Das familiäre papilläre Schilddrüsenkarzinom

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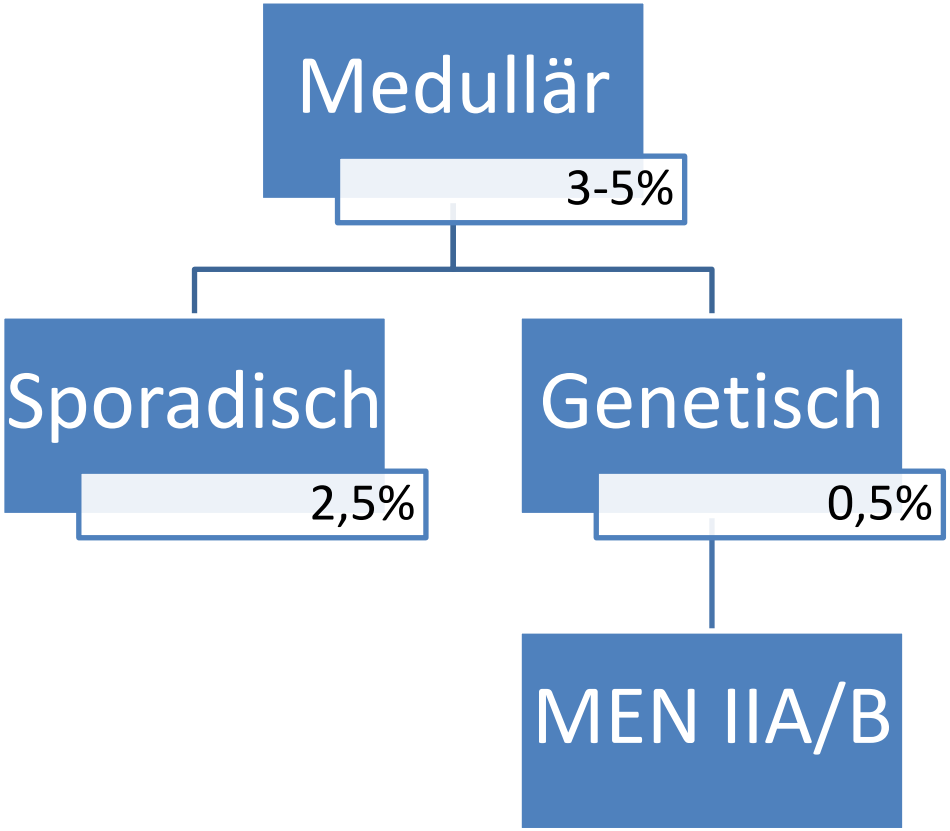
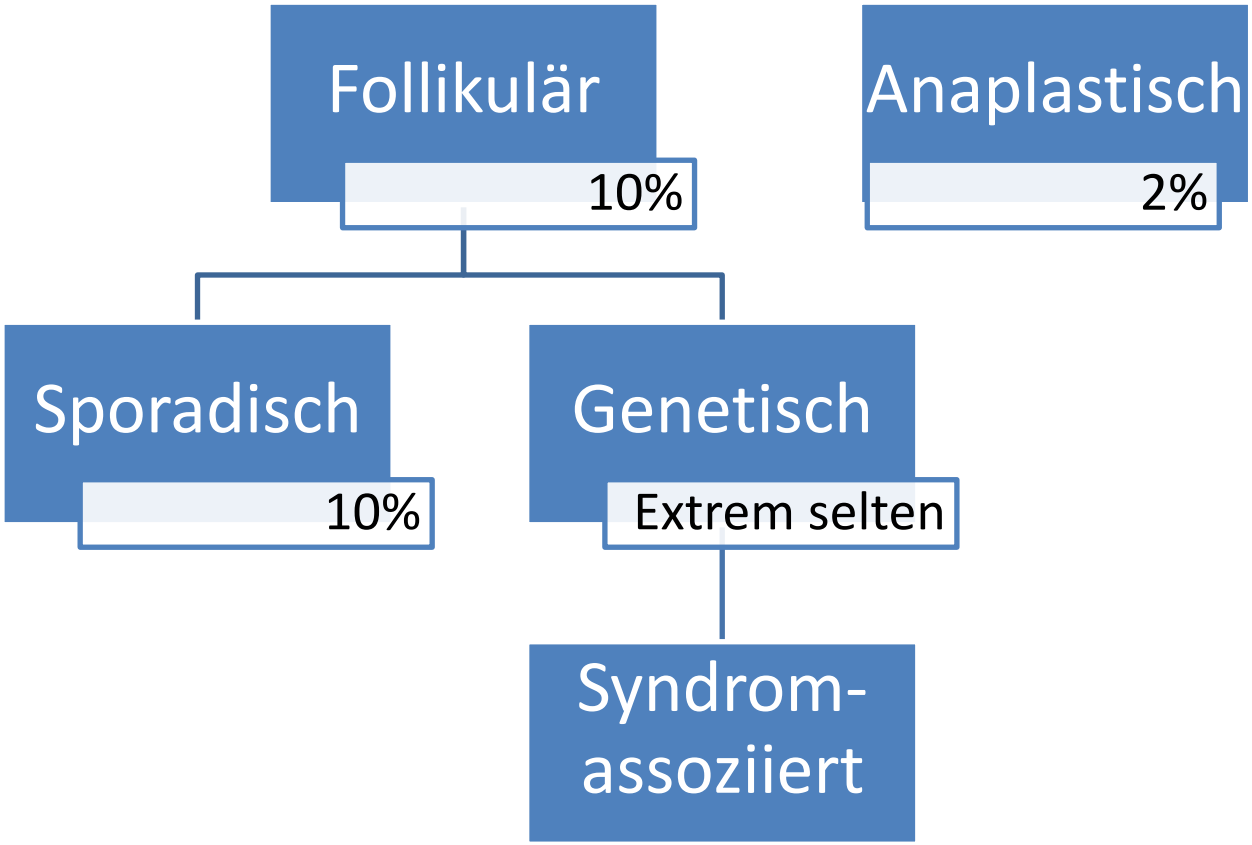
Gliederung der Schilddrüsenkarzinome



Julie Guilmette et Vania Nosé.Hereditary and familial thyreoid tumors. Histopathology (2018): 72, 70-81

Gliederung der Schilddrüsenkarzinome



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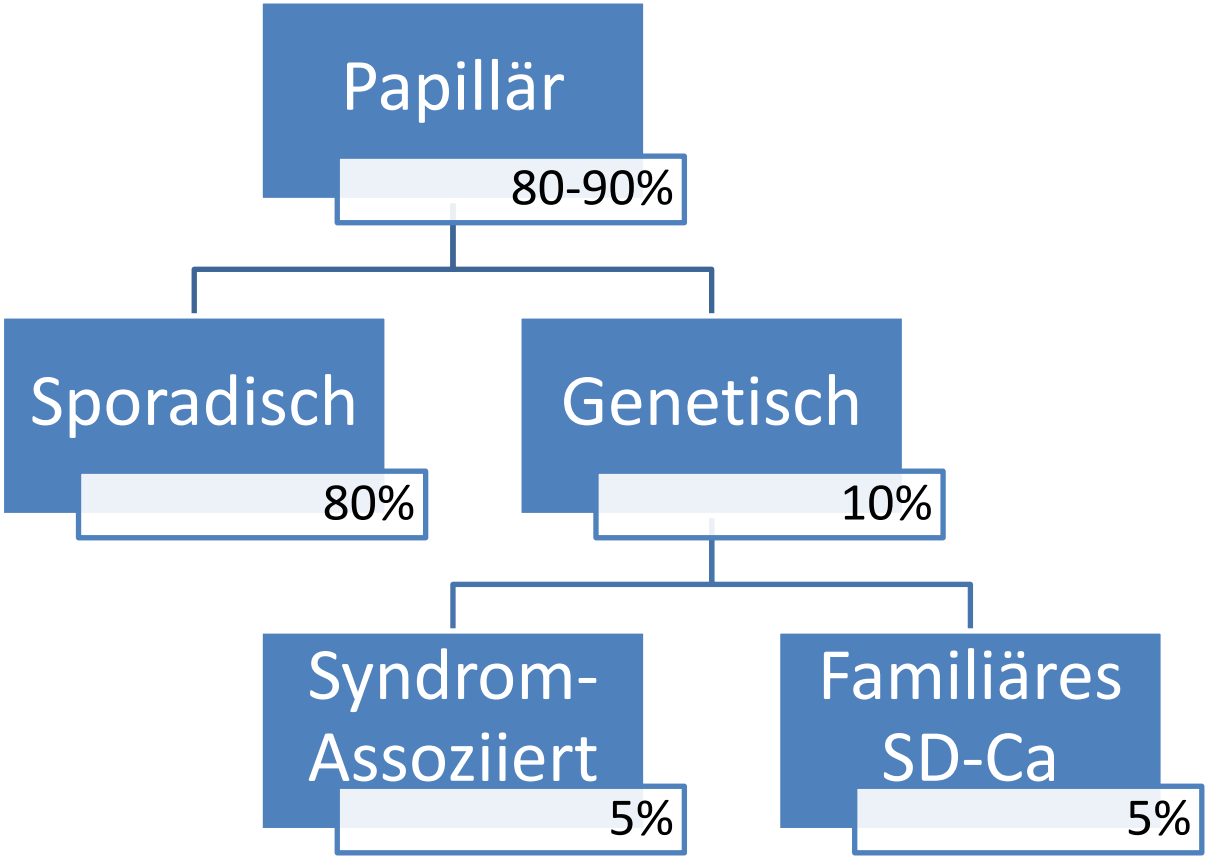


Sporadisches SD-Karzinom: Mutationen

Genetic Alteration	PTC (%)	FTC (%)	ATC (%)	MTC (%)
RET/PTC rearrangement	13-43	0	0	0
RET mutation	0	0	0	50
BRAF mutation	39-69	0	10-35	0
RAS mutation	0-21	40-53	20-60	0
PPARγ rearrangement	1	?36	—	0
CTNNB1 mutation	0	0	66	0
P53 mutation	0-5	0-9	67-88	0

ATC indicates anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

Modified from Refs. 23, 28, 37.

ADVANCES IN ANATOMIC PATHOLOGY

Dotto, Jorge; Nosé, Vânia. Advances in Anatomic Pathology. 15(6):332-349, November 2008.doi: 10.1097/PAP.0b013e31818a64af

Genetische SD-Karzinome (Nicht-medullär)

Table 1. Syndromic and non-syndromic familial non-medullary thyroid carcinoma associated with thyroid disorders and malignancies

Syndrome	Inheritance	Gene location	Gene	Incidence of thyroid cancer (%)	Histological findings
Familial adenomatous polyposis	Autosomal dominant	5q21	*APC*	2–12	PTC-CMV
Cowden syndrome	Autosomal dominant	10q23.3	*PTEN*, *SDH*, *PIK3CA*, *AKT1*, *KLLN*, *SEC23B*	35	PTC (follicular variant), FTC, adenomatous nodules, C-cell hyperplasia
Carney complex	Autosomal dominant	2p16, 17q24	*PRKAR1α*	15	PTC, FTC, follicular adenomas, adenomatous nodules
Werner syndrome	Autosomal recessive	8p11–p12	*WRN*	18	PTC, FTC, ATC
McCune–Albright syndrome		20q13.2–q13.3	*GNAS*		PTC, FTC, follicular adenomas with papillary growth
DICER1 syndrome	Autosomal dominant	14q32.13	*DICER1*	Rare	Nodular hyperplasia
Familial papillary thyroid carcinoma	Autosomal dominant	19p13	*TCO*		PTC
Familial papillary thyroid carcinoma with papillary renal cell neoplasia	Unknown	1q21	*PRN*		PTC
Familial non-medullary thyroid carcinoma type 1	Unknown	2q21	*NMTC1*		PTC
Familial papillary thyroid carcinoma and multinodular goitre	Autosomal dominant	14q32	*MNG1* *PTCSC3*		PTC, nodular hyperplasia

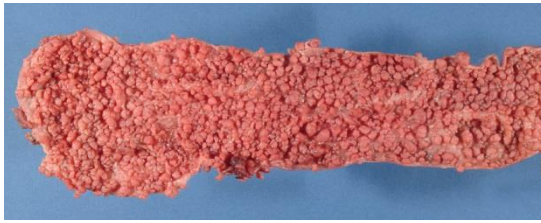
ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma; PTC-CMV, papillary thyroid carcinoma cribriform–morular variant.

Syndrome mit Schilddrüsen-karzinom

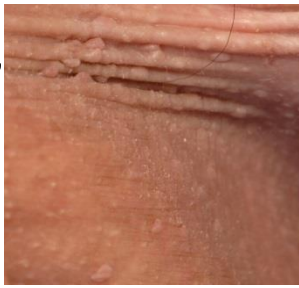
Hauptkarzinom: Schilddrüsen-karzinom

Julie Guilmette et Vania Nosé.Hereditary and familial thyreoid tumors. Histopathology (2018): 72, 70-81

Syndrom-ass. Familiäre SD-Carzinom



- **Familiäre adenomatöse Polyposis (FAP)**
  -100-1000 kolorektale Adenome, Polypen Magen&Duodenum
- **Cowden-Syndrom**
  -multiple Hamartome (Haut, GI-Trakt), Mamma-CA, Uterus-Ca



- **Carney-Complex**
  -Triade: Pigmentflecken, endokrine Überfunktion, Myxome
- **Werner-Syndrom**
  -Progerie (dünne Haut, Faltenbildung, Alopezie, Muskelatrophie), Kleinwuchs, „Alterserkrankungen“ (Diabetes mellitus, pAVK, Osteoporose, Katarakt), multiple Malignome (maligines Melanom, Weichteilsarkome, Osteosarkome)

Julie Guilmette et Vania Nosé.Hereditary and familial thyreoid tumors. Histopathology (2018): 72, 70-81

Familiäres papilläres SD-Karzinom (fPTC)

- **5%** der nicht-medull. SD-Ca

- **Genetik:** Autosom.dom., 6 potentielle Gene
  u.a. Chromosom 19p13 (TCO-Gen), jedoch nicht ubiquitär
  + somatische Mutationen
  zB in BRAF (-45% bei PTC), RET/PTC (-35%)

- Mind. **3 erstgradig** verwandte Familienmitglieder!
  Erkrankungsalter jünger; mehr männl., höhere Zahl an multilok. bzw. bilat. Karzinomen, höhere Metastasierungszahl

- **Histo** ident zu sporadischem papill. SD-Ca

- **Therapie** tendenziell radikaler als bei sporadischem SD-Ca

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Familiäres papilläres SD-Karzinom (fPTC)

Table I. Characteristics of FNMTC versus matched controls at presentation

	FNMTC patients			*Matched controls*			
Predictor	*Female (n = 38)*	*Male (n = 10)*	*Total (n = 48)*	*Female (n = 114)*	*Male (n = 30)*	*Total (n = 144)*	P *value**
Age (y) (mean ± SD)	38 ± 11	341 ± 11	39 ± 11	45 ± 16	50 ± 16	46 ± 15	< .005
Follow-up median (y) (range)			8 (1-15)			7 (1-20)	.97
Tumor size (cm) (mean ± SD)	2.7 ± 1.5	3.4 ± 1.5	2.8 ± 1.5	3.1 ± 1.5	3.2 ± 1.2	3.1 ± 1.5	.28
Extrathyroidal invasion	9	4	13 (27%)	22	8	30 (21%)	.37
Lymph node involvement	15	8	23 (48%)	46	18	64 (44%)	.68
Distant metastasis	2	0	2 (4%)	7	0	7 (5%)	.84
Past history of benign thyroid disease	8	6	14 (29%)	25	5	30 (21%)	.23

**P* value was based on the comparison of total familial versus total matched controls.

Osamah et al: Is familial non-medullary thyroid carcinoma more aggressive than sporadic thyroid cancer? A multicenter series. Surgery 2000;128:1043-51.

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographic data	Date of birth	12.12.1980	07.07.1955	1954	1953	1954
	Sex	F	F	F	F	F
	Relationship	Daugther of Patient 2	Sibling, Mother of Patient 1	Sibling (twin)	Sibling	Sibling (twin)
Thyreoid characteristics	Disease of thyreoid gland	Hashimoto Thyreoditis	Hashimoto Thyreoiditis	Struma multinodosa	Struma multinodosa II	Struma nodosa bds.
	Function	Euthyreosis	Substituted Hypothyreosis	Euthyreosis	Euthyreosis	x
	Size of gland (ml)	Right 1,5, left 2,3	x	Right 3,9, left 5,6	x	x
Laboratory findings preoperative	TSH (µU/ml)	1,8	x	1,4	1,2	x
	fT3 (pmol/l)	4,5	x	4,3	4,8	x
	fT4 (pmol/l)	16,8	x	13,9	12,5	x
	TG				6,7 ng/ml	x
Surgery	Date	28.10.2011	24.11.2014	15.12.2015; 23.12.2015	29.09.2018	20.12.2016
	Age at Surgery	31	59	61	65	62
	What?	Thyreoidektomie+ neck dissection	Thyreoidektomie, LK sampling	Thyreoidektomie; neck dissection right + LK sampling (BKH Schwaz, kein SS)	Thyreoidektomie	Thyreoidektomie, central neck dissection, cervical LK exstirpation left

Characteristics of cancer	Date of diagnosis	28.10.2011	24.11.2014	17.12.2015	29.09.2018	20.12.2016
	Size	15mm	2-8mm	x	7mm	8mm
	Multlocular	No	Yes (3)	No	No	No
	Location	Right lobe	Right lobe	Right	Right	Right
	T	pT1b	pT3(m)	pT3	pT3b	pT3
	N	N0(0/27)	N0 (0/3)	N1a (2/25)	pNx	N1a (1/9)
	M	x	x	x	x	x
	R	0	0	0	0	0
	L	x	1	0	1	1
	V	x	0	0	0	x
	Pn	x	0	x	0	x
	Mutationsanalyse	x	BRAF: pV600E	x	BRAF p.V600E	BRAF positiv
Follow Up	Adjuvant Therapie	1x Hochdosis Radiojod mit 3,55 GBq	1x Hochdosis Radiojod mit 5560,2 MBq	1x Hochdosis Radiojod 5906,72 MBq	1x Hochdosis Radiojod mit 4750 MBq	1xHochdosis Radiojod 5377 MBq
	Follow-up time	09.01.2018	18.01.2018	30.01.2018	18.05.2018	29.01.2018
	Postoperative TG	<0,3ngml	<0,3 ng/ml	<0,3ng/ml	<0,3ng/ml	<0,3ng/ml
	Recurrence?	None	None	None	None	None

- **Ein (**
- Einf
- **Nac**

Table 1. Patient, tumor

Characteristic	*P* value
All patients	NA
Gender	
Male	0.342
Female	
Age at diagnosis (years)	0.679
Race	
White	0.714
Black	
Asian	
Hispanic	
Histology	
Classic papillary	0.003
Follicular variant	
Pathological features	
Thyroid capsule invasi	0.001
Soft tissue invasion	<0.001
Vascular invasion	0.223
Positive margins	0.004
Tumor size (cm)	0.600
Multifocal	0.597
Cervical LN involveme	0.002
Extent of disease	0.004
Thyroid only	0.002
Thyroid and cervical LI	<0.001
Lung metastases	0.172
Bone metastases	0.482
AJCC tumor stage	0.037
T1	
T2	
T3	
T4	
AJCC nodal stage	0.015
N0	
N1a	
N1b	
Initial I-131 dose (mCi)	0.498
Total I-131 dose (mCi)	0.681
Follow-up time (years)	0.306

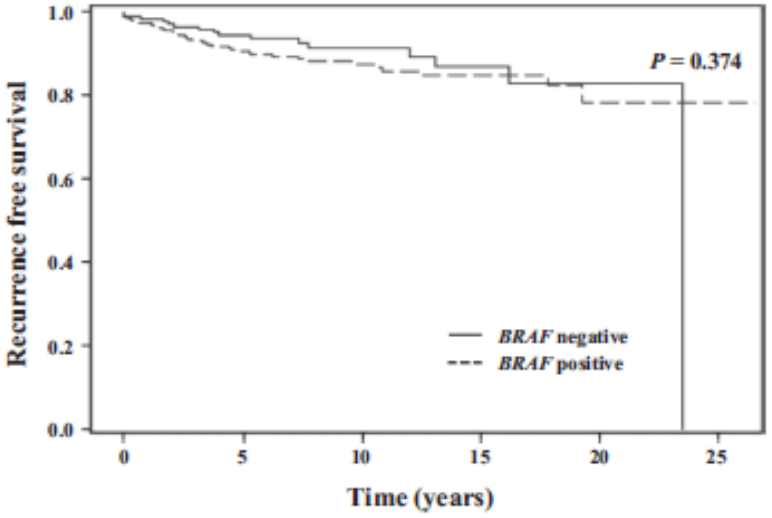

Figure 2. Progression-free survival based on *BRAF* mutational status.

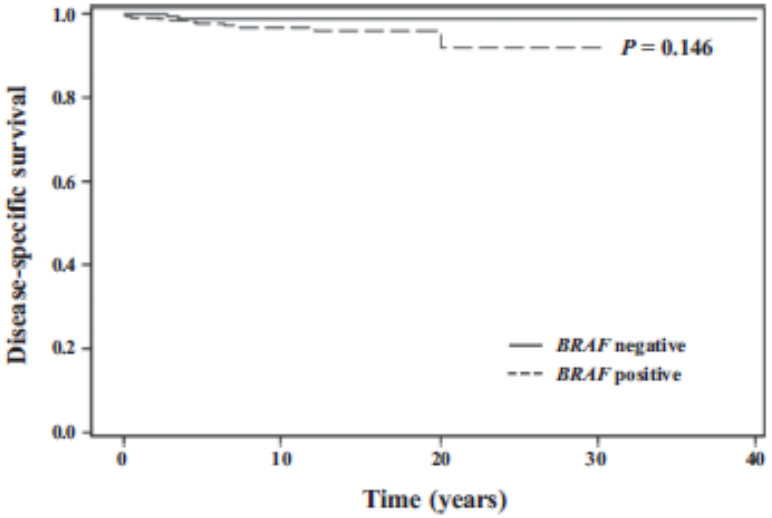

Figure 3. Disease-specific survival based on *BRAF* mutational status.

AF, RET)

Conclusio

- **Familienanamnese** immer!
  ggf. Screening von Geschwistern/Eltern/Kindern empfohlen

- **Multilokuläres** bzw. **bilaterales** pap. SD-Ca oder **sehr junger** Pat: genetische Ursache?!

- **Therapie** ident zu nicht-familiärem papillärem SD-Ca
  aber:
  immer komplette Thyreoidektomie + LK-Sampling, ggf. LK-Diss.

- **Nachsorgen** ident zu nicht-familiärem papillärem SD-Ca

Danke für Ihr Interesse

Kontaktieren Sie uns:

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