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Evolution of Management of Anaplastic Thyroid Carcinoma: From Palliative Surgery to Precision Oncology

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ABSTRACT

Background: Anaplastic thyroid carcinoma (ATC) is among the most lethal human malignancies, accounting for a disproportionate number of thyroid cancer-related deaths despite constituting less than 2% of all thyroid cancers. Historically regarded as universally fatal, with a median survival of only 3–6 months, the management of ATC has undergone a remarkable transformation over the past several decades.

Summary: Early treatment strategies in the mid-20th century relied primarily on palliative surgery and radiotherapy, offering minimal survival benefit. The late 20th century saw the emergence of multimodal therapy combining surgery, external beam radiation, and cytotoxic chemotherapy (doxorubicin, taxanes), which improved locoregional control but failed to significantly impact the high rate of distant metastases. The pivotal turning point arrived with advances in molecular biology, revealing critical oncogenic drivers—most notably BRAF V600E mutations in up to 45% of cases, as well as TERT, RAS, PIK3CA, TP53 alterations, and rare RET/NTRK fusions. This understanding catalysed the development of targeted therapies. The landmark FDA approval of the BRAF inhibitor dabrafenib combined with the MEK inhibitor trametinib in 2018 for BRAF V600E-mutated ATC fundamentally altered the therapeutic paradigm, demonstrating unprecedented response rates (≈70%), durable survival benefits (1-year survival ≈80%), and enabling neoadjuvant conversion of unresectable tumours. Subsequently, immunotherapy (anti-PD-1/PD-L1 agents), next-generation sequencing-guided personalised medicine, and combination strategies have become integral components of modern management.

Conclusion: The evolution of ATC management reflects a dramatic transition from nihilistic palliation to molecularly guided precision oncology. While stage IVC disease remains a formidable challenge, the incorporation of targeted therapy and immunotherapy has provided the first real hope for improved outcomes. This review traces this historical evolution, highlighting key milestones, current standards, and future directions.

Keywords: *Anaplastic thyroid carcinoma, evolution, targeted therapy, BRAF, dabrafenib, trametinib, immunotherapy, precision oncology, multimodal therapy.*

INTRODUCTION

Thyroid malignancies are increasing in frequency, yet anaplastic thyroid carcinoma (ATC) remains a rare but devastating entity. Accounting for only 1–2% of all thyroid cancers, ATC is responsible for up to 50% of thyroid cancer-related deaths.[1,2] Patients typically present in their 6th to 7th decade with a rapidly enlarging, hard neck mass often associated with dysphagia, dyspnoea, hoarseness from recurrent laryngeal nerve invasion, and distant metastases (most commonly to lung, bone, and brain) in over 40% at the time of diagnosis.[3,4]

By definition, all ATCs are stage IV (American Joint Committee on Cancer, 8th edition: IVA, intrathyroidal; IVB, extrathyroidal extension; IVC, distant metastases).[5] Historically, median survival ranged from 3 to 6 months, with a 1-year survival of only about 20%.[6,7] For decades, therapeutic nihilism prevailed, and management was largely palliative.

However, the last two decades have witnessed a paradigm shift. The convergence of enhanced multidisciplinary care, sophisticated radiotherapy techniques (intensity-modulated radiotherapy, IMRT) and, most importantly, the elucidation of the ATC molecular landscape, has ushered in the era of precision oncology. This review analyses the historical evolution of ATC management, from early surgical palliation to modern targeted and immunotherapeutic approaches.

Historical Evolution of ATC Management *[Fig. 1]*

The Early Era (1950–1980): Surgery and Palliation

In the mid-20th century, treatment options were extremely limited. Surgery was the primary modality, but most patients presented with unresectable disease. Ultra -radical resections (e.g., with laryngectomy or esophagectomy) were associated with prohibitive morbidity without survival benefit. Radiotherapy was used palliatively for airway obstruction or pain, and chemotherapy was largely ineffective. The immediate causes of death were often asphyxiation from local progression or pulmonary metastases.[4,8]

The Era of Multimodality Therapy (1980–2010)

Recognition that single-modality therapy was futile led to combined approaches. The 2012 American Thyroid Association (ATA) guidelines formalised a multidisciplinary strategy: rapid diagnosis, airway assessment, stage-based planning, and a combination of surgery (R0/R1 resection when feasible), postoperative external beam radiotherapy (EBRT) (dose >40-45 Gy, preferably IMRT), and concurrent chemotherapy.[1] Doxorubicin was the most studied agent, followed by platinum compounds and taxanes (paclitaxel, docetaxel).[9 – 11]

Studies from this era demonstrated improved locoregional control (≈70-80%) and extended median survival in stage IVA/B patients from approximately 3 months (surgery alone) to 12-25 months (multimodal therapy).[12,13] However, distant metastatic disease remained the primary cause of failure, and outcomes for stage IVC patients remained dismal (median survival 3-5 months).[14] The limitations of cytotoxic chemotherapy were evident.

Figure 1: Historical Timeline of Major Advances in ATC Management (1950–2022)

Era	Time Period	Key Events	Survival Impact
Palliative Era	1950–1980	• First doxorubicin trials • Surgery + palliative RT	Median OS: 3–5 months
Multimodal Era	1980–2010	• Chemoradiation protocols • First ATA Guidelines (2012)	Median OS: 10–14 months (IVA/B)
Molecular Era	2005–2017	• *BRAF, TP53, TERT* mutations discovered	Foundation for targeted therapy
Precision Era	2018–Present	• FDA approval: Dabrafenib + Trametinib (2018) • Immunotherapy trials (2020)	1-year OS: 80% *(BRAF-mutant)*

The Molecular Revolution (2005–2017)

The turning point came from the understanding ATC pathogenesis. ATC often arises via dedifferentiation from pre-existing differentiated thyroid cancer (DTC). Landmark genomic studies (Landa et al., Kunstman et al.) revealed a complex mutational landscape.[15,16] Key findings included:

- *BRAF V600E mutations*: Present in 20-45% of ATCs, often coexisting with *TERT promoter mutations*, driving aggressive behaviour via the *MAPK pathway*.
- *RAS mutations*: Found in 20-30% of cases.
- *TP53 mutations*: Late events in over 50% of ATCs, associated with anaplastic transformation.
- *PI3K/AKT/mTOR pathway* alterations: In up to 50% of cases.
- Rare actionable fusions: *RET, NTRK* (≈1-3%), *ALK*.

These discoveries provided a rational basis for targeted therapy. Early trials of single-agent *BRAF inhibitors* (*vemurafenib*) or multikinase inhibitors (*sorafenib, lenvatinib, pazopanib*) showed modest, transient responses in ATC, but resistance was common.[17,18] The rationale for combined *BRAF* and *MEK* inhibition emerged from melanoma studies to prevent paradoxical *MAPK* activation and delay resistance.

Table 1 lists most of the landmark studies which shaped the evolution of ATC management.

Table 1. Landmark Studies Shaping the Evolution of ATC Management

Era	Study / Author (Year)	Key Intervention	Patient Cohort	Primary Outcome	Historical Significance
Multimodal	Kim & Leeper (1987) [10]	Doxorubicin + Radiation	19 patients	Median OS: 12 months	First evidence that chemosensitization improves locoregional control.
Multimodal	McIver et al. (Mayo, 2001) [4]	Surgery + Post-operative RT	134 patients	Median OS: 5 months	Defined R0/R1 resection as critical prognostic factor.
Multimodal	Prasongsook et al. (2017) [6]	Surgery + IMRT + Docetaxel/ Doxorubicin	30 patients	Median OS: 21 months (Stage IVA/B)	Demonstrated long-term survival in locoregional disease with modern RT.
Targeted	Subbiah et al. (ROAR, 2018) [19]	Dabrafenib + Trametinib	16 (*BRAF*-mutant)	ORR: 69%; 1-yr OS: 80%	Landmark FDA approval; First precision therapy for ATC.
Targeted	Wang et al. (2019) [21]	Neoadjuvant Dabrafenib/ Trametinib	6 (unresectable)	R0/R1 resection: 100%	Introduced paradigm of "neoadjuvant targeted therapy" for downstaging.
Immunotherapy	Capdevila et al. (2020) [23]	Spartalizumab (anti-PD-1)	42 patients	ORR: 19%; 1-yr OS: 40%	Proof-of-concept for PD-1 blockade in refractory ATC.

The Landmark Breakthrough: BRAF-Targeted Therapy (2018–Present)
The most important milestone in ATC history occurred in 2018 when the U.S. Food and Drug Administration (FDA) approved the combination of **dabrafenib** (BRAF inhibitor) plus **trametinib** (MEK inhibitor) for *BRAF V600E-mutated* ATC.[19,20]

Clinical Efficacy: The pivotal phase II ROAR trial (Subbiah et al., 2018) enrolled 16 patients with *BRAF V600E*-mutated ATC. The overall response rate (ORR) by independent review was 69% (including one complete response). The median progression-free survival (PFS) was 6.7 months, but the 12-month overall survival (OS) rate was an unprecedented 80%.[19]

Neoadjuvant Paradigm Shift: Subsequent studies demonstrated that this combination could rapidly shrink unresectable tumours, converting them to resectable. Wang et al. (2019) reported that after neoadjuvant dabrafenib/trametinib, 6 of 6 patients achieved complete R0/R1 resection, with 1-year OS of 83%.[21] This has transformed surgical philosophy: systemic therapy now often precedes surgery in *BRAF-mutant* disease. Real-world experience confirms clinical trial results, with durable responses and manageable toxicities (fatigue, pyrexia, rash, nausea).[22]

Figure 2 summarises the targets and mechanisms of action of various drugs used in the management of ATC.

Figure 2. Mechanisms of Action: From Cytotoxic Chemotherapy to Targeted Therapy

Pathway Component	Target	Traditional Agent	Precision Agent
Cell Membrane Receptors	EGFR, VEGFR, RET	None specific	Lenvatinib (multikinase inhibitor)
MAPK Pathway	BRAF	None	Dabrafenib (BRAF inhibitor)
	MEK	None	Trametinib (MEK inhibitor)
	ERK	None	Under investigation
PI3K/AKT Pathway	PI3K, AKT, mTOR	None	Everolimus (mTOR inhibitor)
DNA/Microtubules	DNA, Tubulin	Doxorubicin, Taxanes	Not applicable
Immune Checkpoint	PD-1/PD-L1	None	Anti-PD-1 antibodies (Pembrolizumab, Spartalizumab)

Emerging Roles: Immunotherapy and Other Targeted Agents [Table 2]
While BRAF-targeted therapy is transformative, it only benefits the ≈45% of ATC patients with the mutation. For BRAF-wildtype ATC, other approaches have emerged as salvage therapy.

Immune Checkpoint Inhibitors: ATCs frequently express high levels of *PD-L1* (≈70-90%) and have an immune-rich but exhausted microenvironment. Single-agent anti-PD-1 therapy (*Spartalizumab, Pembrolizumab*) has shown ORRs of 19-29% in phase II trials, with durable responses in some patients.[23] Preclinical and clinical data suggest synergy between kinase inhibitors and immunotherapy (e.g., Pembrolizumab added to dabrafenib/trametinib or lenvatinib).[24,25]

Other Actionable Targets:

- *Lenvatinib*: A multikinase inhibitor (*VEGFR, FGFR, RET, KIT*) approved for radioactive iodine-refractory DTC. In Japanese studies of ATC, lenvatinib demonstrated an ORR of 24-44% and is approved for ATC in Japan, regardless of mutational status.[26]
- RET Inhibitors (*Selpercatinib, Pralsetinib*): For the rare (<5%) RET fusion-positive ATC, these agents have shown profound responses.[27]
- NTRK Inhibitors (*Larotrectinib, Entrectinib*): For the extremely rare NTRK fusion-positive ATC.[28]

Table 2. Actionable Molecular Targets and Approved/Investigational Agents in ATC

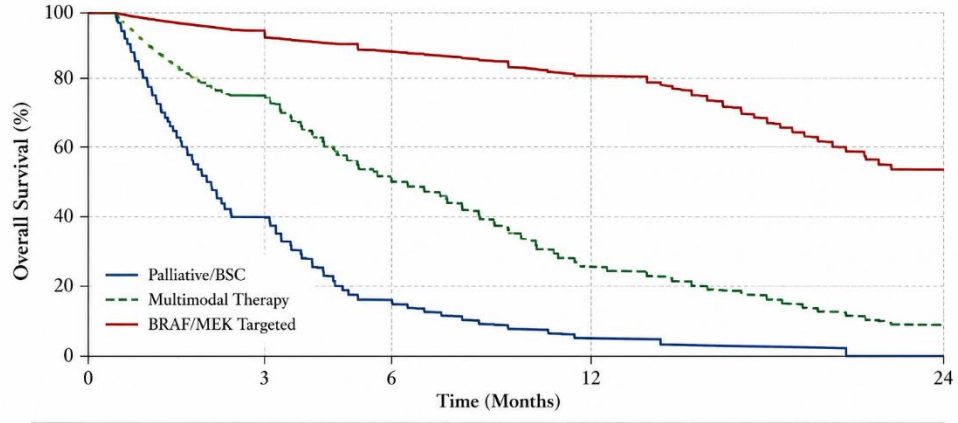
Molecular Target	Prevalence in ATC	FDA-Approved Agent(s)	Key Evidence	Notes
BRAF V600E	20–45%[15]	Dabrafenib + Trametinib[19]	ROAR trial (ORR 69%)	First-line for metastatic/ unresectable mutant ATC.
RET Fusion	<5% (rare)[16]	Selpercatinib, Pralsetinib[27]	LIBRETTO-001 trial	Exceptional responses; CNS activity.
NTRK Fusion	<1–3%[28]	Larotrectinib, Entrectinib	Pooled analysis (ORR 79% in thyroid)	Tissue-agnostic approval.
VEGFR / Multikinase	Overexpressed	Lenvatinib[26]	Japanese phase II (ORR 24–44%)	Approved in Japan for ATC; regardless of mutation.
PD-1/PD-L1	70–90% expression	Spartalizumab, Pembrolizumab[23]	Phase II (ORR 19–29%)	Salvage therapy; best in high PD-L1 expressors.
PI3K/AKT/mTOR	Up to 50%	Everolimus (off-label)	Phase II (limited responses)	Consider if PI3KCA mutation present.

ATC, anaplastic thyroid carcinoma; ORR, overall response rate; CNS, central nervous system.

Evolution of Supportive and Multidisciplinary Care

The modern management of ATC requires rapid, coordinated action by a multidisciplinary team (MDT): onco-surgeons, medical and radiation oncologists, endocrinologists, pathologists, and palliative care specialists. Early integration of palliative care is not "giving up" but rather optimising symptom control (pain, dyspnea, dysphagia), advance care planning, and supporting patients and families through a difficult journey.[1] Ethical considerations, including goals of care, code status, and allow natural death orders, are discussed early. *Figure 3* provides a graphical representation of the changes, and *Table 3* compares therapeutic approaches across different eras.

Figure 3. Kaplan–Meier Curves Illustrating Survival Improvement Across Eras



Time (Months)	0	3	6	12	24
Palliative/BSC (% Survival)	100	40	15	5	0
Multimodal Therapy (% Survival)	100	75	50	25	10
BRAF/MEK Targeted (% Survival)	100	95	88	80	55

BSC, best supportive care; BRAF, B-Raf proto-oncogene; MEK, mitogen-activated protein kinase kinase.

Table 3. Comparison of Therapeutic Approaches Across Eras

Feature	Palliative Era (1950–1980)	Multimodal Era (1980–2010)	Precision Era (2018–Present)
Primary Goal	Airway preservation / Symptom relief	Locoregional control	Durable remission / Downstaging to resection
Surgical Role	Debulking / Tracheostomy	R0/R1 resection if possible	Surgery after neoadjuvant targeted therapy
Radiotherapy	Conventional (palliative doses)	EBRT (45–70 Gy) / IMRT	IMRT for residual disease or adjuvant
Systemic Therapy	Single-agent (Doxorubicin)	Taxanes / Platinum / Doxorubicin	BRAF/MEK inhibitors (if mutant); Lenvatinib
Molecular Testing	None	None	Mandatory (BRAF, NGS panel)
Median OS (IVA/B)	3–5 months	10–14 months	20–25 months (targeted-responsive)
Role of Immunotherapy	None	None	Salvage / Clinical trials (PD-1/PD-L1 inhibitors)

Current Guidelines and Future Directions

The 2021 ATA guidelines[29] and 2022 NCCN guidelines emphasize:

1. Rapid molecular testing (especially for BRAF, but also broad panel NGS) at diagnosis.
2. For BRAF V600E-mutated ATC: Dabrafenib/trametinib as neoadjuvant or definitive therapy.
3. For resectable stage IVA/IVB (BRAF-wildtype): Surgery followed by chemoradiotherapy (IMRT + taxane/platinum).
4. For unresectable stage IVB (BRAF-wildtype): Chemoradiotherapy or clinical trial.
5. For stage IVC: Targeted therapy (if mutation-positive), clinical trial, or best supportive care.

Figure 4 charts the current treatment algorithm in management of ATC. Future directions include overcoming acquired resistance to BRAF/MEK inhibitors (e.g., via PI3K pathway co-inhibition), optimizing immunotherapy combinations, developing antibody-drug conjugates, and utilising liquid biopsy for real-time monitoring.

Figure 4. Modern Stage-Based Treatment Algorithm for Anaplastic Thyroid Carcinoma (ATC)

Step	Decision Point	Action
1	**Diagnosis of ATC** (Biopsy + Staging Imaging)	• Rapid histopathologic confirmation • Assess airway
2	**Molecular Testing**	• BRAF V600E mutation analysis (NGS panel recommended)
3a	**BRAF V600E Mutant**	Neoadjuvant Dabrafenib + Trametinib → Re-stage
3a(i)	After neoadjuvant therapy: Resectable?	**Yes:** Surgery (R0/R1) → Adjuvant chemoradiotherapy
3a(ii)	After neoadjuvant therapy: Unresectable?	• Continue targeted therapy • Consider clinical trial
3b	**BRAF Wild-Type**	Assess resectability (Stage IVA/early IVB vs. IVB unresectable vs. IVC)
3b(i)	Resectable (IVA/early IVB)	Total Thyroidectomy + Neck Dissection → Adjuvant IMRT + Taxane/Platinum
3b(ii)	Unresectable (IVB)	Definitive IMRT + Concurrent Chemotherapy OR Clinical trial
3b(iii)	Metastatic (IVC)	Systemic therapy (Lenvatinib / Clinical trial / Immunotherapy) OR Best supportive care/Hospice
4	**All stages**	Multidisciplinary Tumor Board review at every decision point

CONCLUSION

The management of anaplastic thyroid carcinoma has undergone one of the most dramatic evolutions in modern oncology. From a uniformly fatal disease managed with palliative intent, ATC has become a potentially treatable condition for a subset of patients with actionable mutations, particularly *BRAF V600E*. The approval of dabrafenib plus trametinib represents the single most important therapeutic milestone, offering durable responses, enabling curative-intent surgery, and providing hope where there was none. While significant challenges remain, particularly for stage IVC and BRAF-wildtype disease, the continued integration of precision medicine, immunotherapy, and multidisciplinary care promises to further improve outcomes for patients with this historically devastating malignancy.

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