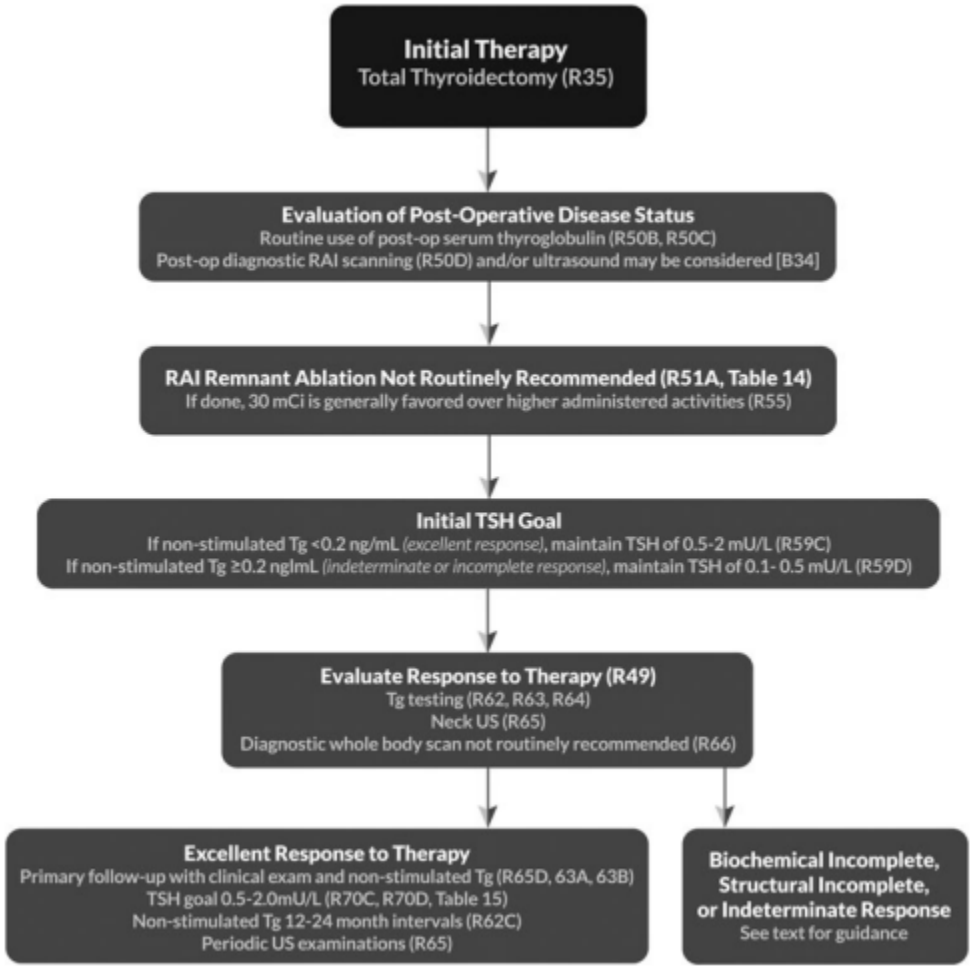
(E) RAI adjuvant therapy is routinely recommended after total thyroidectomy for ATA high risk DTC patients

(Strong recommendation, Moderate-quality evidence)

Grundlage für Änderungen?
Keine neue hoch-qualitative Evidenz…

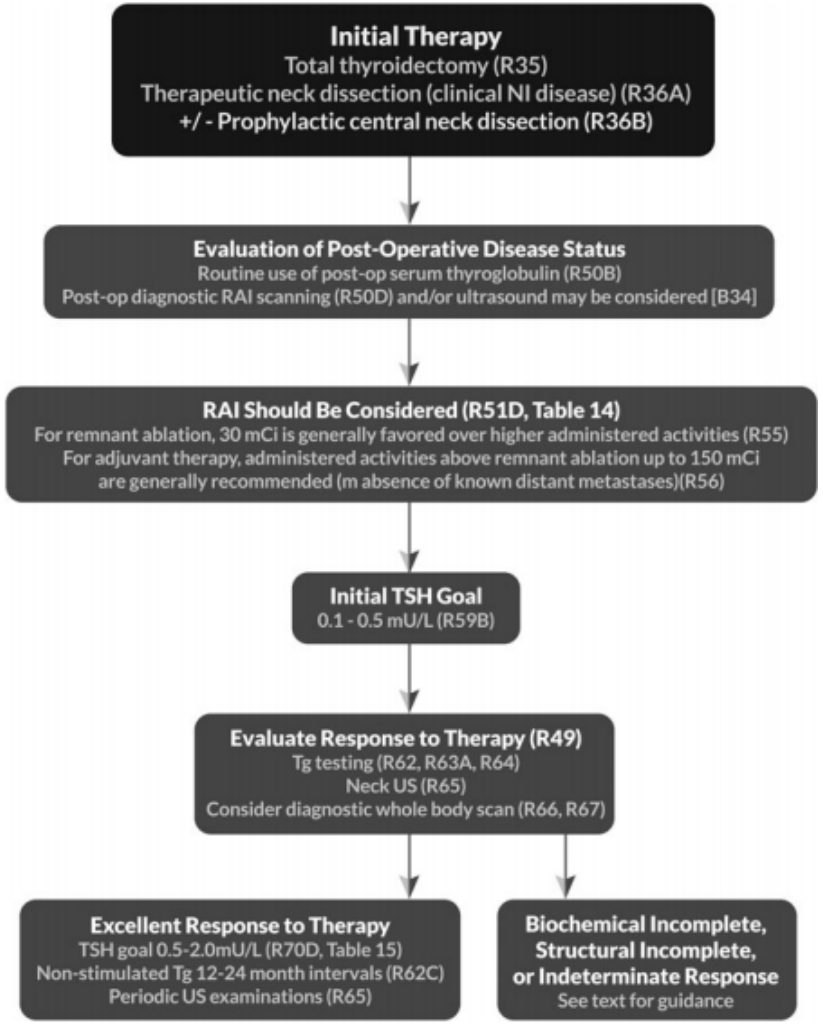
ATA Guideline – Radiojodtherapie
low-risk SD-Ca

ATA risk Staging (TNM)		*Postsurgical RAI indicated?*
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1 cm (uni-or multi-focal)	No
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1–4 cm	Not routine[b]—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).



ATA Guideline – Radiojodtherapie
intermediate-risk SD-Ca

ATA risk Staging (TNM)		*Postsurgical RAI indicated?*
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Consider[b]—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.[a]
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic ETE, any tumor size	Consider[b]—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.
ATA low to intermediate risk T1-3 N1a M0,Mx	Central compartment neck lymph node metastases	Consider[b]—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2–3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a] However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0,Mx	Lateral neck or mediastinal lymph node metastases	Consider[b]—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a]



ATA Guideline – Radiojodtherapie
high-risk SD-Ca

ATA risk Staging (TNM)		*Postsurgical RAI indicated?*
ATA high risk T4 Any N Any M	Any size, gross ETE	Yes
ATA high risk M1 Any T Any N	Distant metastases	Yes

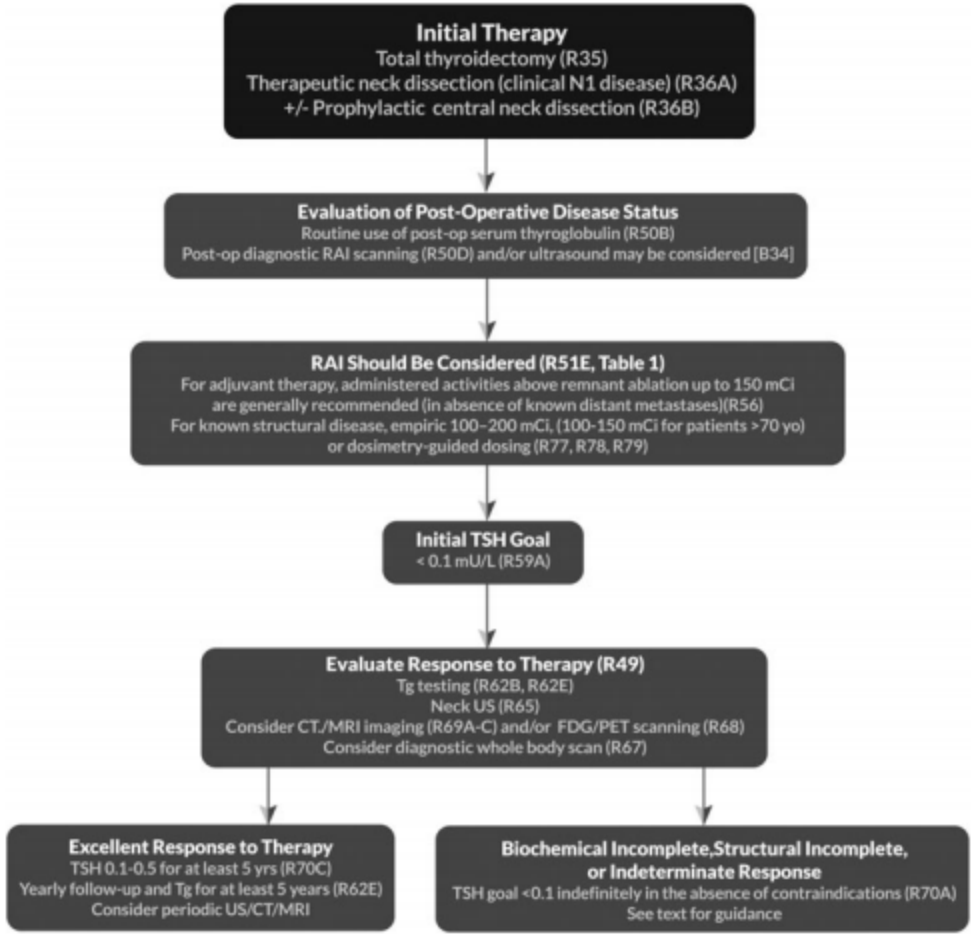


Table 3. ATA 2015[a]: Overview of Strength of Recommendations and Quality of Evidence

Classification	*% (n) of recommendations*[b]
Strength of recommendation	
Strong	55.0% (99/180)
Weak	38.9% (70/180)
None	6.1% (11/180)
Quality of evidence	
High	3.3% (6/180)
Moderate	41.7% (75/180)
Low	49.4% (89/180)
Insufficient	5.6% (10/180)
Strength of recommendation, quality of evidence	
Strong, high	3.3% (6/180)
Strong, moderate	36.1% (65/180)
Strong, low	15.6% (28/180)
Weak, high	0% (0/180)
Weak, moderate	5.6% (10/180)
Weak, low	33.3% (60/180)
No recommendation	6.1% (11/180)

[a]Reference (1)

Luster et al. Thyroid 2019

Was ändert das?

Table 2 Cohort classification ($N = 336$) regarding thyroid remnant ablation: ATA 2015 versus ATA 2009

Classification, % (n)	ATA 2009 [4]	ATA 2015 [5]
Clear indication	32.7 % (110)	26.8 % (90)
Possible indication ("Recommendation")	28.6 % (96)	42.0 % (141)
No indication	38.7 % (130)	31.3 % (105)

Bauchgefühl?
Subjektive Erfahrungen?
Mag ich „meinen“ Nuklearmediziner?

Frangos et al. EJNMMI 2016

Prognose

TABLE 12. AMERICAN THYROID ASSOCIATION RISK STRATIFICATION SYSTEM: CLINICAL OUTCOMES FOLLOWING TOTAL THYROIDECTOMY AND RADIOIODINE REMNANT ABLATION OR ADJUVANT THERAPY

ATA risk	*Study*	*NED, %*	*Biochemical incomplete, %*[b]	*Structural incomplete, %*[c]
Low	Tuttle *et al.* (538)	86	11	3
	Castagna *et al.* (542)	91	ND[a]	ND[a]
	Vaisman *et al.* (539)	88	10	2
	Pitoia *et al.* (543)	78	15	7
Intermediate[a]	Tuttle *et al.* (538)	57	22	21
	Vaisman *et al.* (539)	63	16	21
	Pitoia *et al.* (543)	52	14	34
High	Tuttle *et al.* (538)	14	14	72
	Vaisman *et al.* (539)	16	12	72
	Pitoia *et al.* (543)	31	13	56

[a]Because the ATA intermediate- and high-risk groups were merged into a single "high-risk" group in the series by Castagna *et al.* (542), risk of persistent/recurrent disease for these subgroups is not presented.

[b]Proportion of patients with a biochemical incomplete response. *Definition:* suppressed Tg >1 ng/mL, TSH-stimulated Tg >10 ng/mL, or rising anti-Tg antibody levels in the absence of structural disease.

[c]Proportion of patients with persistent/recurrent disease that is structural. *Definition:* structural disease that is either biopsy-proven or highly suspicious for disease with or without abnormal serum Tg.

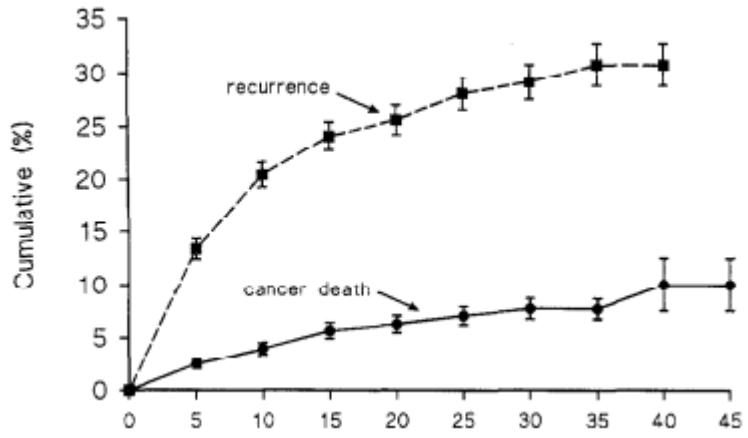
ND, not determined.

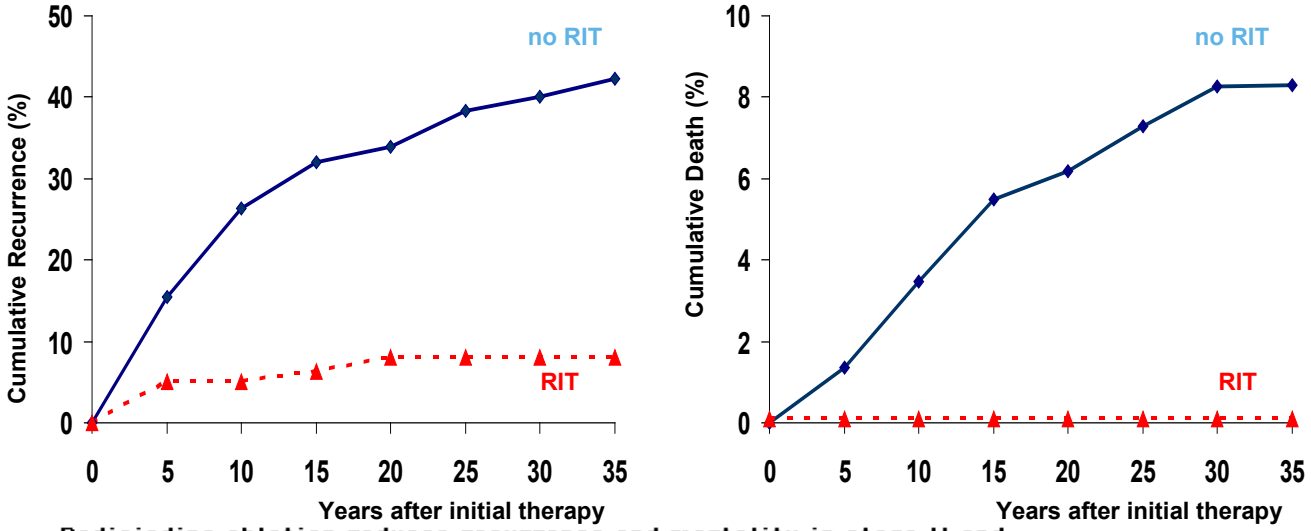
Benefit der Radiojodtherapie

Am J Med 1994; 97: 418

Long-Term Impact of Initial Surgical and Medical Therapy on Papillary and Follicular Thyroid Cancer

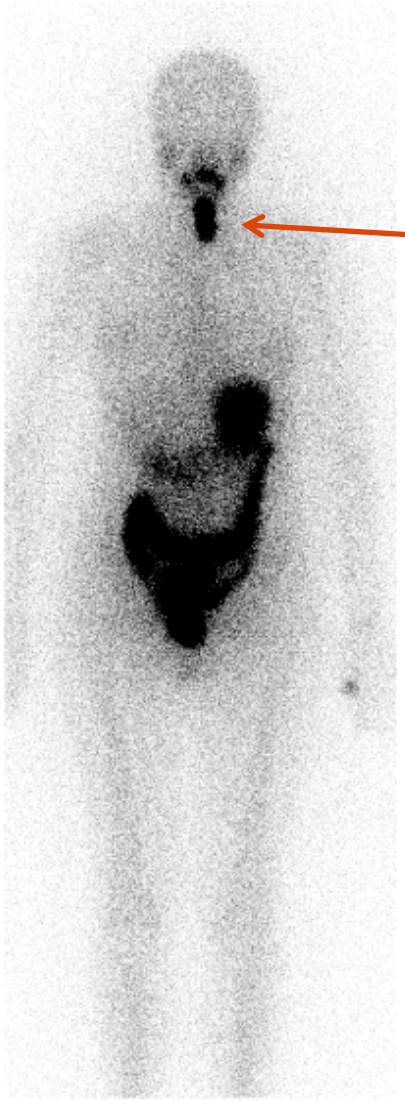
Ernest L. Mazzaferri, MD, FACP, Sissy M. Jhiang, PhD, *Columbus, Ohio*



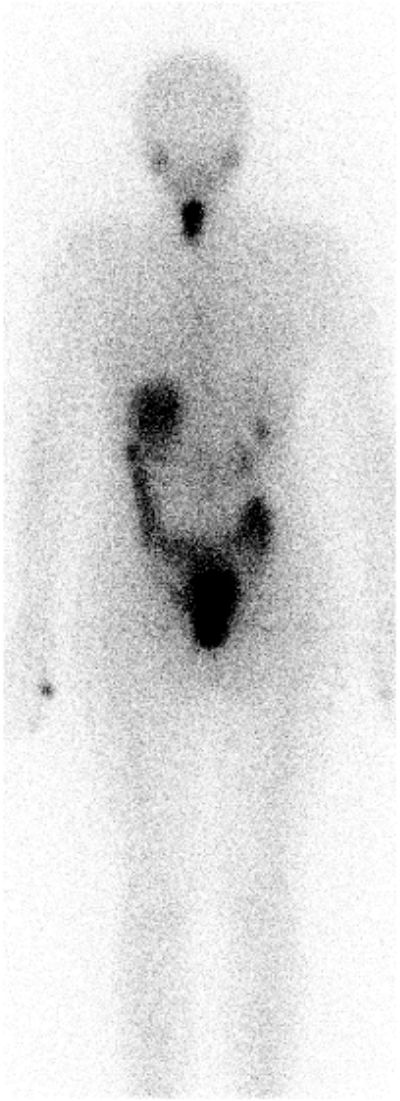


Radioiodine ablation reduces recurrence and mortality in stage II and stage III thyroid cancer Long-term development of recurrent disease (left panel) or death (right panel) from thyroid cancer in patients without distant metastases at presentation, who received either 131-I ablation (red dashed lines) or no ablation (blue solid lines). (Data from Mazzaferri, EL, Jhiang, SM, Am J Med 1994; 97:418.)

Low-dose vs. High-dose RIT



1%!



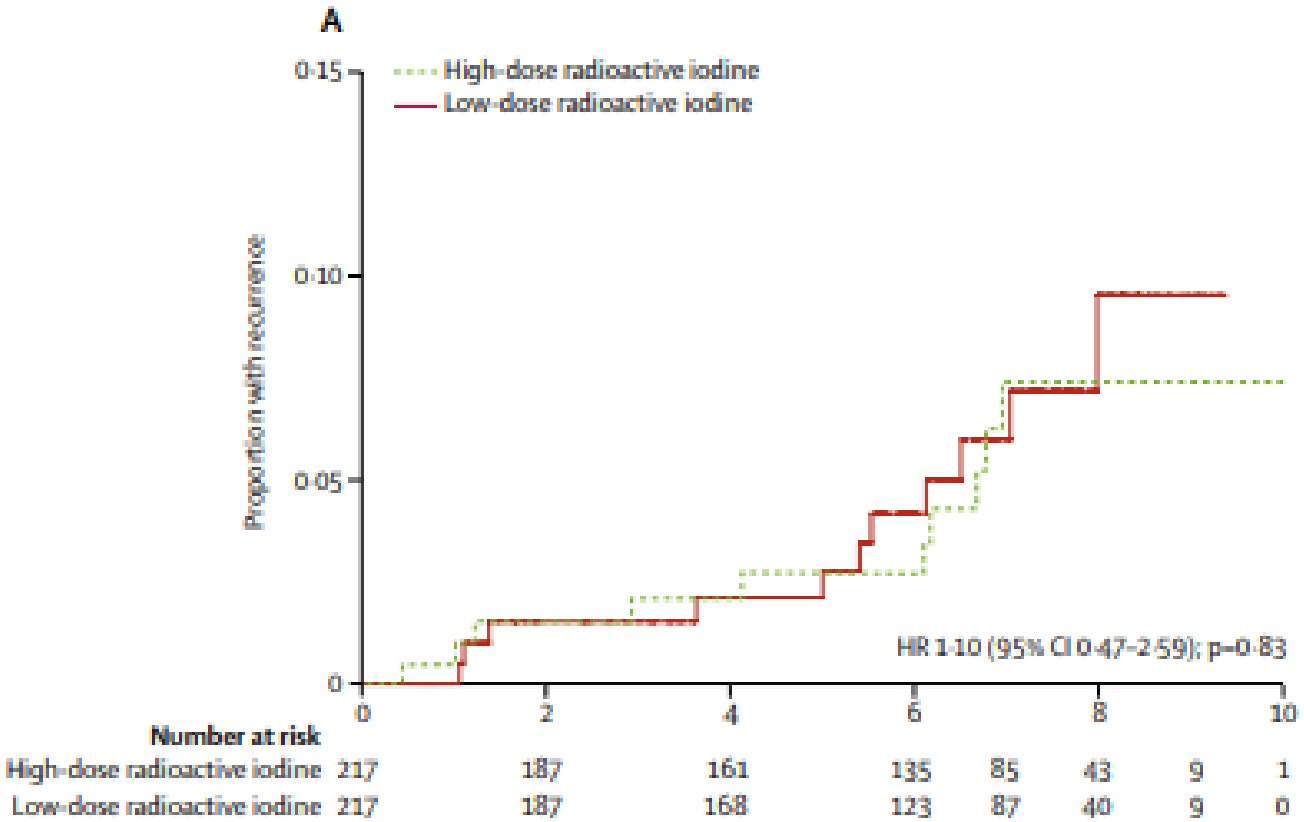
Ablationserfolg:

TG <2,0

Uptake <0,1%

Mallick et al. NEJM 2012

Low-dose vs. High-dose RIT - Rezidiv



Dehbi *et al.*, Lancet Diabet & Endocr, 2018

Prognose - Therapieaktivität

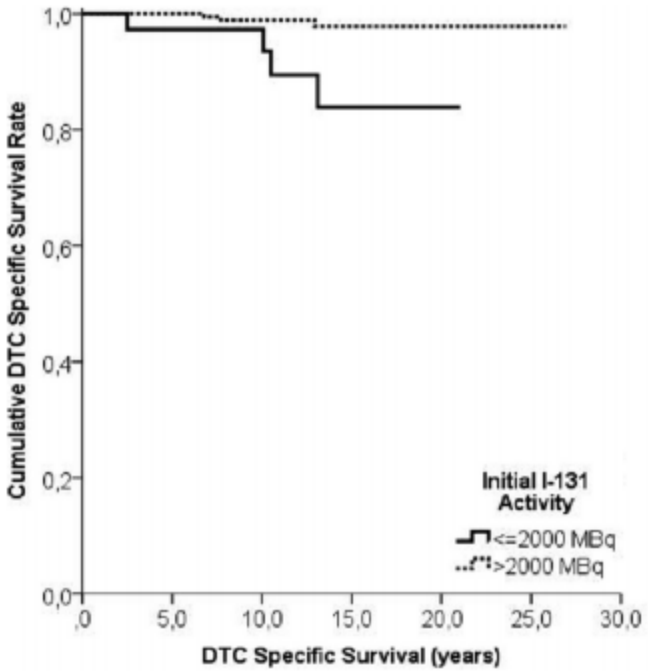


Figure 1. DTC-specific survival in low-risk patients ≥45 years at diagnosis, stratified according to ablation activity.

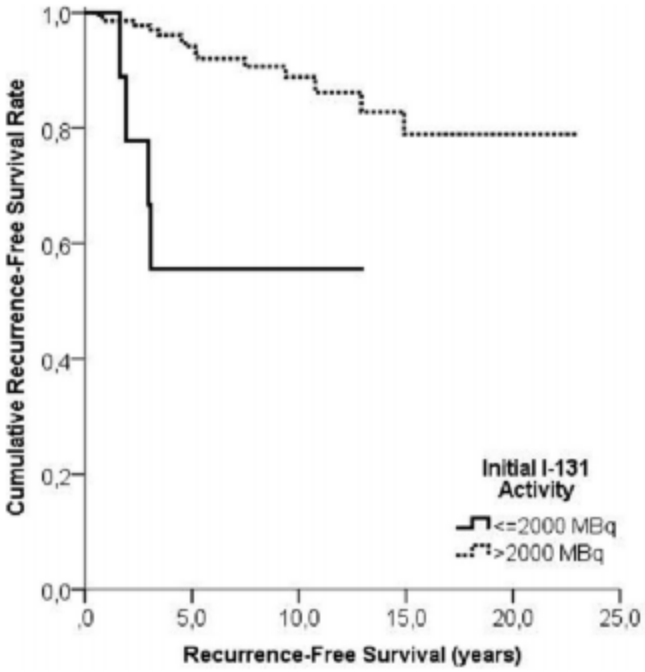
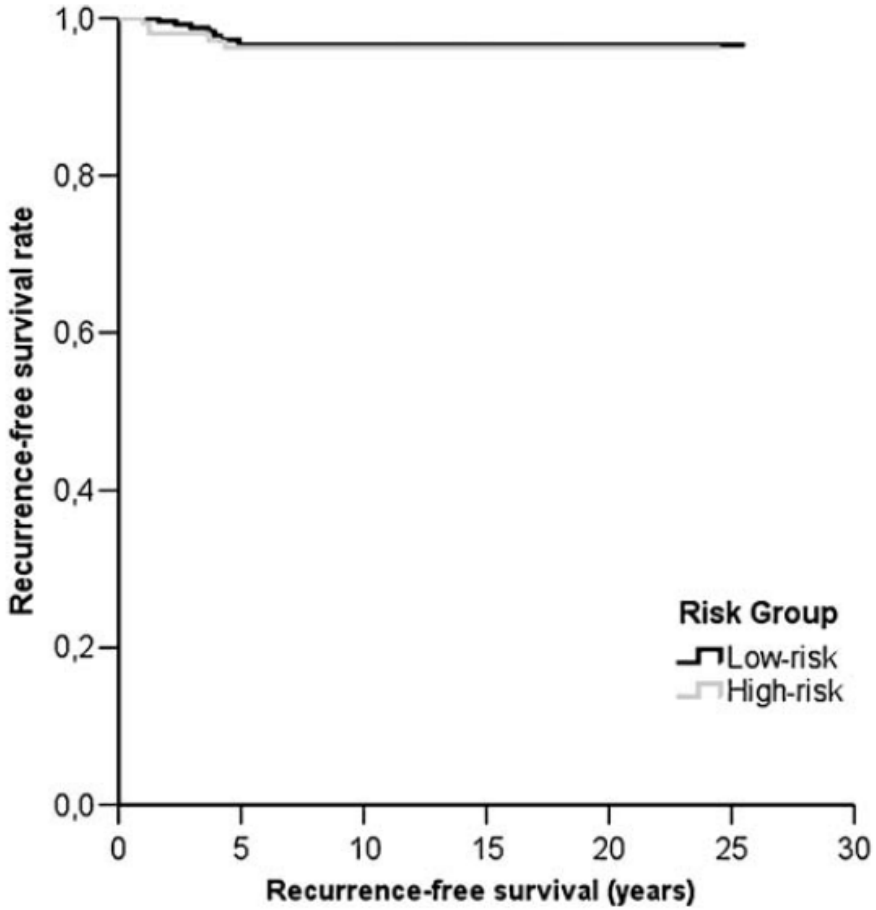


Figure 2. Recurrence-free survival in high-risk patients without distant metastases ≥45 years at diagnosis, stratified according to ablation activity.

Verburg FA *et al.*, J Clin Endocrinol Metab 2014

Radiojodtherapie



Nach einer erfolgreichen RIT gleiche Prognose von low-risk und high-risk Stadien

Verburg FA *et al.*, EJNMMI, 2010

Risiken der RIT

Table 5. Cancer Mortality per 10 000 Person-years at Risk in the Patients With Treated Hyperthyroidism and in the Age- and Sex-matched Control Group

	Patients			Controls			Patients vs Controls	
Cancer	No. of Cases	Person-years	Mortality Rate	No. of Cases	Person-years	Mortality Rate	RR (95% CI)	*P* Value
All cancer sites	267	69 225	38.6	739	209 870	35.2	1.09 (0.95–1.26)	.20
Gastrointestinal cancer	83	69 225	12.0	233	209 870	11.1	1.08 (0.84–1.39)	.55
Gastric cancer	16	69 225	2.3	34	209 870	1.6	1.43 (0.79–2.59)	.24
Lung cancer	44	69 225	6.4	105	209 870	5.0	1.27 (0.89–1.81)	.18
Genitourinary cancer	37	69 225	5.3	145	209 870	6.9	0.77 (0.54–1.11)	.16
Breast cancer	34	69 225	5.8	87	209 870	4.8	1.19 (0.80–1.77)	.39
Hematological malignancies	28	69 225	4.0	73	209 870	3.5	1.16 (0.75–1.80)	.50
Thyroid cancer	15	69 225	2.2	4	209 870	0.2	11.4 (3.77–34.25)	<.01
Other malignancies	26	69 225	3.8	92	209 870	4.4	0.86 (0.55–1.32)	.47

Ryödi, *et al., J Clin Endocrinol Metab 2015,*

Wer braucht eine hochdosierte Radiojodtherapie?

- SD-Ca<2cm N0 R0 → RIT mit ca. 2000 MBq
  - Hervorragende Prognose
  - Risiko unzureichender Ablation
- SD-Ca >4cm ODER „altes“ T3 ODER N1 ODER R1 → RIT mit 3700 MBq
- SD-Ca 2-4cm N0 R0 → Risikofaktoren (Alter, sklerosierend, Lymph-/Angioinvasion)

Zusammenfassung

- Durch neue ATA Guideline Abnahme von Thyreoidektomien (>4cm, cN1/M1, „gross extrathyroidal extension“)
- Durch neue ATA Guideline Zunahme der „Kann-Indikationen“ zur Radiojodtherapie (pT1b-3, N0-1b).
- Zunehmend defensive Haltung zur Radiojodtherapie nicht durch Evidenz unterlegt
- KEINE Studie RIT vs. keine RIT
- Jahrzehntelange Erfahrungen mit Radiojodtherapie, mit nachgewiesenem positiven Effekt
- Nebenwirkungsarme Therapie

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