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Overview

# Anaplastic Thyroid Carcinoma: Pathogenesis and Emerging Therapies

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**Abstract**

Anaplastic thyroid carcinoma ranges from 1.3 to 9.8% of all thyroid cancers globally. Mutations, amplifications, activation of oncogenes and silencing of tumour suppressor genes contribute to its aggressive behaviour, and recent studies (e.g. microarrays, microRNAs) have provided further insights into its complex molecular dysregulation. Preclinical studies have identified numerous proteins over- or underexpressed that affect critical cellular processes, including transcription, signalling, mitosis, proliferation, cell cycle, apoptosis and adhesion, and a variety of agents that effectively inhibit these processes and tumour growth. In clinical studies of 1771 patients, 64% were women, the median survival was 5 months, and 1-year survival was 20%. The variables associated with survival in some series included age, tumour size, extent of surgery, higher dose radiotherapy, absence of distant metastases at presentation, co-existence of differentiated thyroid cancer and multimodality therapy. However, considerable bias exists in these non-randomised studies. Although more aggressive radiotherapy has reduced locoregional recurrences, the median overall survival has not improved in over 50 years. Newer systemic therapies are being tried, and more effective combinations are needed to improve patient outcomes.


*Key words:* Anaplastic; chemotherapy; microarray; mutations; radiotherapy; surgery

## Statement of Search Strategies Used and Sources of Information

This overview will summarise the current understanding of the molecular pathogenesis of anaplastic thyroid carcinoma, preclinical studies identifying promising new therapies, the impact of surgery and radiotherapy on outcomes, and new systemic therapies under investigation. It was prepared from articles obtained from PubMed using the search words 'anaplastic thyroid carcinoma'. The search was limited to English and yielded 1882 articles.

## Introduction

Thyroid cancers comprise 2.5% of all malignancies in the USA. The incidence continues to increase, and was estimated to be 37 200 in 2009, whereas death rates remain low at ~1630 [1]. The increased detection, mostly of small papillary thyroid cancers, in part reflects earlier identification from imaging the head/neck and upper chest for other reasons [2], although early detection may not fully explain the rising incidence [3,4]. Anaplastic thyroid carcinoma (ATC) is the least common type, occurring in only 1.7% of thyroid cancers in the USA [5]. Frequencies in other countries, based on either tumour registries or single centre experience, are: Australia (1.3%) [6], Luxembourg (1.9%) [7], Austria (2.0%) [8], Italy (2.9%) [9], Japan and Jordan (3.6%) [10,11], New Zealand (4.2%) [12], India (4.7%) [13], Israel (7.5%) [14] and the Netherlands (7.9%) [15]. In Germany, the incidence decreased dramatically by decades from 35% to 19% to 7% from 1965 to 1997. The change was attributed to iodised salt for goiter prevention and to more aggressive management of differentiated thyroid cancer [16]. Similar reductions by decade from 1970 to 1999 were also observed in Dublin, Ireland (24.3%; 18.3%; 9.8%, respectively), and attributed to an increase in dietary iodine [17].

Risk factors for ATC are not well understood, but patients may have a history of goiter, prior co-existing differentiated (or rarely, medullary) thyroid cancer or the patient may present with no known thyroid disease history and prior ATC on histological examination. Transformation from differentiated thyroid cancer is usually identified in the

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**Table 1**
Thyroid carcinoma and microRNAs [20,73,74]

| | MicroRNA | | | |
|---|---|---|---|---|
| Tumour | Increase | Decrease | Effect | Gene(s) targeted |
| PTC | 221; 222 | 138; 219 | ↓ growth | KIT; $p27^{kip1}$ |
| | 146; 155; 181b | 26a; 345 | | HOX B2;TRAF6; IRAK1 |
| FTC | 197; 34b | – | – | EFEMP2; ACVR; TSPAN3 |
| | 192; 328 | | | |
| ATC | 17-92; 106a,b | 26a; 125b | ↓ growth | HMGA1 |
| | 221; 222 | 138 | | hTERT |
| | | 30a,d | | Rb; PTEN |
| | 146b; 21 | let7c | | |

ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma.

primary tumour, but may be found only in lymph nodes [18]. A case–control study of 126 patients, using benign goiter surgery patients as controls, found that ATC patients were more likely to have less education, other malignancies, late menarche, early first pregnancy, and blood group B [19]. These risk factors have also been associated with other thyroid malignancies [19].

## Pathogenesis

Differentiated thyroid cancers (papillary, follicular, Hürthle cell) comprise most malignancies, and each tends to have a single mutation. As the tumours dedifferentiate, more mutations develop, with ATCs commonly having multiple genetic abnormalities.

Mutations in ATC have been reported in the following genes: p53 = 12/22 (55%); RAS = 37/166 (22%); BRAF = 61/231 (26%); β-catenin = 20/53 (38%); PIK3CA = 27/156 (17%); Axin = 18/22 (82%); APC = 2/22 (9%); PTEN = 10/84 (12%) [20]. In a recent study of 18 patients, 38% had BRAF, 17% NRAS, 6% HRAS, 6% BRAF/PIK3CA, and 33% had unknown mutations [21].

Abnormalities in chromosome numbers or integrity are gains, losses, amplifications and deletions affecting virtually every chromosome. Recent reports using array-comparative genomic hybridization (CGH) have found abnormalities in regions containing EGFR, MET, BRAF, K-RAS [22], CCND1, FOSL1, UBE2C, CDKN2A [23]. Liu and Xing [24] detected copy number gains in EGFR, VEGFR1/2, PDGFRA/B, PIK3Cα/β, KIT, PDK1, AKT1 and MET. This high level of genomic disarray illustrates the challenge in identifying targets for therapy.

MicroRNAs, recently identified small (~22 nucleotide) non-coding RNAs, seem to provide an additional post-transcriptional level of protein regulation, and can act as either tumour suppressors or oncogenes [25]. Although microRNAs are often underexpressed in cancers, they are frequently overexpressed in thyroid cancers. It is interesting, too, that each thyroid histological type has a different set of microRNAs that are preferentially altered, although overlap exists. Table 1 illustrates some of the microRNAs that have been examined.

In papillary thyroid cancers, the overexpression of microRNAs-221 and -222 can reduce $p27^{kip1}$ and affect the cell cycle [26]. The same investigators [27] found four microRNAs downregulated in ATC that may target proteins involved in the transformation of thyrocytes. Other microRNA targets include E2F (apoptosis and cell cycle), PTEN and hTERT [28]. Antisense inhibitors to several microRNAs have reduced cell growth, supporting their oncogenic role and providing evidence that microRNAs may be therapeutic targets [29].

Gene microarrays have dramatically altered the field of cancer cell biology, identifying many genes heretofore unsuspected to play a role in carcinogenesis, and providing fertile preliminary observations that have led to testable hypotheses. In thyroid cancer, Griffith *et al.* [30] carried out a meta-analysis of 21 studies, but only one included ATC patients. Onda *et al.* [31] studied 10 patient samples and 11 ATC cell lines. They identified 56 underexpressed and 31

**Table 2**
Anaplastic thyroid carcinoma and protein expression [20,35,75–77]

| Function | Overexpressed | Underexpressed |
|---|---|---|
| Transcription | PPAR-γ; HNF-1α; Id1; YBX1; HMG1(Y); Fra1; c–myc | NKX2-1; FOXE1; Pax8; CBX7 |
| Signalling | EGFR; CXR4; pAKt1; pERK; JAK/STAT | SOCS 1,3,5 |
| Mitosis | Aurora kinases; kα1 tubulin; topoisomerase-11 | TACC3 |
| Proliferation | MKI67; OEATC-1; RBBP4; SPAG9 | |
| Cell cycle | Cyclins D1, D3, E | p21; p27 |
| Apoptosis | IAPs; DJ-1; NF-κβ; LCN2 | Bcl2; αB-crystallin |
| Adhesion | β-catenin; ILK1; FAK | E-cadherin |
| Tumour suppressor | p53 | Rb; p16; PTEN |