Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang:2021-B-263 Cabozantinib

Stand: April 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Cabozantinib **[lokal fortgeschrittenes oder metastasiertes differenziertes Schilddrüsenkarzinom]**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Strahlentherapie - Radiojodtherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Lenvatinib: Beschluss vom 15.08.2019 - Selpercatinib: Beschluss vom 02.09.2021
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Cabozantinib L01EX07 Cabometyx	Anwendungsgebiet laut Positive Opinion vom 24.03.2022: CABOMETYX is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy. Anwendungsgebiet laut Fachinformation: CABOMETYX ist als Monotherapie für die Behandlung von Erwachsenen mit lokal fortgeschrittenem oder metastasiertem differenziertem Schilddrüsenkarzinom (DTC) indiziert, die refraktär gegenüber Radiojod (RAI) sind oder dafür nicht in Frage kommen und bei denen während oder nach einer vorherigen systemischen Therapie eine Progression aufgetreten ist.
Zytostatika	
Doxorubicin L01DB01 generisch	• fortgeschrittenes papilläres/follikuläres Schilddrüsenkarzinom • […]
Proteinkinase-Inhibitoren	
Lenvatinib L01XE29 Lenvima	LENVIMA ist indiziert als Monotherapie für die Behandlung von erwachsenen Patienten mit progressivem, lokal fortgeschrittenem oder metastasiertem differenziertem (papillärem/follikulärem/Hürthle-Zell-) Schilddrüsenkarzinom (DTC), das nicht auf eine Radiojodtherapie (RAI) angesprochen hat. […]
Sorafenib L01XE05 Nexavar	<u>Differenziertes Schilddrüsenkarzinom</u> Nexavar ist angezeigt zur Behandlung von Patienten mit progressivem, lokal fortgeschrittenem oder metastasiertem, differenziertem (papillärem/follikulärem/Hürthle-Zell-) Schilddrüsenkarzinom, welches gegenüber radioaktivem Jod refraktär ist. […]
Selpercatinib	Retsevmo als Monotherapie wird angewendet zur Behandlung von Erwachsenen mit:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01EX22 Retsevmo	• fortgeschrittenem RET-Fusions-positivem Schilddrüsenkarzinom, die eine systemische Therapie nach einer Behandlung mit Sorafenib und/oder Lenvatinib benötigen […]

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-263 (Cabozantinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	26. August 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event/s
AM-RL	Arzneimittel-Richtlinie
ATE	Arterial thromboembolic event
AWG	Anwendungsgebiet
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best supportive care
DMFFS	Distant metastasis failure-free survival
DTC	Differenziertes Schilddrüsenkarzinom
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
HRQoL	Health-related quality of life
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LRRFS	Locoregional recurrence-free survival
MTC	Metastatic thyroid cancer
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objetice tumour response rate
OS	Overall survival
PFS	Progression-free survival
RAI	Radiojodtherapie
RR	Relatives Risiko
SGB	Sozialgesetzbuch
SIGN	Scottish Intercollegiate Guidelines Network
TKI	Thyroid kinase inhibitor
TRAE	Treatment-related adverse event
TRIP	Turn Research into Practice Database
VTE	Venous thromboembolic event
WHO	World Health Organization

1 Indikation

Erwachsene und jugendliche Patienten ab 12 Jahren mit einem lokal fortgeschrittenen oder metastasierten differenzierten Schilddrüsenkarzinom (DTC).

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *differenziertes Schilddrüsenkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 19.08.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1062 Referenzen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 8 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [3].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. August 2019 - Lenvatinib (Bewertung nach Aufhebung des Orphan Drug-Status)

Anwendungsgebiet (laut Zulassung vom 20. August 2018):

LENVIMA ist indiziert als Monotherapie für die Behandlung von erwachsenen Patienten mit progressivem, lokal fortgeschrittenem oder metastasiertem differenziertem (papillärem/ follikulärem/Hürthle-Zell-) Schilddrüsenkarzinom (DTC), das nicht auf eine Radiojodtherapie (RAI) angesprochen hat.

Zweckmäßige Vergleichstherapie

Sorafenib

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Jacomina LE et al., 2020 [4].

The Role of postoperative external beam radiotherapy for differentiated thyroid carcinoma: A Systematic review and meta-analysis.

Fragestellung

to update and synthesize current evidence defining the role of RT in the postoperative management of patients with DTC treated in the more recent years.

Methodik

Population:

- Patients with DTC

Intervention/Komparator:

- Patients who underwent curative surgery (i.e., a total or near total thyroidectomy with or without central and/or lateral neck dissection) followed by RAI, and then received RT or no RT

Endpunkte:

- locoregional recurrence-free survival (LRRFS) and overall survival (OS), distant metastasis failure-free survival (DMFFS) and treatment-related toxicity

Recherche/Suchzeitraum:

- PubMed, Scopus, MEDLINE, CINAHL, ASCOpubs, and the Cochrane Library databases in the last 15 years from 2004 to March 6, 2019

Qualitätsbewertung der Studien:

- McMaster Critical Review Form for Quantitative Studies

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of nine studies with a combined study population of 2981
- Only one study was initially designed as a prospective multicenter randomized trial but was carried out as a comprehensive cohort due to poor accrual.

Charakteristika der Population:

- The remaining studies were composed of one prospective propensity-matched case-control study and seven retrospective cohorts. A total of 734 patients were treated with RT using conventional RT, 3DCRT, IMRT, or VMAT. The areas irradiated included the thyroid bed and cervical lymph nodes and/or upper mediastinum with a total dose ranging from 40 to 70 Gray (Gy) in 1.8 to 2.5 Gy per fraction. The average median follow-up was 84.6 months (range 31-135.6 months).

Qualität der Studien:

- All nine studies had sound methodological quality, clear objectives, and clinically relevant outcome measures.
- Because almost all studies were nonrandomized and retrospective, patients who received RT tended to have more adverse baseline characteristics in terms of age, stage of the primary tumor, degree of residual disease.

Studienergebnisse:

- RT improved 5-year locoregional recurrence-free survival but not overall survival and distant metastasis failure-free survival.

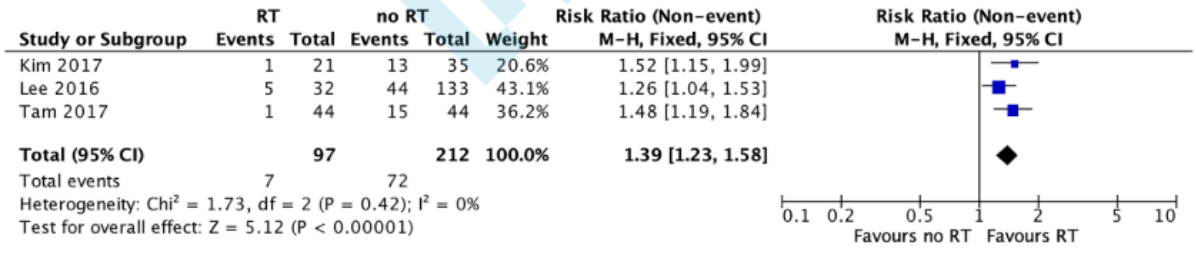


FIGURE 2 Radiotherapy (RT) vs no radiotherapy (no RT), 5-year locoregional recurrence-free survival [Color figure can be viewed at wileyonlinelibrary.com]

- The locoregional control benefit was seen in patients at increased risk for recurrence, including those with advanced age, locoregionally advanced disease, gross or microscopic residual tumor, and structural invasion.
- Serious RT-related acute and late toxicities were rare.

Anmerkung/Fazit der Autoren

In conclusion, current available evidence supports the finding that postoperative RT can improve locoregional control in patients with high-risk DTC after curative surgery and RAI. The subset that might benefit from RT are those at increased risk for locoregional recurrence, including those with advanced age, locoregionally advanced disease (pT4 or pN1b), positive resection margins with gross or microscopic residual tumor, and extensive structural invasion. Locoregional irradiation had a favorable toxicity profile, although it might have no effect on survival and rates of distant metastasis. Further multi-institutional prospective studies are warranted to fully define the role of RT in DTC.

Fleeman N et al., 2019 [2].

A systematic review of lenvatinib and sorafenib for treating progressive, locally advanced or metastatic, differentiated thyroid cancer after treatment with radioactive iodine.

Fragestellung

systematic review of the clinical effectiveness evidence for lenvatinib and sorafenib and discuss how the evidence has impacted on NICE recommendations for clinical practice.

Methodik

Population:

- Adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine

Intervention:

- Lenvatinib or sorafenib monotherapy (or in combination with best supportive care)

Komparator:

- Lenvatinib or sorafenib monotherapy (or in combination with best supportive care), best supportive care, placebo

Endpunkte:

- overall survival, progression-free survival, response rate, adverse effects of treatment, health-related quality of life

Recherche/Suchzeitraum:

- Embase, MEDLINE, PubMed and the Cochrane Library from January 1999 through January 2017

Qualitätsbewertung der Studien:

- criteria set out in the Centre for Review and Dissemination's Guidance

Ergebnisse

Anzahl eingeschlossener Studien:

- 93 papers reporting on 2 RCTs (primary evidence), 9 observational studies and 13 evidence reviews (supporting evidence) were identified

Charakteristika der Population:

- Both of the included RCTs [26, 27] were phase III multicentre double-blind trials designed to compare the intervention of interest (lenvatinib or sorafenib) with placebo.

Subjects were randomized 2:1 to the intervention and comparator arms of the SELECT trial (lenvatinib, n = 261; placebo, n = 131) [26] and 1:1 in the DECISION trial (sorafenib, n = 207; placebo, n = 210) [27]. Both trials permitted some concomitant therapies (such as TSH suppression) in both the intervention and placebo arms. Thus, the placebo arm in both trials could be considered to be equivalent to BSC. The types of concomitant therapies were broadly similar in both trials. However, a potentially important difference between the two trials was that palliative radiotherapy, which is commonly available as part of BSC in clinical practice, was only permitted in the DECISION trial, not the SELECT trial. Nonetheless, rates of palliative radiotherapy administered to patients in the DECISION trial were relatively low: 10.6% of patients treated with sorafenib and 21.4% of patients treated with placebo [25]. Patients were eligible to receive treatment (intervention or placebo) in both the SELECT and DECISION trials until disease progression [26, 27]. In both trials, patients were then enrolled into open extension phases [24, 25].

Qualität der Studien:

- Overall, the risk of bias was considered to be low in both RCTs.
- The quality of nine of the evidence reviews [24, 25, 37–39, 42–45] was considered to be good.

Studienergebnisse:

- Compared to placebo, RCT evidence demonstrated improvements with lenvatinib or sorafenib in median progression-free survival (PFS) and objective tumour response rate (ORR). Overall survival (OS) was confounded by high treatment crossover (≥75%) in both trials.
- Adverse events (AEs) were more common with lenvatinib or sorafenib than with placebo but the most common AEs associated with each drug differed.
- Primarily due to differences in the survival risk profiles of patients in the placebo arms of the RCTs, we considered it inappropriate to indirectly compare the effectiveness of lenvatinib versus sorafenib.
- ORR and AE findings for lenvatinib and sorafenib from the supporting evidence were broadly in line with RCT evidence.
- Health-related quality of life (HRQoL) data were limited.

Table 2 Summary of efficacy findings from the SELECT and DECISION trials

Outcome	SELECT trial		DECISION trial	
	Lenvatinib *N* = 261	Placebo *N* = 131	Sorafenib *N* = 207	Placebo *N* = 210
OS[a]				
Median, months	41.6	34.5	39.4	42.8
(95% CI)	(31.2-NE)	(21.7-NE)	(32.7–51.4)	(34.7–52.6)
Unadjusted HR (95% CI)	0.84 (0.62–1.13)		0.92 (0.71–1.21)	
RPSFTM adjusted OS HR	0.54		0.77	
(95% CI) [b]	(0.36–0.80)		(0.42–1.79)	
PFS[c]				
Median, months	18.3	3.6	10.8	5.8
(95% CI)	(15.1-NE)	(2.2–3.7)	(CIs NR)	(CIs NR)
Stratified HR (95% CI)	0.21 (0.14–0.31)		0.59 (0.45–0.76)	
Objective tumour response				
rate[c, d] (%)	64.8	1.5	12.2	0.5
(95% CI)	(59–70.5)	(0–3.6)	(8–17.7)	(0–2.7)
Odds Ratio (95% CI)	28.87 (12.46–66.86)		NR	
P value	$p < 0.0001$		$p < 0.0001$	

CI Confidence interval, *HR* Hazard ratio, *IPE* Iterative Parameter Estimation, *NE* Not estimable, *NR* Not reported, *OS* Overall survival, *PFS* Progression-free survival, *RPSFTM* Rank Preserving Structural Failure Time Model
[a]Data from final data-cut
[b]Bootstrapping CIs
[c]Assessed by blinded independent review at primary data-cut
[d]Unlike the SELECT trial, patients who were unevaluable for response were excluded from the analyses in the DECISION trial. There were 18 (4.3%) patients who were excluded from the objective tumour response analyses in the DECISION trial, 9 (4.3%) patients in each arm [27]
Source: [26, 27] with additional OS data from Eisai Ltd. 2017 [24] and Bayer HealthCare 2017 [25] and additional ORR data (95% CIs) from European public assessment report (EPAR) for lenvatinib [51] and EPAR for sorafenib [56]

Table 4 Summary of efficacy data from observational studies and meta-analyses

Outcome, months	Lenvatinib	Sorafenib		
	Range from observational studies	Range from observational studies	Estimate from meta-analysis by Thomas et al. 2014 [45]	Estimate from meta-analysis by Shen et al. 2014 [44]
OS, median	31.8–32.3 [2]	23–34.5 [3] [a]	- [c]	- [c]
PFS, median	12.6–25.8 [2]	12–22.1 [4] [b]	17.9	- [c]
95% CI			17.9–18 [7]	
ORR, %	50–68 [2]	15–38.3 [7]	20.9	22
95% CI			14.3–27.5 [6]	15–28 [7]

- = not applicable, *CI* Confidence interval, *ORR* Objective tumour response rate, *OS* Overall survival, *PFS* Progression-free survival
[a]An additional study reported that the median OS had not been met [28]
[b]One other study reported that the median PFS had not been met [28] and another reported mean PFS only (9.7 months) [30]; in this latter study sorafenib was studied at half the dose of all other studies and included only 9 patients
[c] No meta-analyses were identified
[x] denotes the number of studies from which data are derived

Anmerkung/Fazit der Autoren

It is not possible to reliably estimate the relative effectiveness of lenvatinib versus sorafenib for treating RRDTC, but the evidence base clearly demonstrates improvements in PFS and ORR for these treatments when compared with placebo, a proxy for BSC. The improvements in PFS and ORR are, however, accompanied by an increased risk of AEs, whilst the effect on patients' OS and HRQoL remains uncertain. Given the slightly different safety profiles of lenvatinib and sorafenib, the evidence from our review supports clinical guideline recommendations that the choice of treatment should consider each patient's circumstances, including their need for a response to treatment and comorbidities.

Lin S et al., 2019 [5].

Evaluating the effectiveness of targeted therapies for thyroid carcinoma: an updated meta-analysis.

Fragestellung

to evaluate the outcome of targeted therapies and provide quantitative evidence.

Methodik

Population:

- Patients with thyroid carcinoma

Intervention/Komparator:

- targeted therapy

Endpunkte:

- PFS and adverse events

Recherche/Suchzeitraum:

- Ovid, PubMed, EMBASE, ClinicalTrails.gov, and Cochrane Library electronic databases were searched until September 1, 2019

Qualitätsbewertung der Studien:

- Cochrane Risk Bias Assessment Tool for RCTs

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 studies with a total of 1,615 patients, with 991 cases in the drug group and 624 cases in the placebo group

Charakteristika der Population:

Table 1 Basic characteristics of studies included in the meta-analysis

Trial (year)	Tested agent	Study design	Dose (mg)	Pathological type	Number of patients		Progression free survival	Overall survival
					Drug	Placebo		
Wells 2012	Vandetanib	Randomized controlled	300	MTC	231	100	30.5 (95% CI, 0.31 to 0.69) months	NE (95% CI, 0.48 to 1.65)
Leboulleux 2012	Vandetanib	Randomized controlled	300	MDC	73	72	11.1 (95% CI, 7.7 to 14.0) months	NE (99.24% CI, 0.4 to 2.15)
Elisei 2013	Cabozantinib	Randomized controlled	140	MTC	219	111	11.2 (95% CI, 0.19 to 0.40) months	NA
Brose 2014	Sorafenib	Randomized controlled	800	MDC	207	210	10.8 (95% CI, 0.45 to 0.76) months	NE (95% CI, 0.54 to 1.19)
Schlumberger 2015	Lenvatinib	Randomized controlled	24	RAIR-DTC	261	131	18.3 (99% CI, 0.14 to 0.31) months	NE (22.0–NE)

MTC, medullary carcinoma; MDC, metastatic differentiated carcinoma; RAIR-DTC, differentiated thyroid cancer, iodine-131-refractory; NA, not applicable or not reported; NE, not estimable.

Qualität der Studien:

- Four of the studies were rated as high quality and one was evaluated as medium quality

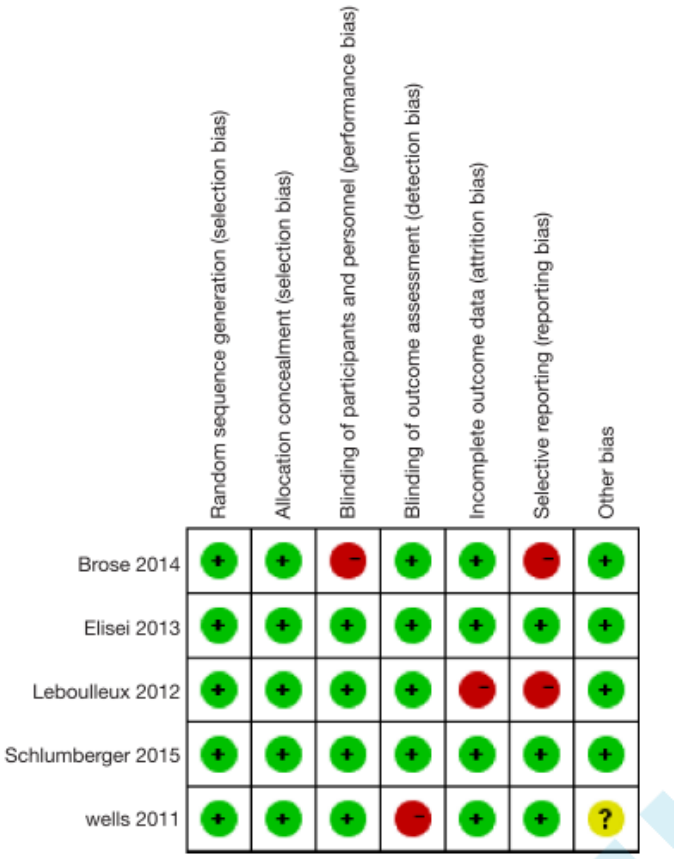


Figure 2 Targeted treatment of thyroid carcinoma included in the literature quality evaluation.

Studienergebnisse:

- Compared with the placebo group, the progression-free survival (PFS) rate of the drug group was significantly improved.
  - The PFS of the drug group was 10.8 to 30.5 months, compared with 4 to 19.3 months for the placebo group (6 months PFS: OR =3.23, 95% CI: 2.57 to 4.05, P<0.00001, 12

months PFS: OR =3.38, 95% CI: 2.58 to 4.42, P<0.00001, 18 months PFS: OR =2.48, 95% CI: 1.74 to 3.54, P<0.00001).

- Overall survival (OS) did not differ significantly in the study (6 months: OR =1.53, 95% CI: 1.00 to 2.35, P=0.05, 12 months: OR =1.26, 95% CI: 0.94 to 1.69, P=0.12, 18 months: OR =1.11, 95% CI: 0.87 to 1.42, P=0.39).
- The incidence of adverse reactions in the drug group was significantly higher than that in the placebo group (OR =4.76, 95% CI: 3.45 to 6.57, P<0.00001), and the subgroup of adverse reactions was still significantly higher than that in the placebo group

Fazit der Autoren

In summary, the findings of this study indicate that targeted drugs can significantly prolong PFS in patients with thyroid carcinoma. Although the incidence of adverse reactions was significantly higher than that of the control group, the patient was still tolerant. At present, most of the targeted research on refractory thyroid carcinoma is in the clinical trial stage, and there is still no strong evidence to confirm its clinical effect. Therefore, the potential risks and benefits must be considered comprehensively before targeted therapy can proceed. It is believed that with the emergence of more targeted therapies, breakthroughs can be made in the clinical treatment of refractory thyroid carcinoma with more substantial benefits being brought to patients.

Yu S et al., 2019 [8].

Treatment-related adverse effects with TKIs in patients with advanced or radioiodine refractory differentiated thyroid carcinoma: a systematic review and meta-analysis

Fragestellung

To explore the frequency of severe adverse effects in advanced or radioiodine refractory differentiated thyroid carcinoma (RR-DTC) patients treated with sorafenib and lenvatinib.

Methodik

Population:

- Patients ≥18 years with advanced or RR-DTC

Intervention/Komparator:

- Sorafenib vs. Placebo; Lenvatinib vs. Placebo

Endpunkte:

- Adverse events (AEs)

Recherche/Suchzeitraum:

- A comprehensive search of computerized databases to include relevant studies published in English between January 2008 and May 2018 was performed, including PubMed, Web of Science, Ovid, EMBASE, and the Cochrane Library, encompassing the period from the drugs' inspection on July 2018

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Seven studies (n=657 patients)

Charakteristika der Population:

Table S1 Baseline characteristics of enrolled studies

Study	Year	Treatment	Number of patients evaluated for toxicity	Number of patients experienced toxicity (grade ≥3)/all grade												
				Hand-foot syndrome	Weight loss	Diarrhea	Rash	Mucositis	Hypocal-cemia	Hyper-tension	Nausea	Fatigue	Anorexia	Voice change	Vomiting	Increased ALT	Increasing AST
Schneider et al[1]	2012	Sorafenib	31	7/22	3/18	2/16	5/17	3/16	0/15	5/15	0/3	NA	NA	NA	NA	NA	NA
Brose et al[2]	2014	Sorafenib	207	42/158	0/97	12/142	10/104	2/48	19/39	20/84	0/43	12/103	5/66	1/25	1/23	6/26	2/23
Cabanillas et al[3]	2015	Lenvatinib	58	NA	7/40	6/39	NA	1/18	NA	6/44	0/29	5/35	1/30	0/25	0/22	NA	NA
Schlumberger et al[4]	2015	Lenvatinib	261	9/83	25/121	21/155	1/42	11/93	7/18	109/177	6/107	24/154	12/131	3/63	5/74	0/1	0/1
Berdelou et al[5]	2017	Lenvatinib	75	0/21	0/44	1/34	NA	2/18	NA	26/50	0/14	6/46	1/27	0/1	0/5	NA	NA
Nervo et al[6]	2018	Lenvatinib	12	2/11	2/11	5/8	NA	1/7	NA	5/9	1/9	1/7	NA	0/3	1/4	NA	NA
Balmelli et al[7]	2018	Lenvatinib	13	0/1	NA	2/4	NA	1/4	NA	1/2	NA	2/6	1/3	0/1	NA	NA	NA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not available.

Qualität der Studien:

Table S2 Risk of bias in enrolled studies

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free selective reporting	Free of other bias
Schneider et al[1]	Yes	No	Yes	No	No	No
Brose et al[2]	Yes	Yes	Yes	No	No	No
Cabanillas et al[3]	Yes	No	Yes	No	No	No
Schlumberger et al[4]	Yes	Yes	Yes	No	No	No
Berdelou et al[5]	Yes	No	No	No	No	No
Nervo et al[6]	Yes	No	No	No	No	No
Balmelli et al[7]	Yes	No	No	No	No	No

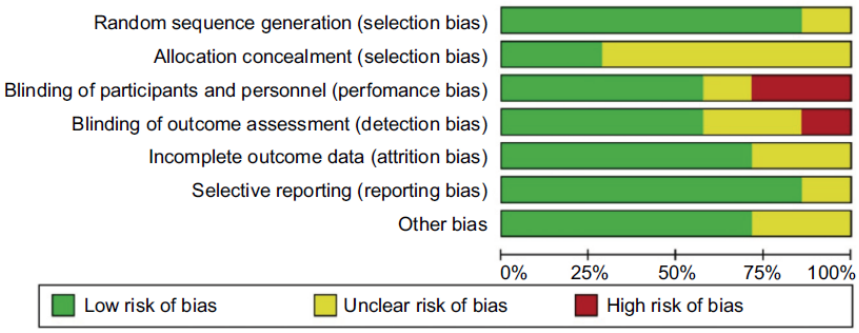


Figure S1 Risk of bias graph.

Studienergebnisse:

Frequency of all-grade treatment-related AEs (TRAEs)

- Significant higher OR of all grade TRAEs in sorafenib vs. lenvatinib
  - All grade hand-foot syndrome: OR=6.56, 95% CI=4.53–9.48, P<0.0001
  - All grade hypocalcemia: OR=3.96, 95% CI=2.25–6.98, P<0.0001
  - All grade rash: OR=5.39, 95% CI=3.56–8.18, P<0.0001
- Significant lower OR of all grade TRAEs in sorafenib vs. lenvatinib
  - All grade voice change: OR=0.49, 95% CI=0.30–0.79, P=0.003
  - All grade hypertension: OR=0.31, 95% CI=0.23–0.42, P<0.0001
  - All grade nausea: OR=0.40, 95% CI=0.27–0.57, P<0.0001

- No significant differences for other all grade TRAEs, including diarrhea, weight loss, anorexia, fatigue, and mucositis

Frequency of severe TRAEs (grade ≥3)

- Significant higher OR of Grade ≥3 TRAEs in sorafenib vs. lenvatinib:
  - Grade ≥3 hand-foot syndrome: OR=8.25, 95% CI=4.19–16.24, P<0.0001
  - Severe hypocalcemia: OR=3.15, 95% CI=1.30–7.63, P=0.009
- Significant lower OR of Grade ≥3 TRAEs in sorafenib vs. lenvatinib
  - Grade ≥3 hypertension: OR=0.22, 95% CI=0.14–0.34, P<0.0001
  - Severe nausea: OR=0.11, 95% CI=0.01–2.09, P<0.05
- No significant differences for grade ≥3 diarrhea, mucositis and anorexia

Fazit der Autoren

Our study has shown that different TKI drugs are associated with a highly increased risk of treatment-related toxicity in advanced or RR-DTC. Early interventions and management of TRAEs based on which TKI drugs are applied can minimize the impacts on patients' QoL, better deploying medical resources. Overall, patients and physicians should be familiar with the risks of TRAEs and early management of their side effects to promote patients' QoL.

Bai Y et al., 2019 [1].

Risk of venous and arterial thromboembolic events associated with tyrosine kinase inhibitors in advanced thyroid cancer: a meta-analysis and systematic review

Fragestellung

To assess the incidence and risk of arterial and venous thromboembolic events (ATEs and VTEs) associated with tyrosine kinase inhibitors (TKIs) in advanced thyroid cancer patients.

Methodik

Population:

- Advanced thyroid cancer patients

Intervention/Komparator:

- Sorafenib vs. Placebo, Cabozantinib vs. Placebo, Vandetanib vs. Placebo, Lenvatinib vs. Placebo (Axitinib vs. Placebo, Sunitinib vs. Placebo = nicht relevant für AWG)

Endpunkte:

- ATEs/VTEs: thrombosis/thrombus/embolism (excluded vascular access related thrombosis if reported separately), arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, myocardial infarction and myocardial ischemia.

Recherche/Suchzeitraum:

- Pubmed, Embase, and Cochrane Library electronic databases up to August 2017

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 studies (n=1,781 patients were available for the meta-analysis)
- Four RCTs, eight phase II trials

Charakteristika der Population:

Table 1: Baseline characteristics of 12 included trials

authors	phase	total	treatment arms	median age (years)	median PFS	No. for analysis
Lam E.T. et al. 2010 [40]	II	16	sorafenib 400 mg bid po	60	17.9	16
Wells Jr S.A. et al. 2012 [39]	III	331	vandetanib 300 mg qd po	50.7	30.5	231
			placebo	53.4	19.3	100
Savvides P. et al. 2013 [37]	II		sorafenib 400 mg bid po	59	1.9	20
Elisei R. et al. 2013 [38]	III	330	cabozantinib 140 mg qd po	55	11.4	214
			placebo	55	4	109
Brose M.S. et al. 2014 [36]	III	416	sorafenib 400 mg bid po	63	10.8	207
			placebo	63	5.8	209
Cohen E.E.W. et al. 2014 [35]	II	60	axitnib 5 mg bid po	59	15	60
Cabanillas M.E. et al. 2015 [30]	II	58	lenvatinib 24 mg qd po	63	12.6	58
Schlumberger M. et al. 2015 [31]	III	392	lenvatinib 24 mg qd po	64	18.3	261
			placebo	61	3.6	131
Bikas A. et al. 2016 [32]	II	23	sunitnib 50 mg qd	61	8	23
Schlumberger M. et al. 2016 [33]	II	59	lenvatinib 24 mg qd po	51.6	9	59
Cabonillas M.E. et al. 2017 [34]	II	25	cabozantinib 140 mg qd po	64	12.7	25
Ravaud A. et al. 2017 [29]	II	71	sunitinib 50 mg qd	66	13.1	71

Abbreviation: PFS, progression-free survival.

Qualität der Studien:

- The quality of the four randomized controlled trials was high. All of these trials were double-blinded, placebo-controlled trials, thus had a Jadad score of 5.

Studienergebnisse (nur für die vier RCTs dargestellt):

- Peto OR of high-grade ATEs in TKIs versus placebo arms was 4.72 (95% CI 1.18–18.95; P = 0.029). The test for heterogeneity was not significant (I2 = 0%, P = 0.73).
- Peto OR of VTEs in TKIs versus placebo arms was non-significant 1.36 (95% CI 0.51–3.64; P = 0.54). The test for heterogeneity was not significant (I2 = 0%, P = 0.70).

Anmerkung/Fazit der Autoren

In conclusion, this study demonstrates that TKIs treatment in advanced TCs patients is associated with a significant increase of high-grade ATEs, but not for VTEs. Given the increasing use of TKIs in TCs patients, it is important for physicians and patients to be aware of the risk of ATEs and prevent accordingly, especially those caused by cardiac toxicity, to maximize the clinical benefits of TKIs in these patients.

Liu JW et al., 2018 [6].

Tyrosine kinase inhibitors for advanced or metastatic thyroid cancer: a meta-analysis of randomized controlled trials

Fragestellung

To evaluate the effectiveness and safety of tyrosine kinase inhibitors (TKIs) for advanced or metastatic thyroid cancer treatment.

Methodik

Population:

- patients with locally advanced, unresectable, or metastatic thyroid cancer

Intervention/Komparator:

- Sorafenib vs. Placebo, Cabozantinib vs. Placebo, Vandetanib vs. Placebo, Lenvatinib vs. Placebo

Endpunkte:

- Primary outcomes: overall survival (OS) and progression-free survival (PFS)
- Secondary outcomes: complete and partial RRs and adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, EMBASE, Scopus, and Cochrane databases were electronically searched for relevant studies published until April 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Six RCTs (n=1,615)

Charakteristika der Population:

- Four trials were initially RCTs, but if independent radiologic review confirmed disease progression, the patients who were receiving the placebo could elect to enter the open-label experimental drug phase 9, 10, 12, 18.
- Three trials enrolled patients with advanced or metastatic DTC 10, 12, 18, and two other trials recruited unresectable, advanced, or metastatic MTC patients 10, 17.
- Among all DTCs, 486 patients with papillary thyroid cancer and 125 patients with follicular thyroid cancer were included

Table 1. Characteristics of the included randomized controlled trials.

First author (year)	Inclusion criteria	Cancer type	No. of patients (% male)	Age, y	Intervention
Brose (2014)[18]	Age ≥18 y; advanced or metastatic radioiodine-refractory DTC	PTC/FTC/Hurthle cell/poorly differentiated/others	S: 207 (50.2) P: 210 (45.2)	S: 63 (24–82) P: 63 (30–87)	S: Sorafenib 400 mg twice P: Placebo
Elisei (2013)[17]	Adult; unresectable, advanced or metastatic MTC	MTC	C: 219 (68.9) P: 111 (63.1)	C: 55 (20–86) P: 55 (21–79)	C: Cabozantinib 140 mg qd P: Placebo
Leboulleux (2012)[9]	Age ≥18 y; advanced or metastatic DTC	PTC/FTC/poorly differentiated	V: 72 (54) P: 73 (53)	V: 63 (29–81) P: 64 (23–87)	V: Vandetanib 300 mg qd P: Placebo
Schlumberger (2015)[12]; Kiyota (2015)[13]	Age ≥18 y; radioiodine-refractory DTC	PTC/FTC/poorly differentiated	L: 261 (48) P: 131 (57)	L: 64 (27–89) P: 61 (21–81)	L: Lenvatinib 24 mg qd P: Placebo
Wells (2012)[10]	Adult; unresectable or metastatic MTC	MTC	V: 231 (58) P: 100 (56)	V: 50.7[a] P: 53.4	V: Vandetanib 300 mg qd P: Placebo

Abbreviations. C, cabozantinib; DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; L, lenvatinib; MTC, medullary thyroid cancer; P, placebo; PTC, papillary thyroid cancer; S, sorafenib; V, vandetanib; y, years.
Data presented as median (range) except where [a]indicates the mean.

Qualität der Studien:

Table 2. Methodological quality assessment of included studies.

First author (year)	Allocation generation	Allocation concealment	Blinding of patients and assessors	Data analysis	Lost to follow-up (%)	Selective reporting	Other bias
Brose (2014)[18]	Computer generated	Unclear	Double blinded	ITT	1.2	Low risk	Industry funded
Elisei (2013)[17]	Unclear	Unclear	Double blinded	ITT	5	Low risk	Industry funded; 20.6% patients took TKIs before the study
Leboulleux (2012)[9]	Computer generated	Unclear	Double blinded	ITT	0	Low risk	Industry funded; majority of patients discontinued vandetanib before data cutoff
Schlumberger (2015)[12]; Kiyota (2015)[13]	Computer generated	Unclear	Double blinded	ITT	0	Low risk	Industry funded; only 47% patients continued to receive study drug at data cutoff point
Wells (2012)[10]	Unclear	Unclear	Double blinded	ITT	0.30	Low risk	Industry funded

Risk of bias was assessed according to the method recommended by the Cochrane Collaboration.
Abbreviation. ITT, intention-to-treat.

Studienergebnisse:

OS:

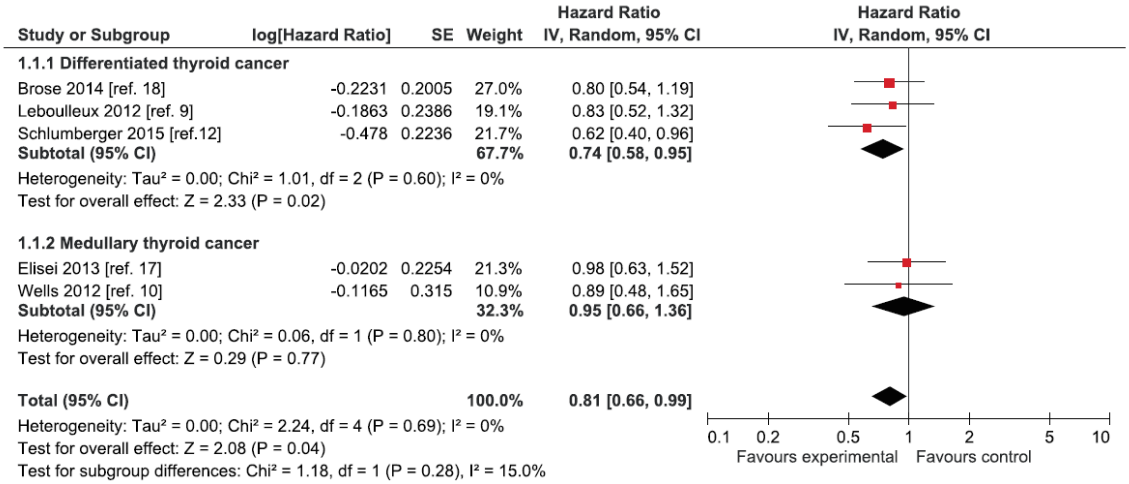


Figure 2. Forest plot of the comparison of the hazard ratio of overall survival between the tyrosine kinase inhibitor treatment and control groups: 1.1.1 differentiated thyroid cancer and 1.1.2 medullary thyroid cancer.

- Among three TKIs, only lenvatinib showed a significantly higher OS (HR=0.62; 95% CI, 0.40–0.96) than the control group (Figure 2, 1.1.1 DTC).

PFS:

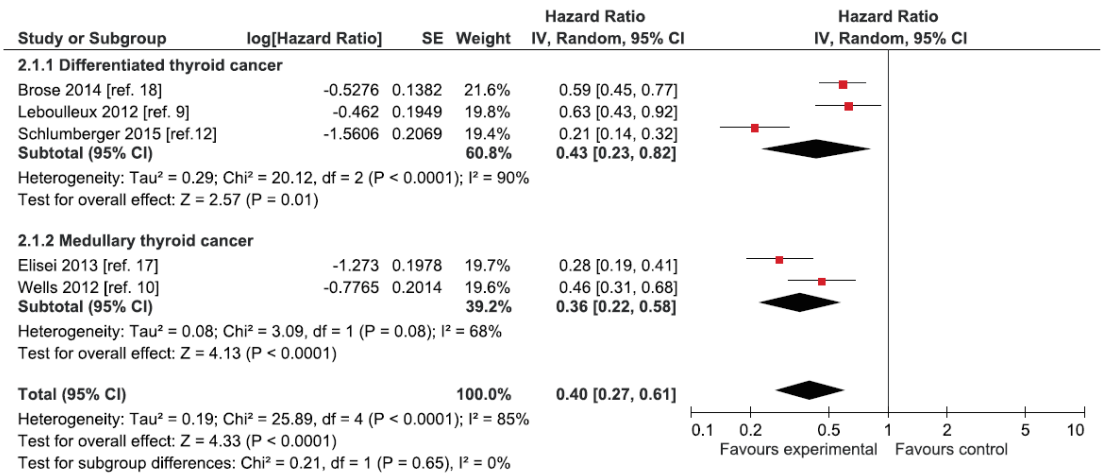


Figure 3. Forest plot of the comparison of the hazard ratio of progression-free survival between the tyrosine kinase inhibitor treatment and control groups: 2.1.1 differentiated thyroid cancer and 2.1.2 medullary thyroid cancer.

AEs:

- All trials reported significantly more AEs of any grade in the TKI treatment group than in the control group (hypertension: risk ratio=5.42; 95% CI, 3.53–8.34; alopecia: risk ratio=6.20; 95% CI, 2.92–13.16; rash: risk ratio=3.91; 95% CI, 2.51–6.10; diarrhea: risk ratio=3.45; 95% CI, 2.13–5.60; nausea: risk ratio=2.10; 95% CI, 1.70–2.60).
- TKI treatment group also exhibited significantly more grade 3+ AEs than the control group did (hypertension: risk ratio=8.96; 95% CI, 3.46–23.17; rash: risk ratio=4.20; 95% CI, 1.11–15.87; diarrhea: risk ratio=7.63; 95% CI, 3.55–16.40).

Response rate:

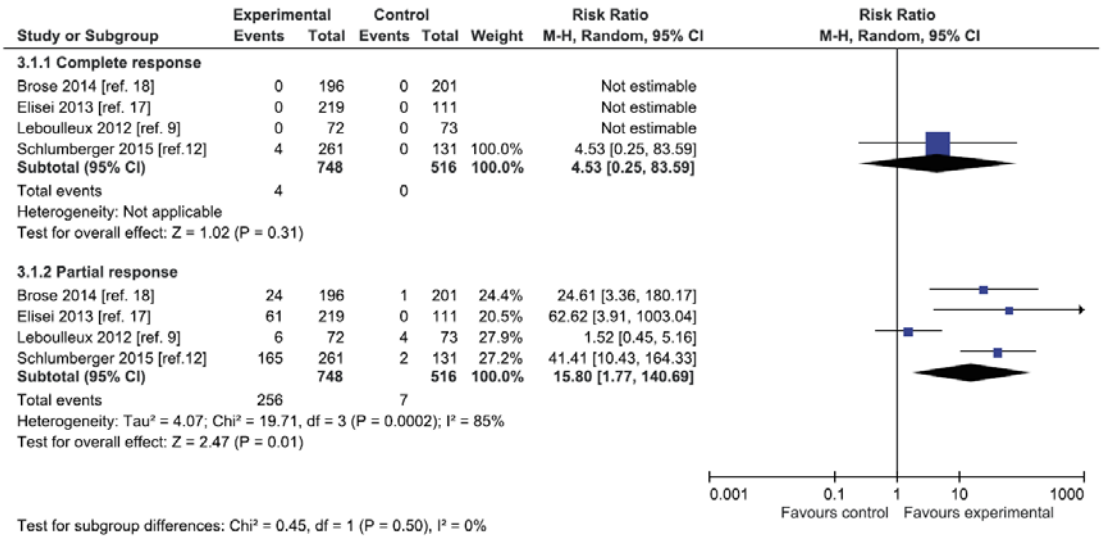


Figure 4. Forest plot of the comparison of the risk ratio of the objective response rate between the tyrosine kinase inhibitor treatment and control groups: 3.1.1 complete response and 3.1.2 partial response.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis revealed that TKI target therapy is promising for patients with radioiodine-refractory advanced or metastatic DTC or MTC. The use of TKIs significantly improved the PFS and RR, and thus prolonged the life expectancy of the patients. Our results indicate that lenvatinib is the most effective but has the highest toxicity among all included TKIs. The optimal choice of TKIs for treatment of patients with advanced or metastatic DTC or MTC must be thoroughly investigated through additional RCTs. However, clinical physicians should consider the high incidence of AEs. The preferences of patients regarding TKI treatments should be discussed with physicians to ensure the most favorable outcome.

Kommentare zum Review

Among the included studies, Schlumberger et al. and Kiyota et al. analyzed patient outcomes from the same trial (the phase 3 SELECT trial) 12, 13. However, Kiyota et al. mainly focused on analyzing the outcome of TKI treatment in Japanese patients.

3.4 Leitlinien

NCCN, 2021 [7].

National Comprehensive Cancer Network (NCCN)

Thyroid Carcinoma. Version 1.2021.

Zielsetzung/Fragestellung

Management of Thyroid Carcinoma.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium unklar
- Interessenkonflikte und finanzielle Unabhängigkeit unklar;
- Systematische Suche, Auswahl und Bewertung der Evidenz unklar
- Formale Konsensusprozesse und externes Begutachtungsverfahren unklar;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz beschrieben;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

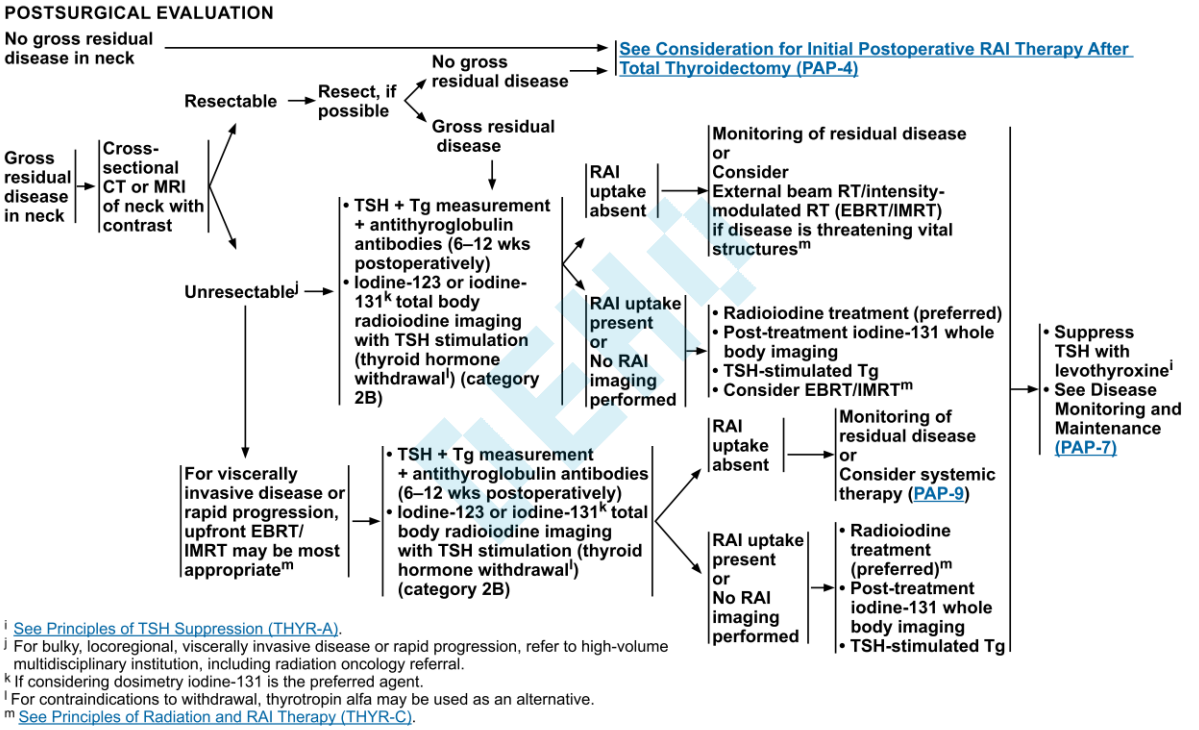
- PubMed Recherche. Zeitraum k.A.

LoE/GoR

- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Recommendations

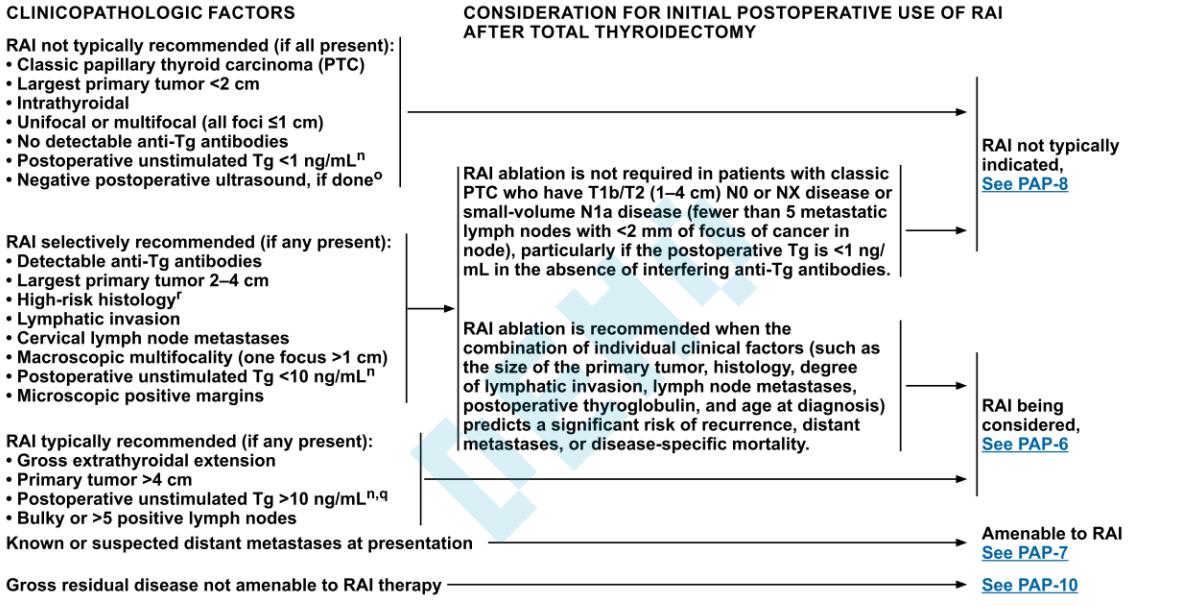
Thyroid Carcinoma – Papillary Carcinoma:



[i] See Principles of TSH Suppression (THYR-A).
[j] For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.
[k] If considering dosimetry iodine-131 is the preferred agent.
[l] For contraindications to withdrawal, thyrotropin alfa may be used as an alternative.
[m] See Principles of Radiation and RAI Therapy (THYR-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PAP-3



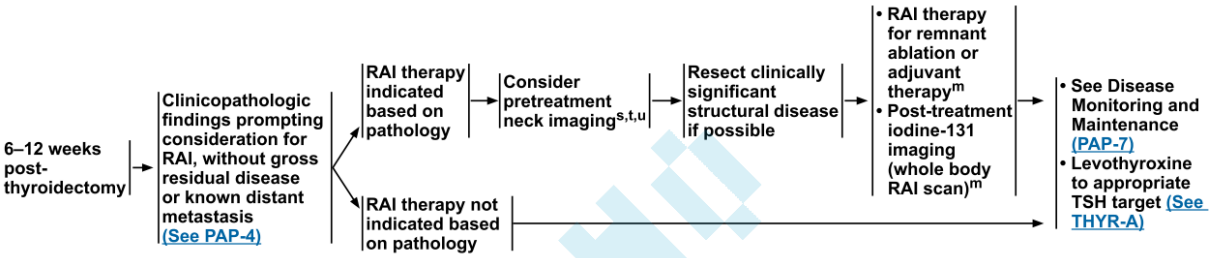
[n] Tg values obtained 6–12 weeks after total thyroidectomy.
[o] If preoperative imaging incomplete, consider postoperative ultrasound including central and lateral neck components.
[q] Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.
[r] ie, poorly differentiated, tall cell, columnar cell, hobnail variants, diffuse sclerosing, and insular.

For general principles related to radioactive iodine (RAI) therapy, see the Principles of Radiation and Radioactive Iodine Therapy (THYR-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PAP-4

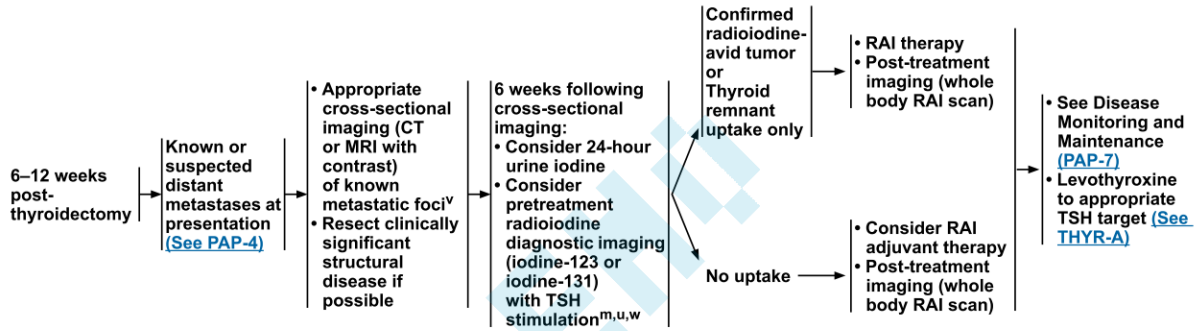
RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



[m] See Principles of Radiation and RAI Therapy (THYR-C).
[s] Even in the absence of thyroid bed uptake RAI treatment may be considered. If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.
[t] A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.
[u] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased glomerular filtration rate (GFR). Dialysis patients require special handling.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



[m] See Principles of Radiation and RAI Therapy (THYR-C).
[u] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative finds, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.
[v] To evaluate macroscopic metastatic foci for potential alterative therapies (eg, surgical resection, external beam irradiation) to prevent invasion/compression of vital structures or pathologic fracture either as a result of disease progression or TSH stimulation.
[w] Thyrotropin alfa may be used for elderly patients for when prolonged hypothyroidism may be risky.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

RECURRENT DISEASE

- Stimulated Tg 1–10 ng/mL and negative imaging
- Non-resectable tumors
- Non-radioiodine responsive[aa]

→ Suppress TSH with levothyroxine[i] → Continue surveillance with unstimulated Tg, ultrasound, and other imaging as clinically indicated (See PAP-7)

- Progressively rising Tg (basal or stimulated)
- Scans (including PET) negative

→ Consider radioiodine therapy with ≥100 mCi[bb] and Post-treatment iodine-131 imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy (minimum of 6–12 months between RAI treatments)

Locoregional recurrence → Consider preoperative iodine total body scan →

- Surgery (preferred) if resectable[cc] and/or Radioiodine treatment,[bb] if radioiodine imaging positive
- or Disease monitoring for non-progressive disease that is stable and distant from critical structures
- or For select patients with unresectable, non–radioiodine-avid, and progressive disease, consider:
  - EBRT (IMRT/SBRT)[m] and/or
  - Systemic therapies (See Treatment of Metastatic Disease PAP-9)
- or For select patients with limited burden nodal disease, consider local therapies when available (ethanol ablation, radiofrequency ablation [RFA])

Metastatic disease →

- RAI therapy for iodine-avid disease[m] and/or
- Local therapies when available[dd] and/or
- See PAP-9 if not amenable to RAI

[aa] Generally, a tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 (1–3 mCi) whole body diagnostic imaging done 6–12 mo after iodine-131 treatment is negative or shows decreasing uptake compared to pre-treatment scans. It is recommended to use the same preparation and imaging method employed for the pre-treatment scan and therapy. Favorable response to iodine-131 treatment is additionally assessed through change in volume of known iodine-concentrated lesions by CT/MRI, and by decreasing unstimulated or stimulated thyroglobulin levels.

[bb] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).

[cc] Preoperative vocal cord assessment, if central neck recurrence.

[dd] Ethanol ablation, cryoablation, RFA, etc.

[i] See Principles of TSH Suppression (THYR-A).

[m] See Principles of Radiation and RAI Therapy (THYR-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

Structurally persistent/recurrent locoregional or distant metastatic disease not amenable to RAI therapy →

- Continue to suppress TSH with levothyroxine[i]
- For advanced, progressive, or threatening disease, genomic testing to identify actionable mutations (including *ALK*, *NTRK*, and *RET* gene fusions), DNA mismatch repair (dMMR), microsatellite instability (MSI), and tumor mutational burden (TMB)
- Consider clinical trial

→ **Unresectable locoregional recurrent/ persistent disease**

→ **Soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)**

→

- Consider systemic therapy
  - For progressive and/or symptomatic disease, consider lenvatinib (preferred)[ee] or sorafenib[ff,gg]
  - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
  - Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
  - Pembrolizumab for patients with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors
  - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[hh,ii]
- Consider resection of distant metastases and/or EBRT (SBRT/IMRT[m])/other local therapies[dd] when available to metastatic lesions if progressive and/or symptomatic (For locoregional disease, see PAP-8)
- Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.[gg] (See PAP-7)
- Best supportive care (See NCCN Guidelines for Palliative Care)

Bone metastases → See PAP-10

CNS metastases → See PAP-10

[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).

[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.

[ii] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

[i] See Principles of TSH Suppression (THYR-A).

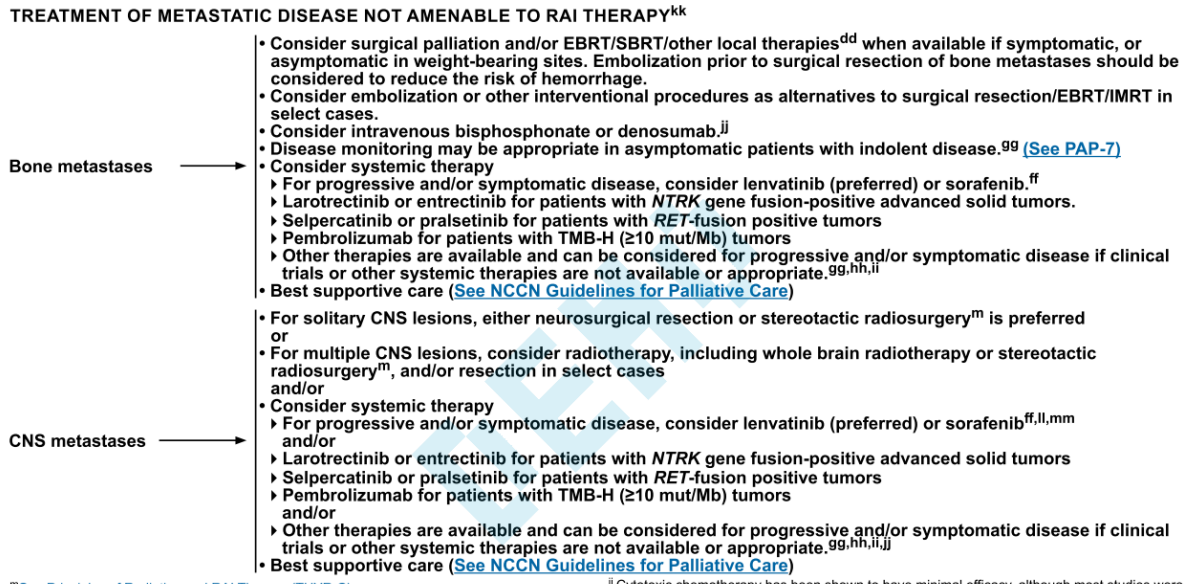
[m] See Principles of Radiation and RAI Therapy (THYR-C).

[dd] Ethanol ablation, cryoablation, RFA, etc.

[ee] In a subset of patients (>65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, et al. J Clin Oncol 2017;35:2692-2699.

[ff] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

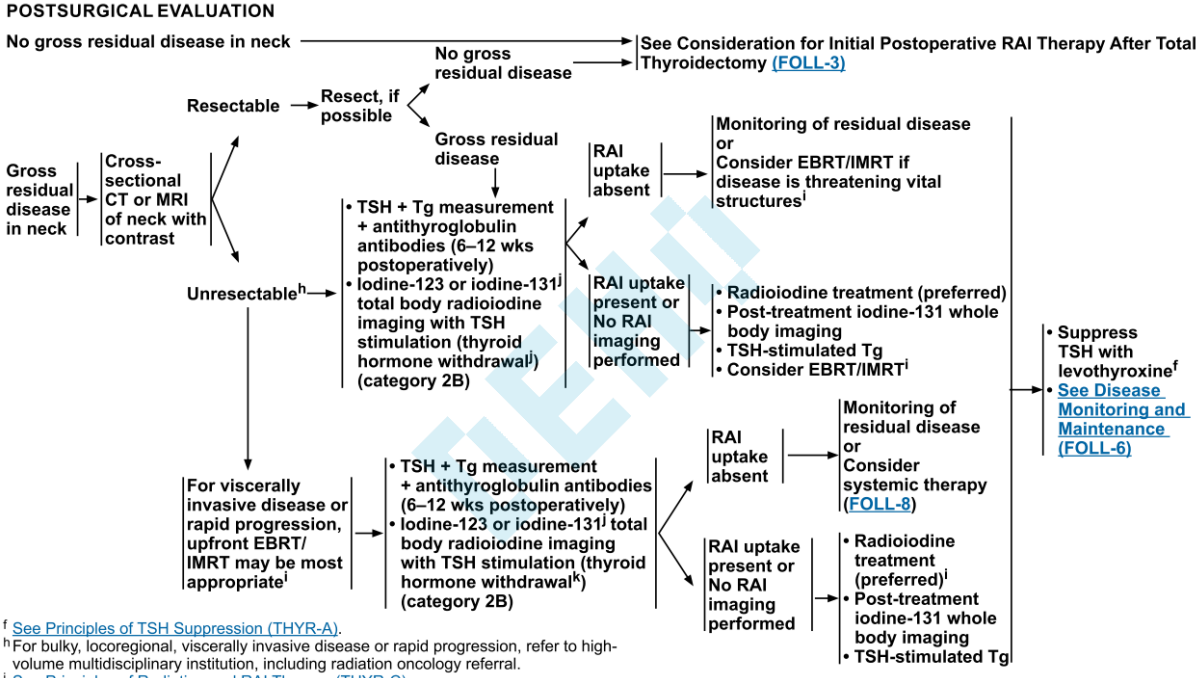


[m] See Principles of Radiation and RAI Therapy (THYR-C).
[dd] Ethanol ablation, cryoablation, RFA, etc.
[ff] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ii] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[jj] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures.
[kk] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[ll] After consultation with neurosurgery and radiation oncology, data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
[mm] TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PAP-10

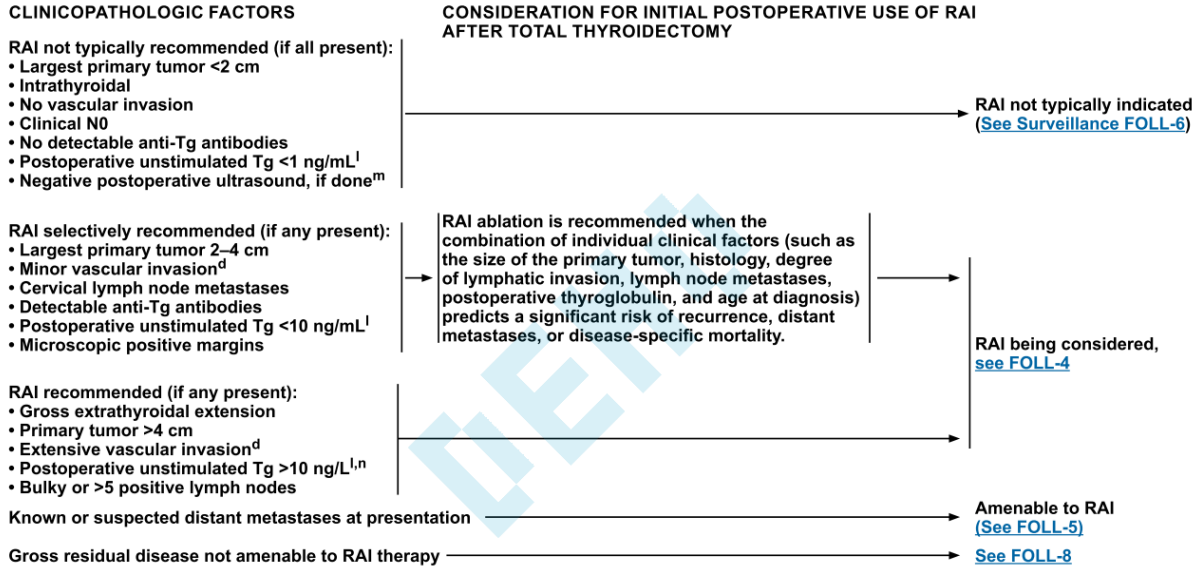
Thyroid Carcinoma – Follicular Carcinoma



[f] See Principles of TSH Suppression (THYR-A).
[h] For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.
[i] See Principles of Radiation and RAI Therapy (THYR-C).
[j] If considering dosimetry iodine-131 is the preferred agent.
[k] For contraindications to withdrawal, thyrotropin alfa may be used as an alternative.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-2



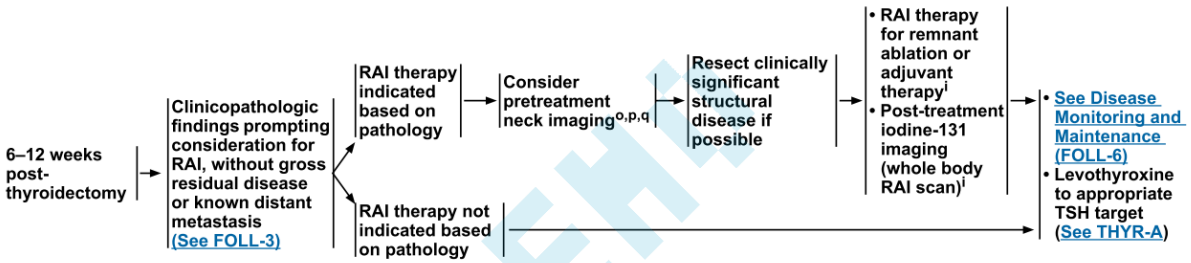
[d] Minimally invasive FTC is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.
[l] Tg values obtained 6–12 weeks after total thyroidectomy.
[m] If preoperative imaging incomplete, consider postoperative ultrasound including central and lateral neck components.
[n] Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

For general principles related to RAI therapy, see the Principles of Radiation and Radioactive Iodine Therapy (THYR-C)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-3

RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES

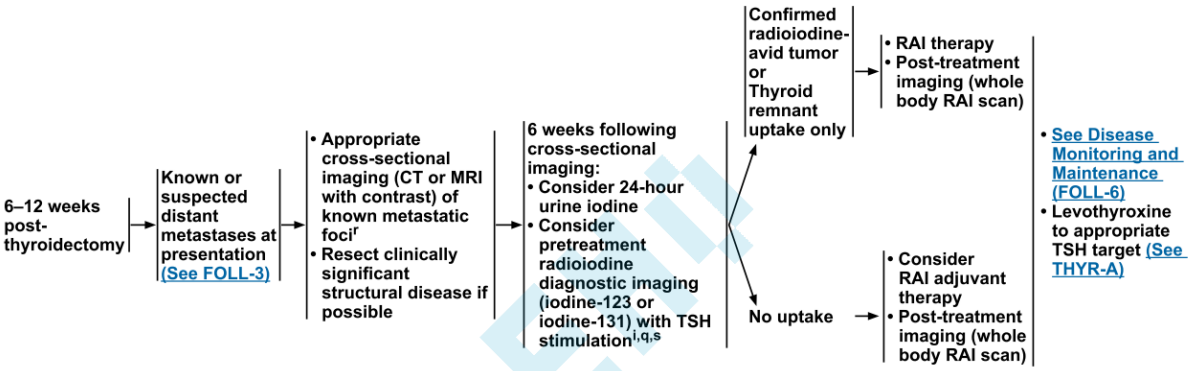


[i] See Principles of Radiation and RAI Therapy (THYR-C).
[o] Even in the absence of thyroid bed uptake RAI treatment may be considered. If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.
[p] A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.
[q] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-4

KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE

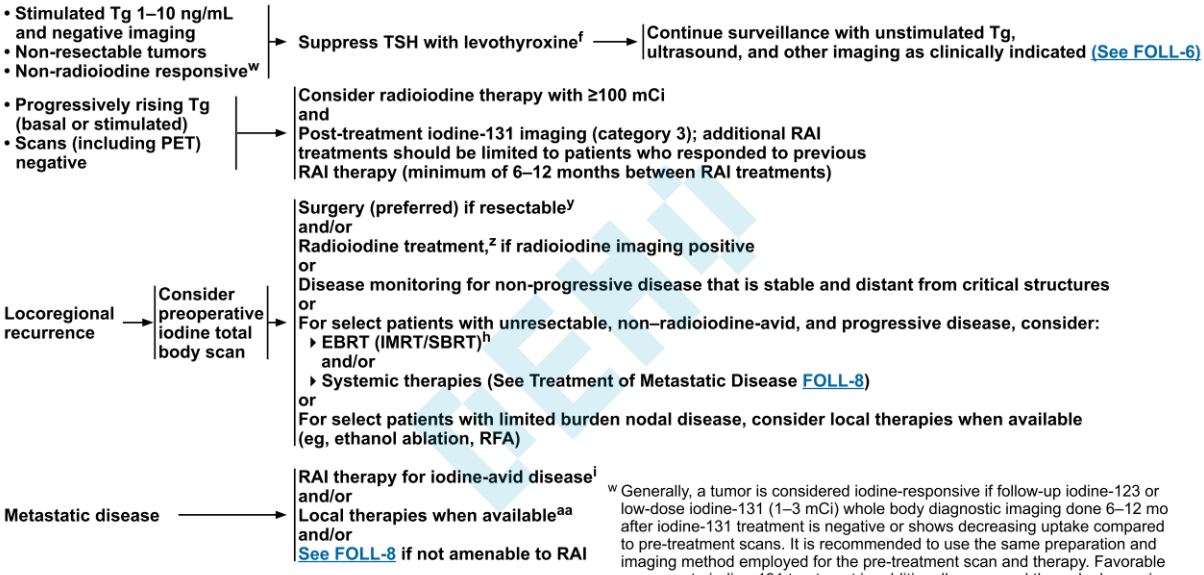


[i] See Principles of Radiation and RAI Therapy (THYR-C).
[q] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.
[r] To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection and/or external beam radiation) to prevent invasion/compression of vital structures or pathologic fracture either as a result of disease progression or TSH stimulation.
[s] Thyrotropin alfa may be used for elderly patients for whom prolonged hypothyroidism may be risky.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-5

RECURRENT DISEASE

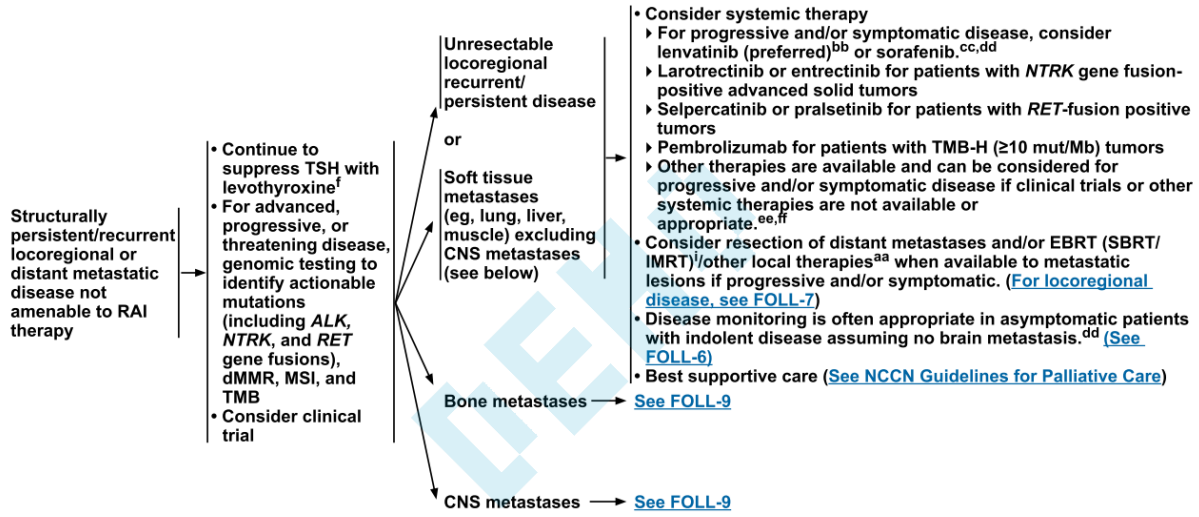


[w] Generally, a tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 (1–3 mCi) whole body diagnostic imaging done 6–12 mo after iodine-131 treatment is negative or shows decreasing uptake compared to pre-treatment scans. It is recommended to use the same preparation and imaging method employed for the pre-treatment scan and therapy. Favorable response to iodine-131 treatment is additionally assessed through change in volume of known iodine-concentrated lesions by CT/MRI, and by decreasing unstimulated or stimulated thyroglobulin levels.
[y] Preoperative vocal cord assessment, if central neck recurrence.
[z] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).
[aa] Ethanol ablation, cryoablation, RFA, etc.
[f] See Principles of TSH Suppression (THYR-A).
[i] See Principles of Radiation and RAI Therapy (THYR-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-7

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

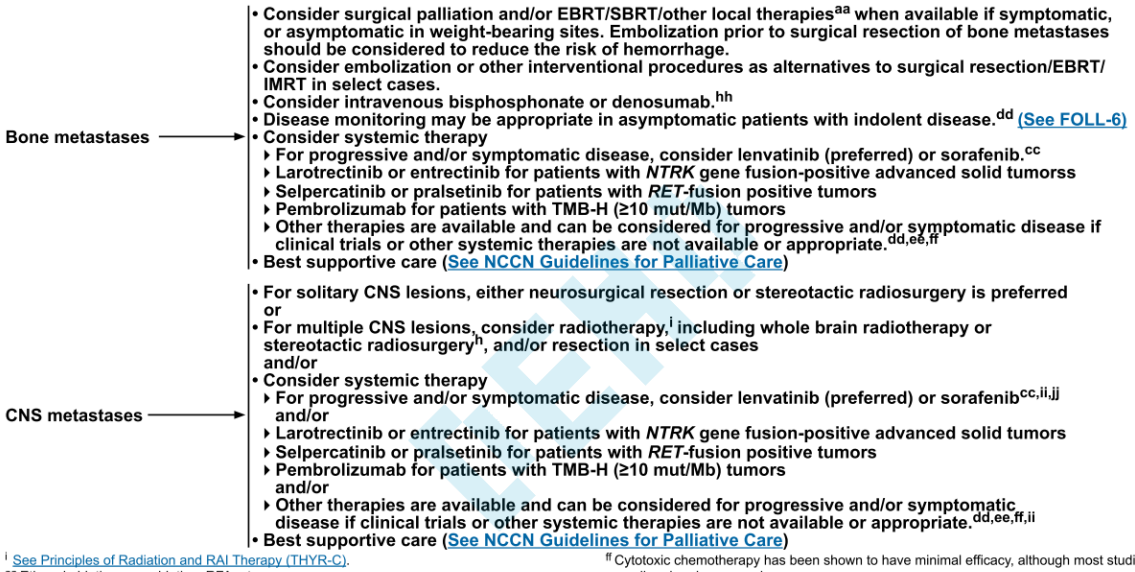


[f] See Principles of TSH Suppression (THYR-A).
[i] See Principles of Radiation and RAI Therapy (THYR-C).
[aa] Ethanol ablation, cryoablation, RFA, etc.
[bb] In a subset of patients (>65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, et al. J Clin Oncol 2017;35:2692-2699.
[cc] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[dd] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[ee] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ff] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-8

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[gg]



[i] See Principles of Radiation and RAI Therapy (THYR-C).
[aa] Ethanol ablation, cryoablation, RFA, etc.
[cc] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[dd] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[ee] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ff] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[gg] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[hh] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures.
[ii] After consultation with neurosurgery and radiation oncology; data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
[jj] TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-9

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 8 of 12, August 2021) am 10.08.2021

#	Suchfrage
1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
2	MeSH descriptor: [Adenocarcinoma, Follicular] explode all trees
3	MeSH descriptor: [Adenocarcinoma, Papillary] explode all trees
4	(thyroid):ti,ab,kw
5	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma*):ti,ab,kw
6	#1 OR #2 OR #3 OR (#4 AND #5)
7	#6 with Cochrane Library publication date from Aug 2016 to present

Systematic Reviews in Medline (PubMed) am 10.08.2021

#	Suchfrage
1	"Thyroid Neoplasms/therapy"[Mesh]
2	"Adenocarcinoma, Follicular/therapy"[Mesh]
3	"Adenocarcinoma, Papillary/therapy"[Mesh] AND thyroid gland[MeSH Terms]
4	thyroid[tiab]
5	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR cancer*[tiab]
6	(#4 AND #5) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
7	#1 OR #2 OR #3 OR #6
8	(#7) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw])

#	Suchfrage
	AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
9	(#8) AND ("2016/08/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT "The Cochrane database of systematic reviews"[Journal]
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 10.08.2021

#	Suchfrage
1	thyroid neoplasms[MeSH Terms]
2	adenocarcinoma, follicular[MeSH Terms]
3	adenocarcinoma, papillary[MeSH Terms] AND thyroid gland[MeSH Terms]
4	thyroid[tiab]
5	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR cancer*[tiab]
6	#1 OR #2 OR #3 OR (#4 AND #5)
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2016/08/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Referenzen

1. **Bai Y, Li JY, Li J, Zhang B, Liu YH, Zhang BY, et al.** Risk of venous and arterial thromboembolic events associated with tyrosine kinase inhibitors in advanced thyroid cancer: a meta-analysis and systematic review. Oncotarget 2019;10(41):4205-4212.
2. **Fleeman N, Houten R, Chaplin M, Beale S, Boland A, Dundar Y, et al.** A systematic review of lenvatinib and sorafenib for treating progressive, locally advanced or metastatic, differentiated thyroid cancer after treatment with radioactive iodine. BMC Cancer 2019;19(1):1209.
3. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. August 2019 - Lenvatinib (Bewertung nach Aufhebung des Orphan Drug-Status) [online]. Berlin (GER): G-BA; 2019. [Zugriff: 16.08.2021]. URL: https://www.g-ba.de/downloads/91-1385-442/2019-08-15_Geltende-Fassung_Lenvatinib_D-428.pdf.
4. **Jacomina LE, Jacinto JKM, Co LBA, Yu KKL, Agas RAF, Co JL, et al.** The role of postoperative external beam radiotherapy for differentiated thyroid carcinoma: a systematic review and meta-analysis. Head Neck 2020;42(8):2181-2193.
5. **Lin S, Shen J, Zhao W, Wang X, Wang X, Zhu J.** Evaluating the effectiveness of targeted therapies for thyroid carcinoma: an updated meta-analysis. Ann Transl Med 2019;7(24):802.
6. **Liu JW, Chen C, Loh EW, Chu CC, Wang MY, Ouyang HJ, et al.** Tyrosine kinase inhibitors for advanced or metastatic thyroid cancer: a meta-analysis of randomized controlled trials. Curr Med Res Opin 2018;34(5):795-803.
7. **National Comprehensive Cancer Network (NCCN).** Thyroid Carcinoma. Version 1.2021 [online]. Plymouth Meeting (USA): NCCN; 2021. [Zugriff: 11.08.2021]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.
8. **Yu ST, Ge JN, Luo JY, Wei ZG, Sun BH, Lei ST.** Treatment-related adverse effects with TKIs in patients with advanced or radioiodine refractory differentiated thyroid carcinoma: a systematic review and meta-analysis. Cancer Manag Res 2019;11:1525-1532.

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2021-B-263

Kontaktdaten

Deutsche Gesellschaft für Endokrinologie (DGE)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Deutsche Gesellschaft für Nuklearmedizin (DGN)

Indikation gemäß Beratungsantrag

Monotherapie bei erwachsenen und jugendlichen Patienten ab 12 Jahren mit lokal fortgeschrittenem oder metastasiertem differenziertem Schilddrüsenkarzinom (DTC), die refraktär gegenüber Radiojod (RAI) sind oder dafür nicht in Frage kommen und bei denen während oder nach einer vorherigen systemischen Therapie eine Progression aufgetreten ist.

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Die Therapie bei Patient*innen mit differenziertem, Radiojod-refraktärem Schilddrüsenkarzinom und Progression während oder nach einer vorherigen systemischen Therapie richtet sich nach der Vortherapie, biologischen Markern und dem Allgemeinzustand. Therapieoptionen sind:

○ nach Therapie mit Lenvatinib	Sorafenib
○ nach Therapie mit Sorafenib	Lenvatinib
○ bei Nachweis von *NTRK*-Genfusionen	Entrectinib oder Larotrectinib
○ bei Nachweis von *RET*-Genalterationen	Selpercatinib
○ bei stark reduziertem Allgemeinzustand, nach Therapie mit Lenvatinib und Sorafenib bzw. molekular gezielten Kinase-Inhibitoren	Best Supportive Care

Fragestellung

Die Zahl der jugendlichen Patient*innen mit differenziertem, Radiojod-refraktärem Schilddrüsenkarzinom und Progression während oder nach einer vorherigen systemischen Therapie ist sehr klein, s. u.. Die Aussagen dieser Stellungnahme beziehen sich auf erwachsene Patient*innen.

Kontaktdaten

Deutsche Gesellschaft für Endokrinologie (DGE)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Deutsche Gesellschaft für Nuklearmedizin (DGN)

Indikation gemäß Beratungsantrag

Monotherapie bei erwachsenen und jugendlichen Patienten ab 12 Jahren mit lokal fortgeschrittenem oder metastasiertem differenziertem Schilddrüsenkarzinom (DTC), die refraktär gegenüber Radiojod (RAI) sind oder dafür nicht in Frage kommen und bei denen während oder nach einer vorherigen systemischen Therapie eine Progression aufgetreten ist.

Stand des Wissens

Das Schilddrüsenkarzinom ist die häufigste, maligne Erkrankung des endokrinen Systems. Die Zahl aller Neuerkrankten an Schilddrüsenkarzinom in Deutschland wurde für das Jahr 2016 auf 5.280 Frauen und 2.500 Männer geschätzt [1]. Die meisten Schilddrüsenkarzinome entstehen aus maligne transformierten, follikulären Zellen und werden histologisch in papilläre (72%), follikuläre (12%), Hürthle-Zell- und anaplastische Karzinome unterteilt. Die ersten drei Subentitäten werden auch unter dem Oberbegriff des differenzierten Schilddrüsenkarzinoms (engl.: Differentiated Thyroid Cancer (DTC)) zusammengefasst.

Die Inzidenz des Schilddrüsenkarzinom ist in Deutschland und anderen Staaten der westlichen Welt in den letzten Jahren deutlich angestiegen, allerdings vor allem bei den papillären Karzinomen im Durchmesser <2 cm, die bei Ultraschalluntersuchung aus anderer Indikation diagnostiziert wurden.

Die Therapie erfolgt stadienabhängig. Im lokal begrenzten Stadium besteht eine hohe Heilungschance durch frühzeitige Operation, adjuvante Radiojodtherapie und konsekutive TSH-Suppression. Die krebsspezifischen 5-Jahres-Überlebensraten für alle Schilddrüsenkarzinome liegen in Deutschland bei über 90%. 7-23% der Patienten mit differenziertem Schilddrüsenkarzinom entwickeln Fernmetastasen, von ihnen werden im Verlauf etwa zwei Drittel Radiojod-refraktär. Die 10-Jahres-Überlebensrate der Patienten mit Radiojod-refraktärem Schilddrüsenkarzinom liegt bei etwa 10%, gemessen ab dem Zeitpunkt des Nachweises von Fernmetastasen [2, 3].

5-10% der Patienten mit differenzierten Schilddrüsenkarzinom haben bei Diagnosestellung eine lokal fortgeschrittene Erkrankung, bei etwa 10% der Patienten treten Fernmetastasen auf. Häufigste Lokalisation von Fernmetastasen sind Lunge und Knochen. Standard in der Therapie des metastasierten, differenzierten Schilddrüsenkarzinoms ist die Gabe von Radiojod. Bei Radiojod-refraktären Patienten ist Doxorubicin als einzige zytotoxische Chemotherapie in Deutschland zugelassen. Die Remissionsraten liegen <20% ohne Verlängerung der Überlebenszeit. Ein Vorteil von Kombinationschemotherapien gegenüber Doxorubicin Monotherapie ist nicht gesichert [4]. Doxorubicin wird derzeit von internationalen Leitlinien nicht als Therapieoption beim radiojodrefraktären Schilddrüsenkarzinom empfohlen [5].

Standard ist heute der Einsatz von Multikinase-Inhibitoren. Zugelassen sind Lenvatinib und Sorafenib.

- Das erste zugelassene Arzneimittel aus dieser Substanzklasse war Sorafenib. In der randomisierten DECISION-Studie erzielte Sorafenib eine Remissionsrate von 12,2% und eine Verlängerung des progressionsfreien Überlebens von 10,8 vs 5,8 Monaten gegenüber Placebo [6]. Die Überlebenszeit war nicht signifikant verlängert.

Kontaktdaten

Deutsche Gesellschaft für Endokrinologie (DGE)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Deutsche Gesellschaft für Nuklearmedizin (DGN)

Indikation gemäß Beratungsantrag

Monotherapie bei erwachsenen und jugendlichen Patienten ab 12 Jahren mit lokal fortgeschrittenem oder metastasiertem differenziertem Schilddrüsenkarzinom (DTC), die refraktär gegenüber Radiojod (RAI) sind oder dafür nicht in Frage kommen und bei denen während oder nach einer vorherigen systemischen Therapie eine Progression aufgetreten ist.

- Lenvatinib führte in der Zulassungsstudie SELECT gegenüber Placebo zur Verlängerung des progressionsfreien Überlebens mit einem Hazard Ratio von 0,21 [7]. Nebenwirkungen sind unter Lenvatinib häufig und führten bei der Mehrzahl der Patienten in der Zulassungsstudie zu Dosisreduktionen bzw. Therapieunterbrechungen. Im indirekten Vergleich erscheint Lenvatinib wirksamer als Sorafenib, belegt ist dieser Unterschied durch die bisher vorliegenden Daten nicht.

In der Pathogenese metastasierter, differenzierter Schilddrüsenkarzinome sind unterschiedliche Signalwege aktiviert. Häufig sind aktivierende Mutationen in *BRAF, HRAS, KRAS und NRAS,* seltener kommen aktivierende Fusionsereignisse vor, die in ca. 6% das *RET*-Gen betreffen und in ca. 2% die *NTRK1* und *NTRK3* Gene [8, 9].

Eingesetzt werden Entrectinib oder Larotrectinib bei Nachweis von *NTRK1*-Genfusionen und das kürzlich zugelassene Selpercatinib beim Nachweis von *RET*-Genalterationen. In den zur Zulassung führenden Phase-I/II-Studien wurden durch Selpercatinib Remissionsraten von 80% erzielt [10].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „*erwachsenen und jugendlichen Patienten ab 12 Jahren mit lokal fortgeschrittenem oder metastasiertem differenziertem Schilddrüsenkarzinom (DTC), die refraktär gegenüber Radiojod (RAI) sind oder dafür nicht in Frage kommen und bei denen während oder nach einer vorherigen systemischen Therapie eine Progression aufgetreten ist***“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Ja, diese sind für Erwachsene in den obigen Ausführungen enthalten und begründet.

Die Zahl der Kinder und Jugendlichen mit jugendlichen Patienten ab 12 Jahren mit lokal fortgeschrittenem oder metastasiertem differenziertem Schilddrüsenkarzinom (DTC), die refraktär gegenüber Radiojod (RAI) sind oder dafür nicht in Frage kommen, ist sehr klein. In einer aktuell publizierten Studie zu Cabozantinib (COSMIC-311) in dieser Therapiesituation waren formal Patient*innen ab 16 Jahre eingeschlossen. Die uns vorliegenden Auswertungen zeigen allerdings, dass die jüngsten Patient*innen ≥32 Jahre waren.

Bei den Kinder und Jugendlichen gibt es keinen eigenen, evidenzbasierten Therapiestandard. Neben den Daten aus einem Evidenztransfer von Erwachsenen würde eine systemische Therapie bei Kindern und Jugendlichen auch durch die Zulassungsbestimmungen beeinflusst: Lenvatinib (Lenvima®) ist formal nur für Erwachsene zugelassen.

Kontaktdaten

Deutsche Gesellschaft für Endokrinologie (DGE)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Deutsche Gesellschaft für Nuklearmedizin (DGN)

Indikation gemäß Beratungsantrag

Monotherapie bei erwachsenen und jugendlichen Patienten ab 12 Jahren mit lokal fortgeschrittenem oder metastasiertem differenziertem Schilddrüsenkarzinom (DTC), die refraktär gegenüber Radiojod (RAI) sind oder dafür nicht in Frage kommen und bei denen während oder nach einer vorherigen systemischen Therapie eine Progression aufgetreten ist.

Literatur/Referenzen

1. Gesellschaft der epidemiologischen Krebsregister in Deutschland / Robert - Koch Institut: Krebs in Deutschland 2015/2016, Häufigkeiten und Trends: Schilddrüse, 12. Ausgabe; 118 – 121, 2019.
2. Busaidy NL, Cabanillas ME. Differentiated thyroid cancer: management of patients with radioiodine nonresponsive disease. J Thyroid Res 2012:618985. 2012. DOI: 10.1155/2012/618985
3. Durante C, Haddy N, Baudin E, et al.: Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 91:2892-2899, 2006. PMID: 16684830
4. Tumino D, Frasca F, Newbold K: Updates on the Management of Advanced, Metastatic, and Radioiodine Refractory Differentiated Thyroid Cancer. Front Endocrinol 8:312, 2017. DOI: 10.3389/fendo.2017.00312
5. Haugen BR, Alexander EK, Bible KC et al.: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 26:1-133, 2016. DOI: 10.1089/thy.2015.0020
6. Brose MS, Nutting CM, Jarzab B, et al.: Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 384:319-328, 2014. DOI: 10.1016/S0140-6736(14)60421-9
7. Schlumberger M, Tahara M, Wirth LJ et al.: Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 372:621-630, 2015. DOI: 10.1056/NEJMoa1406470
8. Romei C, Elisei R: A Narrative Review of Genetic Alterations in Primary Thyroid Epithelial Cancer. Int J Mol Sci 22:1726, 2021. DOI: 10.3390/ijms22041726
9. Van der Tuin K, Garcia MV, Corver WE et al.: Targetable gene fusions identified in radioactive iodine refractory advanced thyroid carcinoma. Eur J Endocrinol 180:235-241, 2019. DOI: 10.1530/EJE-18-0653
10. Wirth LJ, Sherman E, Robinson B et al.: Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers. N Engl J Med 383:825-835, 2020. DOI: 10.1056/NEJMoa2005651

Stand: 19.09.2021