Il carcinoma anaplastico
Inquadramento clinico e diagnostico

CARCINOMA DELLA TIROIDE 2023
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European Reference Network
for rare or low prevalence complex diseases
Network Adult Cancers (ERN EURACAN)

Endo-ERN
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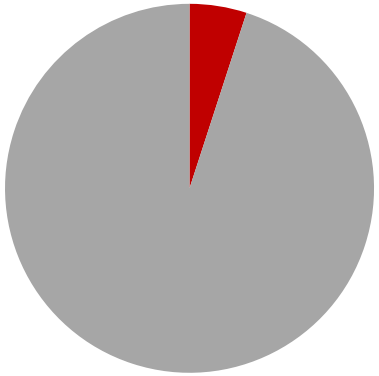
Anaplastic thyroid cancers are undifferentiated tumors of the thyroid follicular epithelium

Anaplastic cancers are extremely aggressive, with a disease-specific mortality approaching 100 percent

Given the very rapid course of disease progression and the poor treatment outcomes,
end of life issues and
plans for comfort care measures are an integral part of initial disease management

Anaplastic thyroid cancer



Incidence: 1-2 cases/million/year
2-5% of all thyroid cancers

Mean age 65 yrs
(< 10% younger than 50 yrs)
50-70% women

Median survival: 3-6 months
1 year survival: 20-35%
5 years survival: 5-14%

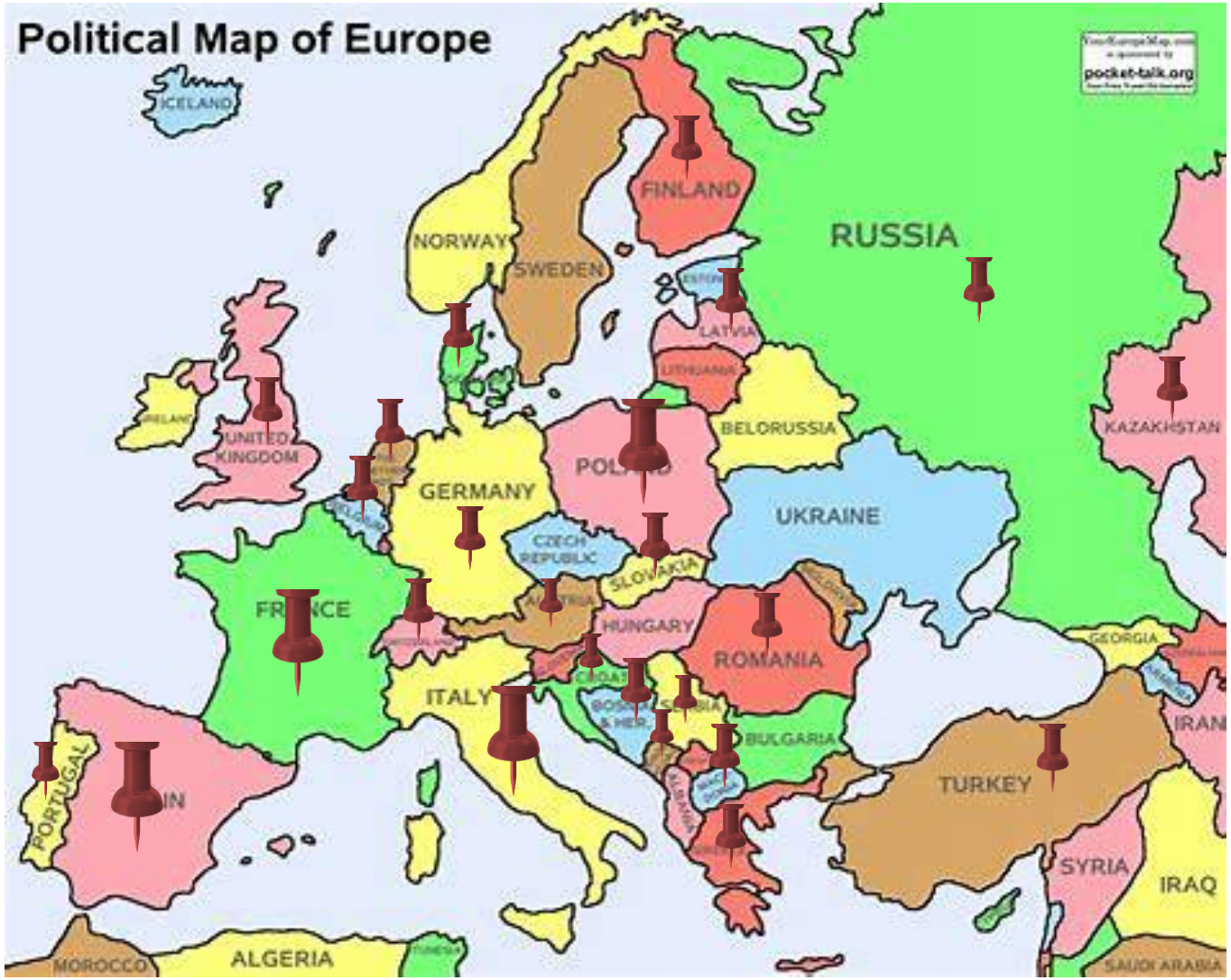
Disease specific mortality nearly 100%

EUropean **TH**yroid **CA**ncer **N**etwork

Anaplastic survey

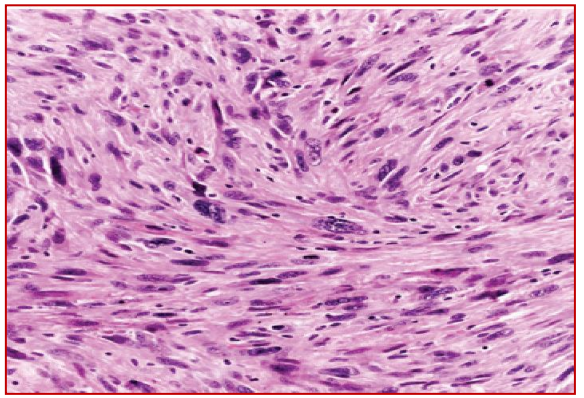
May 2021

414 responders from 29 different Countries



Argentina
Egypt
India
Israel

The importance of histopathology



3 main histological growth patterns

Spindle cell
Pleomorphic giant cell
Squamoid

no known prognostic significance

WHO 2022

Differential diagnosis

Poorly differentiated thyroid cancer: lower mitotic activity, less extended tumor necrosis; preservation of immunohistochemical markers of epithelial and thyroid differentiation

Primary squamous cell carcinoma of the thyroid: extremely rare; its appearance is identical to squamous carcinoma arising elsewhere

Large cell lymphoma

Medullary carcinoma, metastatic carcinoma (in particular a sarcomatoid renal primary), melanoma, sarcomas

TABLE 2. PANEL OF ROUTINE IMMUNOHISTOCHEMICAL MARKERS FOR THE EVALUATION OF SUSPECTED ANAPLASTIC THYROID CANCER AND EXPECTED RESULTS COMPARED WITH OTHER TUMOR TYPES

IHC marker	*DTC*	*PDTC*	*ATC*	*MTC*	*SCC*	*Lymphoma*
Pan-cytokeratins	+++	+++	+++/–	+++	+++	–
Thyroglobulin	+++	+/–	–	–	–	–
Thyroid-transcription factor 1	+++	+/–	–/+	+/–	–	–
$BRAF^{V600E}$	+/–	–/+	–/+	–	–	–
PAX8	+++	+++	+/–	+/–	–	+/–[a]
Ki-67[b]	<5%	5–30%	>30%	<20%	>30%	variable
Chromogranin	–	–	–	+++	–	–
Calcitonin	–	–	–	+++/–	–	–
Carcinoembryonic antigen	–	–	–	+++	–	–
p53	– (rare +)	–/+	+/–	–	+/–	+/–
CD45, other lymphoid markers	–	–	–	–	–	+++

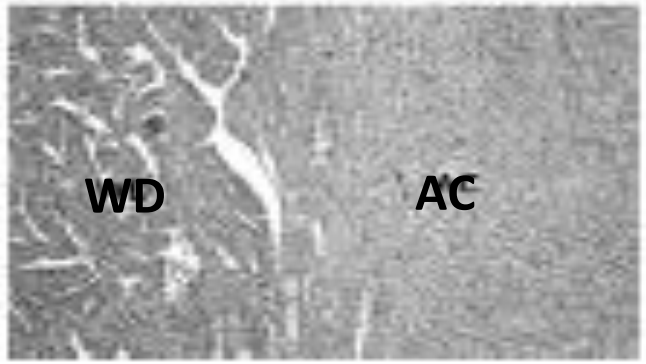
Immunostaining is mandatory

The diagnosis is often one of «exclusion» when there is no evidence of other lesions that can mimic ATC

From: Bible et al., Anaplastic Thyroid Cancer Guidelines , 2021

Approximately 20% of patients with anaplastic thyroid cancer have a history of differentiated thyroid cancer (mostly papillary), and 20 to 30% have a coexisting differentiated cancer

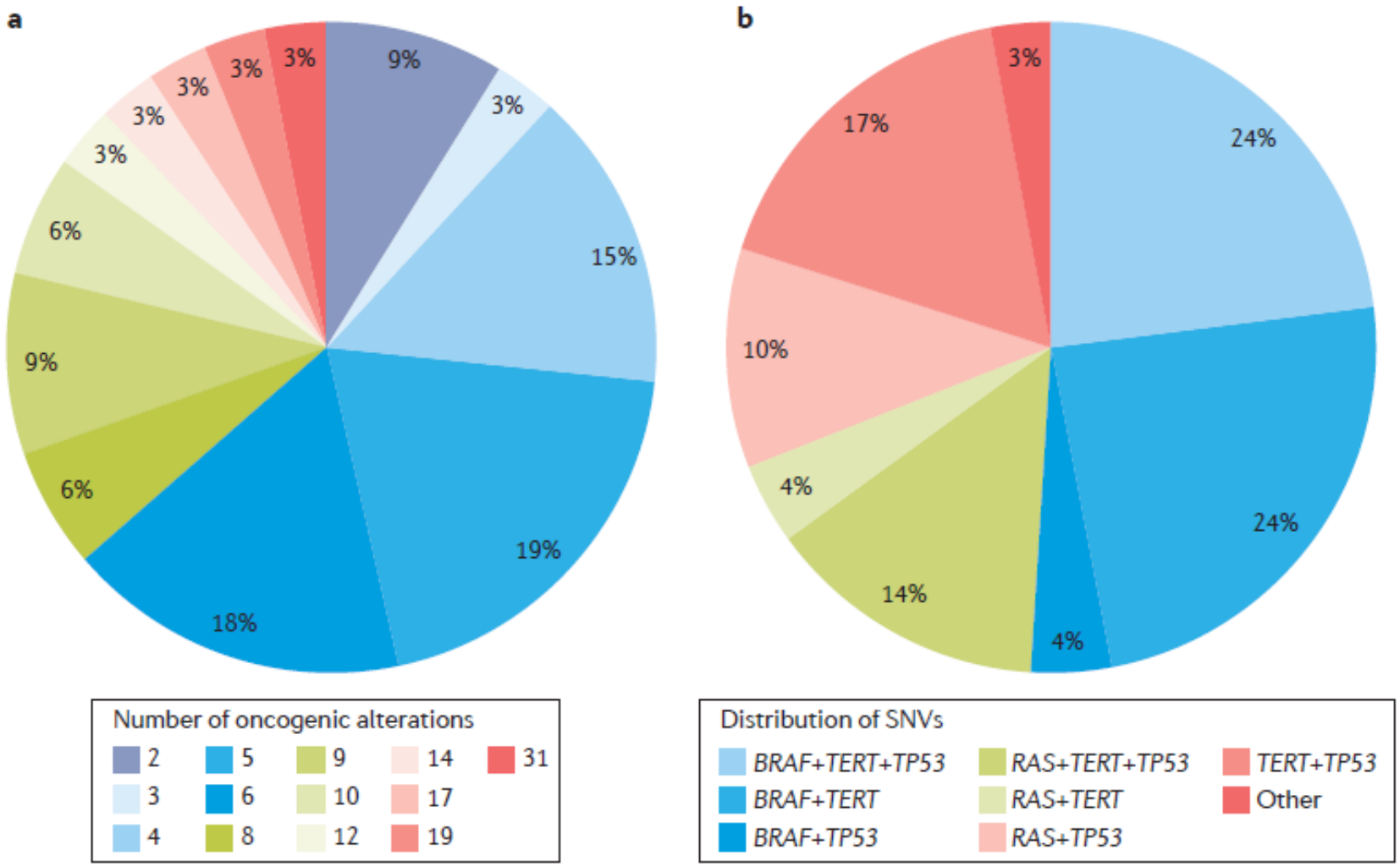
These findings lend support to the hypothesis that anaplastic cancer develops from more differentiated tumors as a result of one or more dedifferentiating events



Anaplastic
BRAF+

(*Nikiforova et al., JCEM 2003*)

GENETIC PATTERN



Data from Landa et al., 2016

Molinaro et al., 2017

The American Joint Committee on Cancer (AJCC)

All ATCs are stage IV (AJCC 8th Edition)

Stage IVA: T1-T3a (intrathyroidal), N0, M0

Stage IVB: T3b-T4 (gross extrathyroidal extension), any N, M0

Stage IVC: any T, any N, M1

Distant metastases in ATC

TABLE 7. PERCENT OF ANAPLASTIC PATIENTS WITH DISTANT METASTASES

Reference	*N*	*Metastatic disease identified at diagnosis (%)*	*New metastatic disease identified during follow-up (%)*	*Metastatic disease at any time (%)*
McIver *et al.*, 2001 (58)	134	46	22	68
Wang *et al.*, 2006 (168)	47	17	34	51
Swaak-Kragten *et al.*, 2009 (156)	75	40	35	75
Rodriguez *et al.*, 2000 (231)	14	21	27	48
Lam *et al.*, 2000 (59)	38	—	—	47
Schlumberger *et al.*, 1991 (162)	20	45	20	65
Kim and Leeper, 1987 (232)	19	32	47	79
Levendag *et al.*, 1993 (167)	51	43	32	75
Busnardo *et al.*, 2000 (176)	29	76	21	97
De Crevoisier *et al.*, 2004 (161)	30	20	43	63
Venkatesh *et al.*, 1990 (15)	121	11	42	53
Hadar *et al.*, 1993 (233)	55	—	—	42
Demeter *et al.*, 1991 (113)	7	—	—	57

~40% **50-90%**

ATC prognostic factors

Kim (45)	2007	121	10	Age <60, tumor <7 cm, lower extent of disease
Increased mortality				
Sugitani (46)	2001	47	16	Acute symptoms, WBC >10 k, tumor >5 cm, DM
Akaishi (47)	2011	100	21	Age >70, WBC >10 k, ETE+, DM
Sugitani (32)	2012	677	15	Age >70, acute symptoms, WBC >10 k, tumor >5 cm, T4b, DM

ATC, anaplastic thyroid cancer; ETE, extrathyroidal extension; XRT, external beam radiation; WBC, white blood cell count; DM, distant metastases.

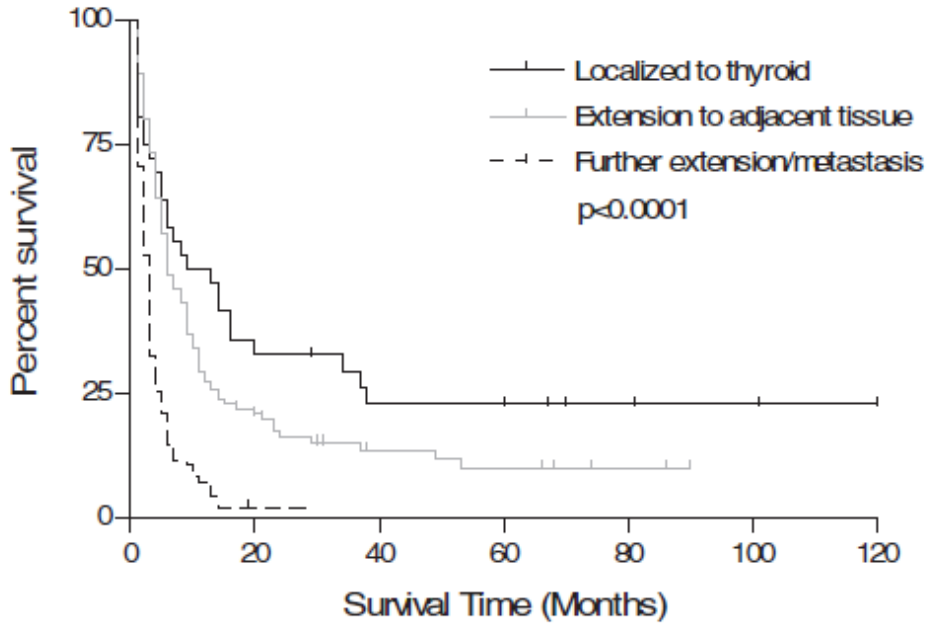


FIGURE 1. Overall survival for patients stratified by extent of disease.

Table 3 Prognostic factors in ATC patients. Bold values indicate statistical significance $P<0.05$.

	Univariate analyses				Multivariate analyses		
Prognostic factors	Median survival (days)	6-month survival rate (%)	1-year survival rate (%)	*P* (log rank)	HR	95% CI	*P* (cox regression)
Pretreatment factors							
Sex							
Male ($n=48$)	207	37	27	0.132			
Female ($n=52$)	251	32	25				
Age at initial diagnosis (years)							
<70 ($n=46$)	340	60	33	**<0.0001**			
≥70 ($n=54$)	140	69	29		1.048	1.015–1.082	**0.004**
T status							
4a ($n=11$)	458	56	44	0.064			
4b ($n=79$)	192	27	21				
N status							
N0 ($n=24$)	537	65	49	**0.001**			
N1 ($n=55$)	178	24	17		1.601	0.759–4.068	0.217
M status							
M0 ($n=40$)	519	61	48	**<0.0001**			
M1 ($n=55$)	148	17	12		2.718	1.384–5.342	**0.004**
Aerodigestive infiltration							
No ($n=67$)	304	42	33	**0.005**			
Yes ($n=31$)	140	23	15		1.915	0.901–4.068	0.091
Complete local resection							
Yes ($n=14$)	1098	71	71	**0.001**			
No ($n=79$)	180	30	20		5.539	1.858–16.514	**0.002**
DTC tumor part							
No ($n=78$)	197	32	28	0.179			
Yes ($n=17$)	395	55	24				
Treatment factors*							
Thyroid surgery							
Radical ($n=51$)	264	33	28	0.376			
Other or none ($n=49$)	169	37	25		2.201	1.186–4.086	**0.012**
External beam radiation							
≥40 Gy ($n=61$)	366	50	38	**<0.0001**			
<40 Gy ($n=14$)	124	9	0		0.339	0.152–0.759	**0.008**
Chemotherapy							
No ($n=44$)	131	21	17	**0.003**			
Yes ($n=56$)	338	45	33		11.636	2.424–60.394	**0.003**

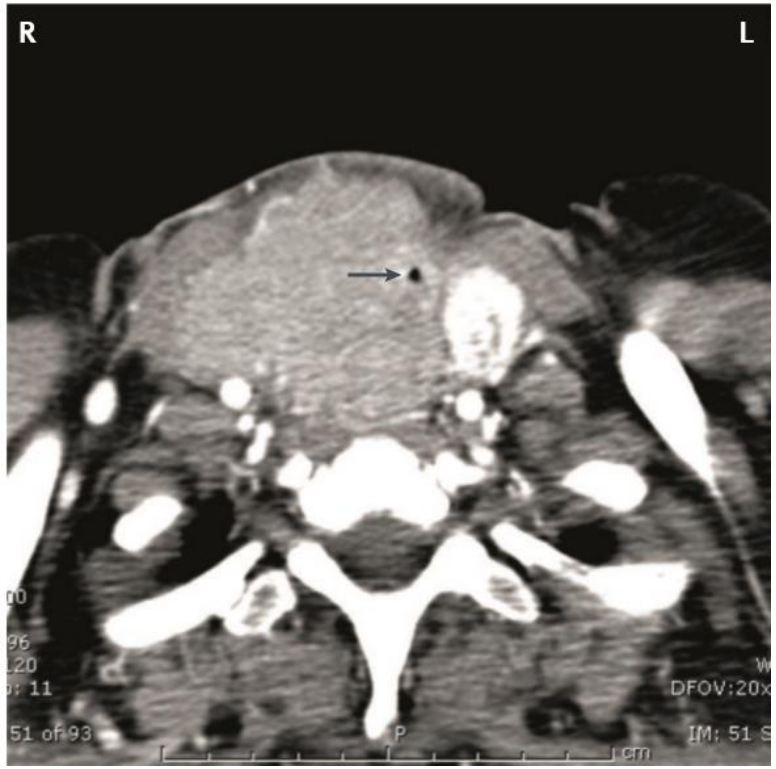
*Corrected for age and tumor stage at initial diagnosis.

Wendler et al., 2016

CLINICAL ASPECTS

Approximately 97% of patients with ATC present with a rapidly enlarging thyroid mass ranging from 3 cm to 20 cm in size, with the volume usually doubling within 1 week

Local symptoms, related to mechanical compression: hoarseness, cervical pain, dysphagia, dyspnoea and stridor



Haemorrhage into the thyroid mass might manifest as rapid enlargement accompanied by pain, and the appearance of haemoptysis might indicate the extension of the tumour into the trachea

2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer

American Thyroid Association Anaplastic Thyroid Cancer Guidelines Task Force

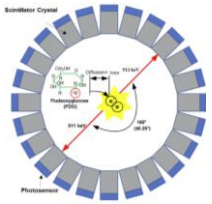
Table 3. Initial Evaluation for Staging, Tests, and Procedures

Laboratory tests
- CBC with differential
- Comprehensive chemistry panel (electrolytes, calcium, blood urea nitrogen, creatinine, glucose, and liver tests)
- Thyroid function tests (TSH, free thyroxine), TG/TG antibody

Imaging
- ^{18}F FDG PET/CT (preferred, whole body)[a]
- CT of neck, chest, abdomen, and pelvis with contrast *or* MRI (acceptable if PET unavailable—and as needed for surgical decision-making)

Recommended and if clinically indicated[b]
- MRI of brain with and without contrast

Procedures
- Laryngoscopy, also esophagoscopy as indicated
- BRAF assessment by IHC and NGS testing of tumor[c]



ATC stadio **IVA (intratiroideo)**/IVB

Possibile resection

R0 (complete resection with negative microscopic margins)/
R1 (complete resection of all grossly visible tumors but with microscopically involved resection margins)

Surgical resection STRONGLY recommended (REC#12)

Strenght or recommendation: strong

Quality of evidence: low

From: Bible et al., Anaplastic Thyroid Cancer Guidelines , 2021

ATC stadio **IVB/IVC**

Radical resection

Including laryngectomy, tracheal/esophageal resection and/or major vascular or mediastinal resections

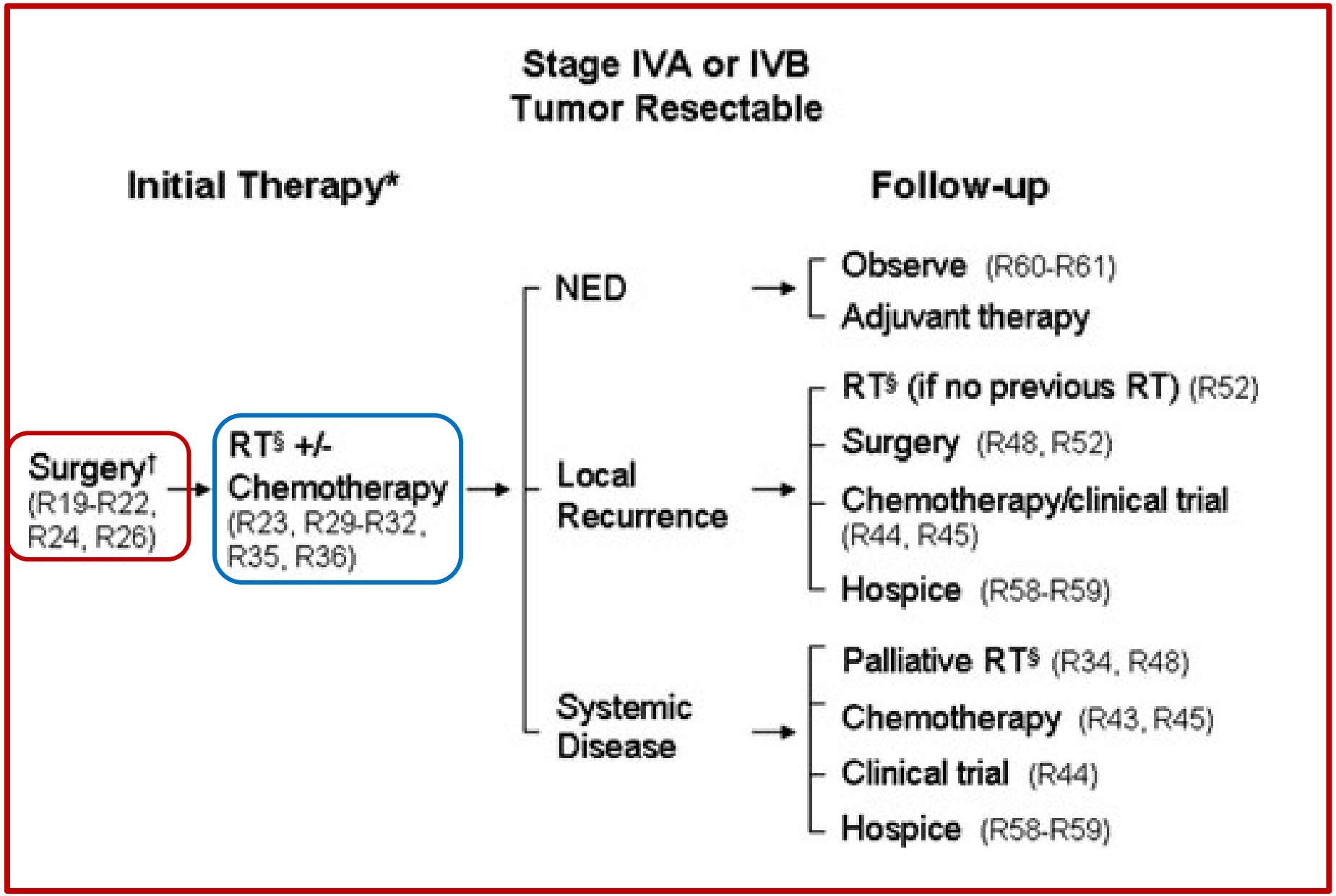
Only in very selected cases, balancing risk/benefits (REC#13)

Strenght or recommendation: strong

Quality of evidence: low

From: Bible et al., Anaplastic Thyroid Cancer Guidelines , 2021

IVA: intrathyroidal, N0, M0; IVB: gross extrathyroidal extension, any N, M0



Smallridge, ATA guidelines 2012

ATC: chemotherapy regimens

Table 5. Examples of Adjuvant/Radiosensitizing Chemotherapy Regimens in Anaplastic Thyroid Carcinoma

Regimen	*Agents/dosages*	*Frequency*
Paclitaxel/carboplatin	Paclitaxel 50 mg/m^2, carboplatin AUC[a] 2 mg/m^2 IV	Weekly
Docetaxel/doxorubicin	Docetaxel 60 mg/m^2 IV, doxorubicin 60 mg/m^2 IV (w/ pegfilgrastim) *or* Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2	Every 3–4 weeks Weekly
Paclitaxel	Paclitaxel 30–60 mg/m^2 IV	Weekly
Cisplatin	Cisplatin 25 mg/m^2 IV	Weekly
Doxorubicin	Doxorubicin 60 mg/m^2 IV	Every 3 weeks
Doxorubicin	Doxorubicin 20 mg/m^2 IV	Weekly

Table 6. Examples of Chemotherapy Regimens in Advanced Anaplastic Thyroid Carcinoma

Regimen	*Agents/dosages*	*Frequency*
Paclitaxel/carboplatin	Paclitaxel 60–100 mg/m^2, carboplatin AUC 2 mg/m^2 IV	Weekly
Paclitaxel/carboplatin	Paclitaxel 135–175 mg/m^2, carboplatin AUC 5–6 mg/m^2 IV	Every 3–4 weeks
Docetaxel/doxorubicin	Docetaxel 60 mg/m^2 IV, doxorubicin 60 mg/m^2 IV (w/ pegfilgrastim) *or* Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2 IV	Every 3–4 weeks Weekly
Paclitaxel	Paclitaxel 60–90 mg/m^2 IV	Weekly
Paclitaxel	Paclitaxel 135–200 mg/m^2 IV	Every 3–4 weeks
Doxorubicin	Doxorubicin 60–75 mg/m^2 IV	Every 3 weeks
Doxorubicin	Doxorubicin 20 mg/m^2 IV	Weekly

Smallridge, ATA guidelines 2012

ATC: radiotherapy

Definitive radiotherapy: high-dose radiation given with or without concurrent chemotherapy, with the intent of maximizing the chance of long-term local control.
50 Gy in 20 fractions (2.5 Gy per fraction over 4 weeks)
70 Gy in 35 fractions (2 Gy per fraction over 7 weeks)

Palliative radiotherapy: is lower dose radiotherapy given over a shorter time period with the aim of improving local symptoms. It may be directed to the primary tumor or to metastases.
20 Gy in five fractions (4 Gy per fraction over 1 week)
30 Gy in 10 fractions (3 Gy per fraction over 2 weeks)

Conformal radiation
Intensity-modulated radiotherapy
Radiosurgery and stereotactic body radiotherapy

Smallridge, ATA guidelines 2012

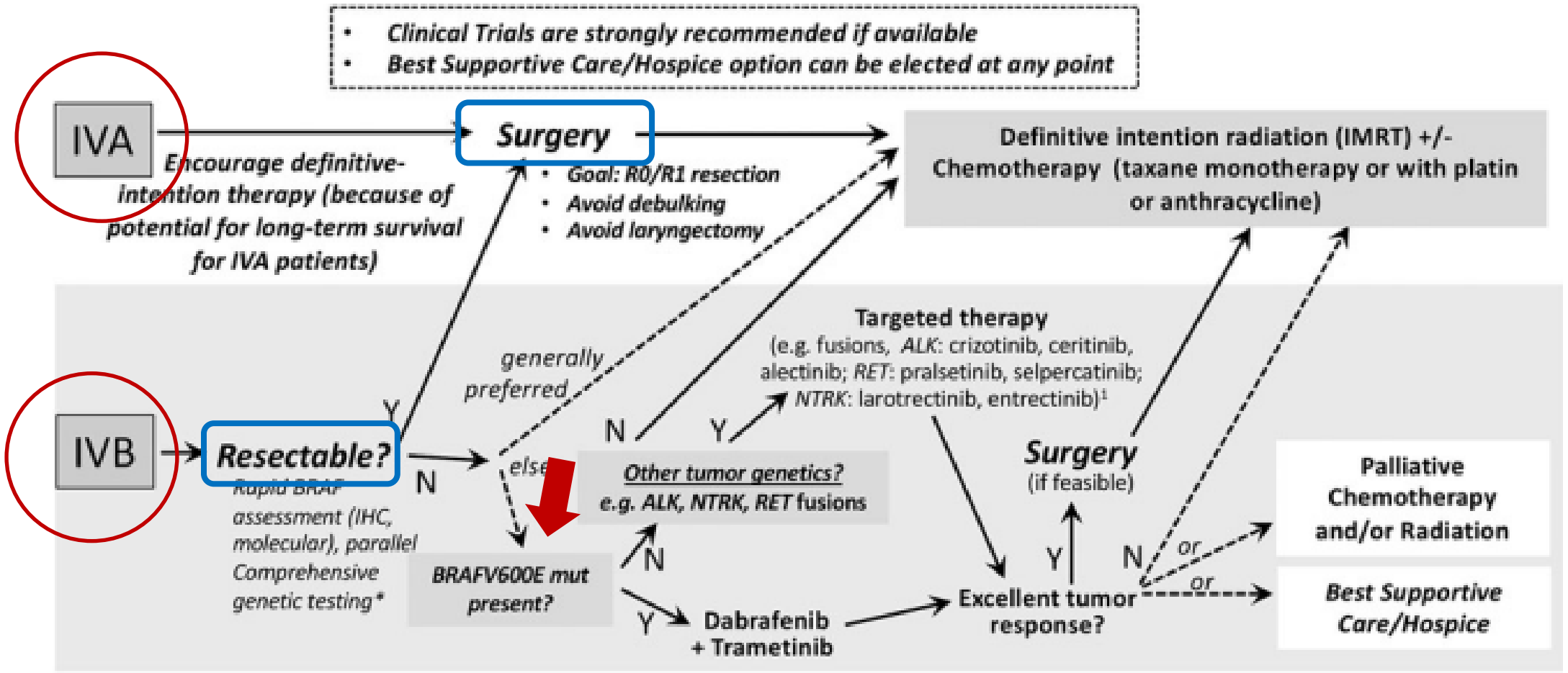
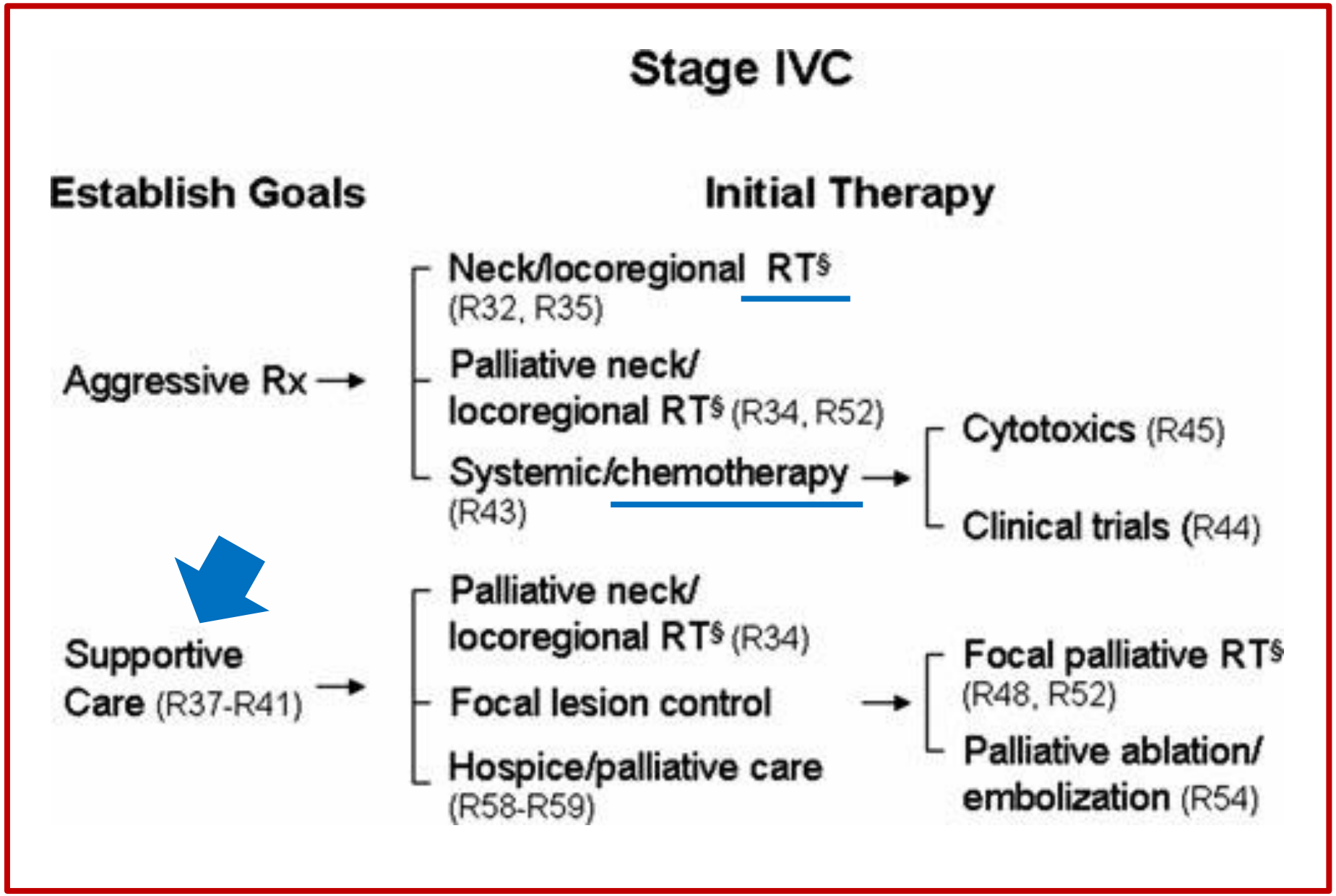


FIG. 1. Initial treatment of stages IVA and IVB ATC. [1]Additonal agents exist and are in development, listing not meant to be comprehensive; clinical trials preferred if available; see text. *Cytotoxic chemotherapy may be started as a "bridge" while awaiting genomic information or while awaiting targeted therapy (e.g., dabrafenib and trametinib). Dashed arrows depict circumstances where competing therapeutic options may be of consideration. ATC, anaplastic thyroid cancer.

Bible, ATA guidelines 2021

IVC: distant metastases



Smallridge, ATA guidelines 2012

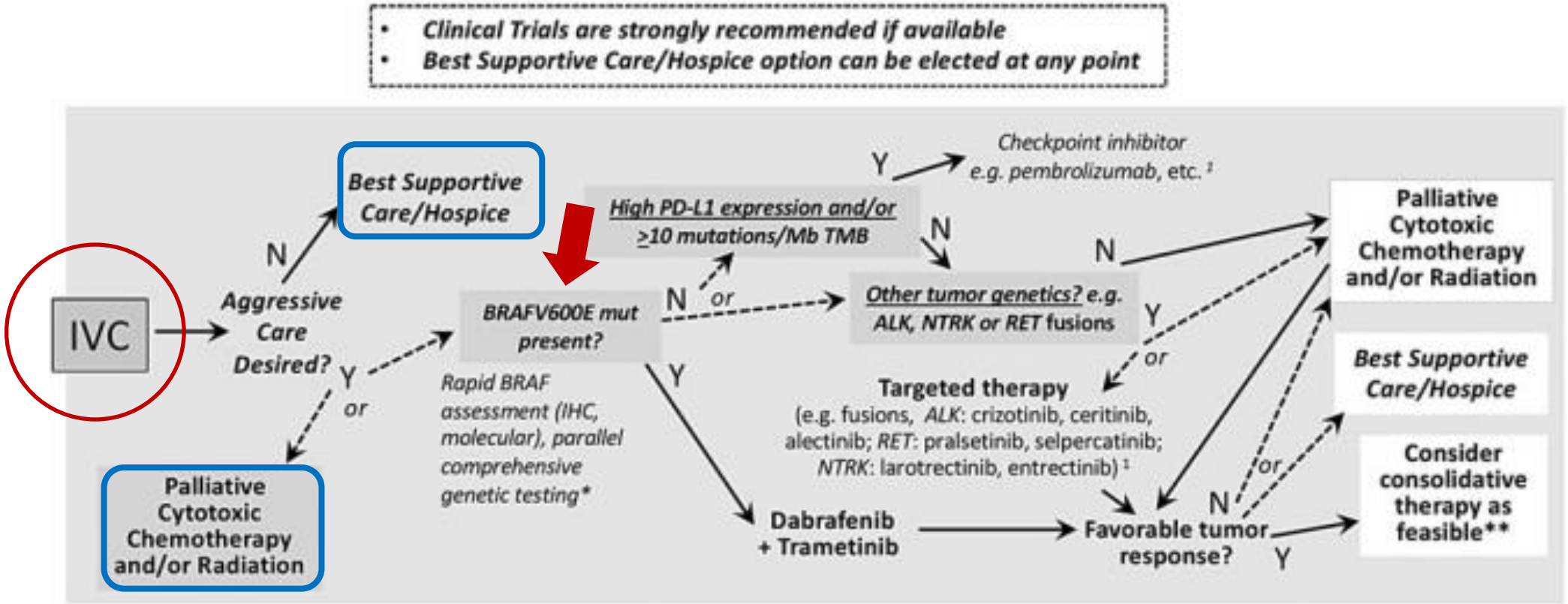


FIG. 2. Initial treatment of stage IVC ATC. [1]Additonal agents exist and are in development, listings not meant to be comprehensive; clinical trials preferred if available; see text. *Cytotoxic chemotherapy may be started as a "bridge" while awaiting genomic information or while awaiting targeted therapy (e.g., dabrafenib and trametinib). **Consolidate Rx refers to focal therapy intended to control residual macrometastatic disease among those electing aggressive therapy. Dashed arrows depict circumstances where competing therapeutic options may be of consideration. TMB, tumor mutational burden.

Bible, ATA guidelines 2021

„It is our pleasure to invite all Thyroidologists and guests to Milan for the 45th Annual Meeting of the European Thyroid Association. The Local Organizing Committee is delighted to host the ETA Annual Meeting in Milan for the second time after the successful meeting of 1999."

Laura Fugazzola & Luca Persani
Chairs of the Local Organizing Committee

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