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Current Picture of Anaplastic Thyroid Carcinoma: A Review of Literature

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Francisco Vitorino Azeiteiro

Summary

Anaplastic thyroid carcinoma (ATC) is a rare thyroid disease, corresponding to 1-2 % of all thyroid neoplasms. It's one of the most aggressive solid tumors in humans and its responsible for up 50% of all deaths attributed to thyroid cancer with a median overall survival of 3-6 months. Thankfully, its incidence is thought to be decreasing globally. A longstanding goiter and age are important risk factors for the development of ATC. In the majority of cases, ATC presents as a rapid growth of a thyroid mass and its symptoms are mostly due to compression of cervical structures. Metastatic disease is very frequent and most commonly affects the lungs, pleura, bones, and brain. In the absence of treatment, most patients die from asphyxiation.

The definitive diagnosis relies on cytologic, or histologic confirmation, and radiological studies are necessary to complete tumor staging and every patient should undergo a direct visualization of the airway during initial evaluation. All ATC cases are considered stage IV disease.

ATC is thought to originate from well-differentiated carcinomas that undergo anaplastic transformation, and loss of expression of thyroid differentiation markers is a hallmark of this neoplasm. ATC has a high mutation burden and frequent genomic alterations include TP53, TERT, BRAF V600E and RAS mutations.

Conversations about end-of-life care should be initiated early and goals of care should be determined. Therapies are done at the individual level together with a multidisciplinary team. Treatment options include surgery, if possible, radiotherapy and chemotherapy, the latter showing disappointing results. Recent therapies, like targeted therapies (in patients with targetable mutations) and immunotherapies have been showing satisfactory and promising results, however, more studies are needed. Tracheostomy is not routinely recommended and should be avoided. Patients should be encouraged to engage in clinical trials, considering the urgent need for new treatments.

Keywords: anaplastic thyroid cancer; BRAF V600E mutation; anaplastic transformation; targeted therapies; genomic alterations

Resumo

O carcinoma anaplásico da tiróide (CAT) é uma neoplasia rara que correspondente a 1-2 % de todas as neoplasias da tiróide. Dada a sua raridade, a sua verdadeira incidência não é totalmente conhecida, mas prevê-se que seja entre 1-2 casos por milhão de habitantes por ano. Enquanto a incidência do cancro da tiróide tem vindo a aumentar, não é claro se a incidência do CAT tem sofrido alterações durante o mesmo período, no entanto, parece existir uma tendência global para a sua diminuição. O CAT é um dos tumores sólidos mais agressivos em humanos, apresentando um péssimo prognóstico, correspondente até 50% de todas as mortes atribuídas ao cancro da tiróide, com uma sobrevivência global média que varia entre 3 e 6 meses.

Este carcinoma ocorre mais frequentemente em mulheres e idosos e acredita-se que o bócio de longa data seja o fator de risco mais importante. Outros fatores de risco desta patologia incluem idade avançada, baixo nível de escolaridade, carcinoma diferenciado da tiróide, obesidade e IMC elevado e história de exposição a radiação. Os fatores com um bom valor prognóstico incluem idade mais jovem, menor número de comorbilidades, tumores N0 e M0, doença primária confinada à tiróide, tumores de pequeno tamanho (≤ 6 cm) e margens cirúrgicas negativas. Os fatores de mau prognóstico incluem idade avançada, história de exposição à radiação, presença de hipercalcemia ou leucocitose, maior extensão tumoral, presença de metástases à distância, expressão de p53 e sexo masculino.

Na maioria dos casos, o CAT apresenta-se como um crescimento rápido de uma massa tiroideia que facilmente invade os órgãos adjacentes. Os sintomas mais comuns devem-se à compressão das estruturas cervicais, causando disfagia, alterações da voz e/ou rouquidão, estridor e tosse, podendo também surgir sintomas constitucionais. Cerca de 50% dos doentes apresentam-se inicialmente com doença metastática e outros 25% irá desenvolvê-la ao longo da história natural da doença. Os locais mais comumente afetados são, por ordem decrescente, o pulmão e pleura, osso e cérebro. O CAT não tem um marcador tumoral associado. Na ausência de tratamento, a principal causa de mortalidade é a asfixia causada diretamente pela invasão das vias respiratórias pelo tumor.

Relativamente ao estadiamento, todos os CAT são classificados como estadio IV, dada a sua agressividade, e encontram-se subdivididos em 3 grupos: o estadio IVA corresponde a doença intra-tiroideia, sem doença nodular ou metástases; o estadio IVB corresponde inclui doença intra-tiroideia com doença nodular ou doença extra-tiroideia com ou sem envolvimento nodular; já o estadio IVC engloba todos os doentes com metástases à distância, independentemente do T ou N.

O diagnóstico definitivo depende da confirmação citológica ou histológica, assim como da exclusão de outras causas com um prognóstico mais favorável. Na maioria dos casos, o diagnóstico correto é possível através da citologia aspirativa com agulha fina; no entanto, em alguns casos, pode ser necessária biópsia por punção ou, mais raramente, uma biópsia aberta. O recurso a procedimentos ecoguiados permite a identificação de áreas mais adequadas para a colheita de amostras. Ao exame microscópico, o CAT apresenta uma morfologia altamente maligna com áreas marcadas de necrose e inflamação do estroma, sem evidência da normal arquitetura tiroideia.

Uma característica interessante é a íntima relação que o tumor estabelece com macrófagos, que formam uma densa rede semelhante à microglia, e asseguram propriedades pró-tumorigénicas que contribuem para a resistência ao tratamento e pior prognóstico. Os principais tipos histológicos encontrados são a morfologia sarcomatóide, de células gigantes pleomórficas e epitelioide. As células anaplásicas da tiróide são normalmente negativas para proteínas específicas da tiróide (tiroglobulina) e para marcadores da linhagem tiroideia (TTF-1). Em contrapartida, são normalmente positivas para PAX-8 e citoqueratinas, o que valida a sua origem folicular. A coloração positiva para p53 e mutações BRAF, especialmente BRAF V600E, apoiam este diagnóstico.

A avaliação imagiológica é crucial para o estadiamento do tumor e fornece informações importantes sobre o prognóstico e o tratamento. A ecografia permite uma avaliação rápida do tumor primário, a sua extensão e invasão, assim como o envolvimento das cadeias nodulares. O estadiamento inicial do tumor deve incluir TAC com contraste do pescoço, tórax, abdómen e pélvis, no entanto, a RM com gadolínio é uma boa alternativa. ^{18}FDG PET-TC é o melhor método para avaliar a existência de

metástases à distância. Todos os doentes com diagnóstico de CAT devem ser submetidos a uma avaliação completa da via aérea com laringoscopia de fibra óptica, durante a sua avaliação inicial. Esofagogastroduodenoscopia e/ou a broncoscopia podem ser consideradas para visualizar a invasão direta do tumor nesses órgãos. Os diagnósticos diferenciais mais importantes incluem outros carcinomas primários ou metastáticos que afetam a tiroideia, assim como condições benignas como a tiroidite aguda e a tiroidite de Riedel.

Dentro dos carcinomas da tiróide, o ATC apresenta o maior número de mutações. A perda de expressão dos marcadores de diferenciação da tiroideia é uma característica distintiva desta neoplasia. Alterações genómicas frequentes incluem mutações inativadoras do TP53 e mutações ativadoras do TERT, BRAF e RAS. Mutações do TP53 e TERT são sugestivas de serem um evento tardio na carcinogénese e essenciais para a transformação anaplásica. A mutação BRAF V600E é a alteração BRAF mais frequente e as mutações BRAF e RAS são mutuamente exclusivas. Pensa-se que ambas são *driver mutations* que ocorrem precocemente no desenvolvimento tumoral. Outras alterações genómicas incluem a ativação e inativação de genes, alterações em vias de sinalização, rearranjos cromossómicos, fusões de genes, alterações do número de cópias e amplificações de genes, bem como modificações epigenéticas. Por este motivo, é recomendada a realização de testes moleculares em doentes com CAT, uma vez que os doentes podem ser encaminhados para terapias dirigidas.

A verdadeira origem deste tumor ainda não foi identificada. No entanto, a maioria dos autores acredita que o CAT é originário de carcinomas bem-diferenciados que sofrem um processo de desdiferenciação através da aquisição de sucessivas alterações genómicas.

Quando as células anaplásicas metastizam, sofrem um processo designado transição epitélio-mesênquima, em que mudam a expressão de genes do fenótipo epitelial (como a E-caderina, claudina e ocludina) para genes típicos do fenótipo mesenquimal (como a N-caderina, vimentina e catenina). Através de um processo inverso, as células são capazes de retornar ao seu fenótipo epitelial, dando início à formação de um tumor metastático num local secundário.

A comunicação com os doentes, os seus familiares e prestadores de cuidados é extremamente importante. Os médicos devem discutir as opções terapêuticas, os riscos e benefícios dos procedimentos, e os potenciais resultados devem ser comunicados de forma realista. Cuidados de fim de vida e gestão da via aérea devem ser abordados precocemente, assim como a determinação dos objetivos, quer terapêuticos, quer paliativos. O tratamento deve ser decidido a nível individual, em conjunto com uma equipa multidisciplinar.

Doentes em estadio IVA ou IVB podem ser candidatos a intervenção cirúrgica, devendo ser recomendada se for possível obter uma ressecção completa do tumor com uma morbilidade mínima.

Alguns doentes em estadio IVC também podem ser elegíveis para cirurgia para controlo loco-regional da doença e intenção paliativa. Enquanto a maioria dos estudos afirma que a ressecção completa está associada a um prolongamento da sobrevida-livre-de-doença e da sobrevida global, uma revisão sistemática recente não encontrou qualquer diferença significativa na sobrevida dos doentes em função do tipo de ressecção, e margens negativas podem não apresentar benefícios para a sobrevida. As ressecções radicais são de benefício questionável e não são recomendadas.

Os melhores resultados nos estadios IVA e IVB são alcançados através de ressecção cirúrgica completa/quase, completa, seguida de radioterapia, por vezes em associação com quimioterapia. Os estudos são consistentes com o facto de doses de radiação mais elevadas conduzirem a uma sobrevida prolongada, sendo doses mais baixas oferecidas para paliação. Radioterapia com modulação da intensidade é a técnica recomendada, uma vez que minimiza a exposição dos tecidos saudáveis circundantes à radiação.

Relativamente aos doentes em estadio IVC, opções terapêuticas incluem quimioterapia citotóxica, com ou sem radioterapia, assim como abordagens imunoterapêuticas e terapias dirigidas, caso sejam detetadas mutações-chave. Infelizmente, a quimioterapia apresenta resultados dececionantes e acarreta uma elevada toxicidade e diminuição da qualidade de vida. Em raras exceções, a quimioterapia pode permitir a ressectabilidade em doentes com doença inicial irressecável.

A traqueostomia não é recomendada por rotina e deve ser evitada, se possível, pois embora prolongue no imediato, está associada a uma diminuição da sobrevida a longo prazo.

Dada a raridade deste tumor e do seu prognóstico preocupante, as diretrizes atuais da ATA recomendam que os doentes suficientemente saudáveis devem ser encorajados a participar em ensaios clínicos, numa tentativa de encontrar as melhores abordagens terapêuticas, tendo em conta a urgente necessidade de novos tratamentos. A mutação BRAF V600E, atualmente, é a que tem maior aplicabilidade no tratamento do CAT. O tratamento com drabafenib (inibidor BRAF) mais trametinib (inibidor MEK) para doentes com esta mutação tem mostrado resultados encorajadores e é recomendado quando esta é encontrada. Estudos atuais com outros fármacos mostram resultados satisfatórios e promissores, no entanto, é necessária mais investigação de forma a caracterizar melhor a sua segurança e eficácia.

Palavras-chave: carcinoma anaplásico da tiróide; mutação BRAF V600E; transformação anaplásica; terapias direcionadas; alterações genómicas

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List of abbreviations

^{18}FDG	18-Fluorodeoxygluocose
AJCC	American Joint Committee on Cancer
AKT	Protein kinase B
ALK	Anaplastic lymphoma kinase
APC	Adenomatous polyposis coli
aPTT	Activated partial thromboplastin time
AS	Angiossarcoma
ATC	Anaplastic thyroid carcinoma
ATJCC	Anaplastic Thyroid Carcinoma Research Consortium of Japan
ATM	Ataxia-telangiectasia mutated
AXIN1	Axin-1
BAG3	Bcl-2-associated anthanogene 3
BMI	Body mass index
CA4P	Combrestastatin A4 phosphate
CAR-T	Chimeric antigen receptor T
CCDC6	Coiled-Coil Domain Containing 6
CCL20	C-C motif ligand 20
CCR6	C-C Motif Chemokine Receptor 6
CD	Cluster of differentiation
CDH1	Cadherin 1
CDKN2A	Cyclin Dependent Kinase Inhibitor 2A
CEA	Carcinoembryonic Antigen

ChT	Chemotherapy
CK1	Casein kinase 1
CREB	cAMP Response Element-Binding Protein
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
CTNNB1	Catenin Beta-1
DTC	Differentiated thyroid carcinoma
DUSP26	Dual-Specificity Phosphatase 26
EGF	Epithelial growth factor
EGFR	Epithelial growth factor receptor
EIF1AX	Eukaryotic translation initiation factor 1A
EMA	European Medicines Agency
EMP	Epithelial-mesenchymal plasticity
EMT	Epithelial-to-mesenchymal transition
EPHA3	Ephrin type-A receptor 3
ERK	eEtracellular signal-regulated kinases
FC	Follicular carcinoma
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FLT3	Fms-like tyrosine kinase 3
FNA	Fine-needle aspiration
fT4	Free thyroxine
FTC	Follicular thyroid carcinoma

FOXD3	Forkhead Box D3
GCSF	Granulocyte colony-stimulating factor
GDP	Guanosine diphosphate
Gli1	Glioma-associated oncogene-1
GLUT1	Glucose transporter 1
GSK3β	Glycogen Synthase Kinase 3 Beta
GTP	Guanosine triphosphate
Gy	Gray (unit)
hCG	Human Chorionic Gonadotropin
HDAC	Histone deacetylase
HMB-45	Human Melanoma Black-45
HMTs	Histone methyltransferases
IDH1	Isocitrate dehydrogenase 1
IGF	Insulin growth factor
IkB	Inhibitor of kB
IL-6	Interleukin 6
JAK/STAT	Janus kinase/signal transducer and activator of transcription
KMT2A	Lysine Methyltransferase 2A
M-CSF	Macrophage colony-stimulating factor
MEN1	Multiple Endocrine Neoplasia Type 1
MET	Tyrosine-protein kinase Met
miRNA	Micro-RNA
MLH1	Human mutL homolog 1

MMR	Mismatch repair
MRI	Magnetic Resonance Imaging
MSH2/6	MutS homolog 2/6
MTC	Medullary thyroid cancer
mTOR	mammalian target of rapamycin
MTV	metabolic tumor volume
NF1/2	Neurofibromatosis type 1/2
NF-Kb	nuclear factor kappa B
NICD	NOTCH intracytoplasmic domain
NOXA	Nuclear Protein 1 (PMA-Inducible) Activator
NRTK	"Nuclear Protein 1 (PMA-Inducible) Activator
OCL-GC	Osteoclast-like giant cells
OS	Overall survival
pAKT	phosphorylated protein kinase B
PAX	Paired box gene
PC	Papillary carcinoma
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PDK1	Pyruvate Dehydrogenase Kinase 1
PD-L1/PD-L2	Programmed death-ligand 1/2
PDTC	Poorly differentiated thyroid cancer
PET	Positron emission tomography
PFS	Progression-free survival

PI3K	Phosphoinositide 3-kinase
PI3KCA	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol 3,4,5-trisisphosphate
PPAR-γ	Peroxisome proliferator-activated receptor gamma
PTC	Papillary thyroid carcinoma/cancer
PTCH1	Patched 1
PTC-PC	Papillary thyroid carcinoma with pleomorphic tumor giant-cells
PTEN	Phosphatase and tensin homolog
PTHrP	Parathyroid hormone-related protein
RAI	Radioactive iodine
RAF	Rapidly Accelerated Fibrosarcoma
RANK	Receptor activator of nuclear factor kappa beta
RAS	Rat sarcoma
RASAL1	RAS Protein Activator Like 1
RasGAP	Ras GTPase activating
RB1	Retinoblastoma gene 1
ROS1	ROS proto-oncogene 1
RT	Radiotherapy
RTK	Receptor tyrosine kinase
SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology and End Results
SETD2	SET domain-containing protein 2

SHH	Sonic hedgehog
shRNA	Short hairpin RNA
SMADs	Mothers against decapentaplegic homolog
SMO	smoothened, frizzled class receptor
SOX-10	SRY-box transcription factor 10
STRN	Striatin
SUVmax	Standardized Uptake Value Maximum
SWI-SNF	SWItch/Sucrose Non-Fermentable
TAMs	Tumor-associated macrophages
TERT	telomerase reverse transcriptase
TGF-β	Transforming growth factor beta
TLG	Total lesion glycolysis
TSH	Thyroid stimulating hormone
TSHR	Thyroid stimulating hormone receptor
TTF-1	Thyroid transcription factor-1
TUG1	Taurine upregulated gene 1
TXNIP	Thioredoxin interacting protein
US	United States (of America)
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WDTC	Well-differentiated thyroid carcinoma
WHO	World Health Organization
WNT	Wingless/Integrated

1. INTRODUCTION

Anaplastic Thyroid Carcinoma (ATC), regardless of being a rare thyroid pathology, accounting for approximately 1-2% of all thyroid neoplasms (Molinaro *et al.*, 2017), is also one of the most aggressive solid tumors in humans (Molinaro et al., 2017). It has a very poor prognosis, supported by its significant contribution to thyroid cancer-related deaths, with 15-50% of said deaths attributed to this condition (Molinaro et al., 2017). The majority of patients have an estimated survival rate of 3-6 months following diagnosis (Yang & Barletta, 2020).

These neoplastic cells originate from the follicular cells of the thyroid (Tirrò et al., 2019). However, during their evolutionary process, they lose the characteristics and functions of their precursors, transforming into an undifferentiated tumor (Landa et al., 2016; Tirrò et al., 2019). In contrast to differentiated thyroid tumors, such as Follicular Carcinoma (FC) and Papillary Carcinoma (PC), which maintain the normal cellular architecture (Molinaro et al., 2017), ATC does not, in addition, it lacks the ability to uptake iodine from the bloodstream, synthesize thyroglobulin, or respond to thyroid-stimulating hormone (TSH) (Landa et al., 2016; Tirrò et al., 2019).

Frequently, thyroid tissue samples identified as ATC also contain foci of well-differentiated thyroid carcinomas (Jannin et al., 2022). This suggests that ATC may arise from more differentiated neoplasms and progressively lose their differentiation through the acquisition of new mutations, resulting in increased aggressiveness (Landa et al., 2016). However, the association between ATC and differentiated thyroid carcinomas is not yet fully understood (Capdevila et al., 2018).

Patients typically present with a long-standing goiter and a rapidly growing mass in the neck, and the most common symptoms arise from the compression of structures by the primary tumor (Bible et al., 2021). Distant metastases are very frequent in this particular cancer, and when not present at initial diagnosis, about a quarter of patients will end up developing a systemic disease, underlying its aggressive nature (Abe & Lam, 2021; Remick et al., 2011). Definitive diagnosis requires cytologic or histopathologic assessments (Bible et al., 2021; Podany et al., 2022) and, in most cases, the diagnosis can be done through fine-needle aspiration (FNA) cytology,

however, in some instances, a biopsy might be needed to assess a larger tissue sample (Bible et al., 2021).

Managing ATC is not easy and involves a multidisciplinary team. Treatment options for locoregional disease ATC are a combination of surgery, radiation, and chemotherapy. In advanced stages, surgery and radiation therapy have a more limited role and can be used for palliative purposes or to manage local complications and symptoms. More recent therapies, focused on target mutations altered in this undifferentiated carcinoma and in abnormal immune responses, have been tested in ATC patients for metastatic disease and are showing encouraging results (Bible et al., 2021). Due to the aggressive nature of ATC and its limited response to traditional treatments, new therapies are currently being investigated to address this challenge (Abe & Lam, 2021).

2. EPIDEMIOLOGY

According to the Global Cancer Statistics 2020, thyroid cancer corresponded to 3.0% of all human tumors in 2020, ranking in 9th in incidence (Sung et al., 2021). However, Anaplastic Thyroid Cancer corresponds only to 1-2% of all thyroid tumors (Molinaro et al., 2017).

Owing to its rarity, its true incidence is not entirely known. Nonetheless, it is described that its incidence might be superior in Europe in comparison to the United States (US). The estimated incidence is projected to be around 1-2 cases per million habitants per year (Amaral et al., 2020; Molinaro et al., 2017).

Since the beginning of the 1980's, the incidence of thyroid cancer has been increasing, especially in developed countries (Lamartina et al., 2022). Even so, this increase is, almost exclusively, caused by small papillary thyroid carcinomas (PTC) (dimensions ≤ 2 cm). (Albores-Saavedra, Henson, et al., 2007) Possible causes for this reported increase in incidence include: an earlier diagnosis of this disease and in its earlier stages, thanks to fine-needle aspiration (FNA) and the importance of thyroid echography in the detection of microscopic tumors; changes in diagnostic criteria that resulted in the reclassification of some tumors, now being categorized as of papillary variant (Albores-Saavedra, Henson, et al., 2007); improvement in economic status and improvement of healthcare access (Pereira et al., 2020).

However, this reported rise in incidence of thyroid cancer is not a true increase of incidence of the disease, but rather represents an increased rate of detection of thyroid cancer, caused by the discovery of small tumors that would, otherwise, not be discovered owing to its indolent growth and lack of symptoms. Mortality rate registries of thyroid carcinomas are compatible with this hypothesis since its mortality rate remained at a constant low level during the same period in which there was a reported rise in incidence rate (Albores-Saavedra, Henson, et al., 2007; Jegerlehner et al., 2017).

In a study carried out by Albores-Saavedra *et al.*, the SEER (Surveillance, Epidemiology and End Results) database was used to obtain and analyze epidemiological patterns of anaplastic thyroid cancer inside the US. The SEER-9 registry and the time limit between 1973 and 2003 were chosen in accordance with the study

objectives. From that analysis, even though the incidence of thyroid cancer increased in an annual percentage of 3.4%, specifically the incidence of ATC diminished by 22% in 30 years with an annual decrease of 1.1%, which was statistically relevant. This study also confirmed the increase in ATC's incidence in older adults (Albores-Saavedra, Henson, et al., 2007).

Potential causes for the regression of ATC's incidence include: the successful treatment of more differentiated thyroid neoplasms, under the premise that this type of carcinoma is an evolution of pre-existing thyroid tumors (Albores-Saavedra, Henson, et al., 2007); the increase of dietary consumption of iodine through enriched-salts supplementation implemented in various countries, leading to a reduction of endemic goiter, which is a major risk factor for this type of tumor and the improvement of histopathological diagnosis, allowing for the correct reclassification of certain types of cancer that would, otherwise, be misdiagnosed, for example, thyroid lymphoma and undifferentiated medullary thyroid cancer (Molinaro et al., 2017).

In a similar retrospective study, the authors analyzed the data from the SEER-9 registries, this time regarding the period between 1986 and 2015. From that observation it was concluded that, regarding the anaplastic variant, although there were fluctuations of the incidence rate, there was no clear trend. The calculated age-standardized incidence rate was 0.07/100,000 and the median age of diagnosis was 71 years. It was also concluded that the incidence was greater in women and in people with higher social status. On the other hand, the latter shows increased numbers of M0 tumors in people of higher socio-economic status, which may be explained by easier access to health care, allowing for an earlier detection of tumors. In this study, the long-term survival of this type of tumor did not change over the years. Median survival was 4 months and only 35% of patients survived until 6 months after diagnosis (Lin et al., 2019).

Pereira *et al.* also used the SEER-9 registry in their study to analyze demographic and clinical outcomes about ATC. Data was collected from 1975 to 2016. In this investigation, ATC corresponded to 1.23% out of all thyroid cancers diagnosed between said time and its incidence rate was constant during the analyzed period (Pereira et al., 2020).

Locati *et al.* carried out a study in Europe to assess the overall incidence of ATC across the continent. They used the RARECAREnet's database, which included data from 24 European countries, for their analysis. Age-standardized incidence was 0.1/100,000 for both male and female individuals, with limited variations across countries. The incidence peak varied across different subtypes, with ATC occurring most frequently in individuals between 80-84 years, for both sexes, making it the subtype with the oldest peak incidence rate. There were no significant changes observed in the incidence of ATC from 2000 and 2007, according to their analysis (Locati et al., 2020).

Miranda-filho et. al pursued a more global approach and investigated international trends of thyroid cancer incidence by histological subtypes. They did so by using data from the International Agency for Research on Cancer (IARC) covering the period 1998-2012, such data contains information from 25 countries. They concluded that the anaplastic subtype showed the lowest incidence rate and exhibited less geographical variation compared to the others. Interestingly, its incidence showed a practically global declining trend, even in countries where the overall incidence rate of thyroid cancer was increasing. Incidence also increased with age (Miranda-Filho et al., 2021).

ATC occurs more often in the elderly (Amaral et al., 2020) and has a median age at diagnosis of 65-70 years (Yang & Barletta, 2020). Its incidence peak is between the 6^{th} and 7^{th} decade of life and most patients are older than 50 years old (Molinaro et al., 2017).

This pathology, like most thyroid tumors, is more frequent in women (Amaral et al., 2020), with a woman to man ratio of 1.5-2:1 (Yang & Barletta, 2020).

Even though Thyroid Carcinoma is generally linked to a good prognosis, the anaplastic subtype does not share the same tendency. Despite corresponding to <2% of all thyroid carcinomas, ATC is one of the most aggressive solid tumors that is currently known, having a very reserved prognosis. ATC represents 14-50% of all deaths attributed to thyroid cancer which highlights its high lethality rate (Glaser et al., 2016; Molinaro et al., 2017; Remick et al., 2011).

The median overall survival rate after diagnosis differs among different studies, varying from 3 to 6 months (Amaral et al., 2020; Glaser et al., 2016; Remick et al., 2011; Yang & Barletta, 2020). Objectively, 1-year, 2-years, 5-years and 10-years survival rates are, respectively, 10-20% (Amaral et al., 2020; Remick et al., 2011), 10-15% (Molinaro et al., 2017; Yang & Barletta, 2020), <10% (Yang & Barletta, 2020) and <5% (Amaral et al., 2020; Remick et al., 2011).

As a result of its lethality rate, the prevalence of this particular type of tumor is low, ranging from 1.3%-9.8% across different studies (Molinaro et al., 2017).

3. RISK FACTORS AND PROGNOSTIC FACTORS

Identifying potential risk factors for Anaplastic Thyroid Cancer is of great importance, considering the overall poor prognosis, since it might allow its prevention or early detection (Bible et al., 2021).

History of goiter, a long-standing self and familial, is believed to be ATC's most important risk factor (Amaral et al., 2020). This disease is more commonly found in areas with endemic goiter and iodine supplementation has been shown to decline its incidence (Remick et al., 2011).

Age is an important risk factor for Anaplastic Thyroid Cancer. This disease is rare in younger populations, and increases its incidence with age, with most cases happening in populations older than 65 years (Remick et al., 2011).

Starting in 2004, Zivaljevic *et al.* ran a series of case-control studies to identify potential risk factors for ATC. Their research extended throughout 2014, with additional patients and different control groups. From their latest results, when comparing the ATC group with a control group drawn from the general population, independent risk factors for ATC included low education level, type B blood group, and goiter or thyroid nodules. Low education level is thought to be a risk factor due to lower health awareness, and later healthcare attendance. In contrast with their results from 2004, the authors found that diabetes and personal history of non-thyroidal malignancies were no longer considered independent risk factors. Additionally, living in an endemic goiter area could not be correctly assessed, as both the experimental and control group resided in the same area. When using patients operated for goiter as the control group, five variables were identified to be independently related to the development of ATC, those were, lower level of education, type B blood group, a personal history of nonthyroidal malignancies, late menarche (at age 15 or later) and early pregnancy (defined as before age of 19). These two reproductive variables are known risk factors for thyroid cancer in female patients. However, when the control group was formed by patients with papillary thyroid cancer, age proved to be the only independent risk factor for the development of ATC, using the same experimental group (Zivaljevic et al., 2014).

A rare percentage of ATC arises from anaplastic transformation of more differentiated thyroid carcinomas, for this reason, DTC might be seen as a risk factor for ATC. TERT promoter mutation is pointed as a potential independent factor associated in anaplastic transformation (Bible et al., 2021).

In a meta-analysis conducted by Schmid *et al.*, the potential link between adiposity and thyroid cancer was evaluated. In their analysis obesity was associated with a 93% statistically significant increased risk for the anaplastic thyroid cancer subtype. Additionally, elevated Body mass index (BMI) is associated with an increased risk of developing papillary, follicular, and anaplastic thyroid carcinomas, however, it has a negative correlation with the medullary subtype. In euthyroid individuals, TSH levels are shown to have a positive correlation with obesity. Higher TSH levels are associated with thyroid gland cancer, as TSH is involved in mitogenic pathways of thyroidal cells. Experimental studies show that diet-induced obesity in mice led to increased leptin levels, which has been linked to an increase in thyroid cancer. Leptin is believed to inhibit cell migration for this type of malignancy (Schmid et al., 2015).

Other risk factors include history of radiation exposure to the chest or neck (Molinaro et al., 2017). Cases of patients with anaplastic thyroid carcinoma following irradiation for Hodgkin's disease have been described (Paul Gétaz et al., 1979). It has also been suggested that treating differentiated thyroid tumors with radiotherapy might contribute to their dedifferentiation (Graceffa et al., 2022).

Age has been long known to be an important prognostic factor for thyroid cancers and, on that account, it is even included in the American Joint Committee on Cancer (AJCC) staging system for differentiated thyroid carcinomas. Despite that, it is not included as a staging parameter for anaplastic thyroid carcinoma, even though several studies link older ages to a worse prognosis. An example is a study conducted by Kong *et al.*, where data was used from the SEER database from 2004 to 2017, in which they concluded that age had an influence on the prognosis of ATC, with patients diagnosed at an older age having a worse prognosis. (Kong et al., 2021). Since age seems to be a clear prognostic factor for the anaplastic type, one wonders if it should be included as a staging parameter, as it is used for more differentiated subtypes, in AJCC's staging manual.

Glaser *et al.* published a retrospective study using data from the National Cancer Data Base. From their analysis, several factors were associated with an improved overall survival for patients suffering from ATC, these include younger age, lower comorbidity score (using Charlson-Deyo comorbidity score), higher facility volume (facilities handling > 5 cases per year), no evidence of nodal disease (stage N0), no evidence of distance metastasis (stage M0), primary tumor confined to the thyroid (T1-T3a according to the 8th edition of AJCC's manual, or T4a, according to the 7th edition), smaller tumor size (≤ 6 cm) and negative surgical margins (Glaser et al., 2016). T and M staging are shown to independently affect prognosis (Abe & Lam, 2021).

Other favorable prognostic factors consist of female sex, absence of leukocytosis, total thyroidectomy, prior or coexisting DTC, and ATC cellular subtype (Rao & Smallridge, 2023; Yang & Barletta, 2020).

Indicators of poor prognosis are history of radiation exposure, history of surgical resection, presence of hypercalcemia or leukocytosis, tumor extension (> 5 cm and extrathyroidal invasion) and presence of distant metastasis. Other variables that may predict a worse prognosis include male sex and p53 expression (Abe & Lam, 2021).

4. CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Anaplastic thyroid carcinoma usually presents in more than 80% of cases as rapid growth of a firm and fixed palpable thyroid mass, overt a period of weeks, that may have been present in the thyroid gland for years (Lloyd et al., 2017; Molinaro et al., 2017; Santos & Horta, 2018). The median size of the primary tumor is 6.8 cm (Rao & Smallridge, 2023) and it can be ulcerated with areas of necrosis (Brunicardi et al., 2014). Being a highly aggressive local carcinoma, it infiltrates adjacent organs like the perithyroidal fat and muscle, esophagus, trachea, larynx, vocal cords, laryngeal recurrent nerve, blood vessels and lymph nodes. It can also directly infiltrate the skin of the neck (Abe & Lam, 2021b) and on examination, the skin might often be warm and discolored (Williams).

Most common symptoms are due to the compression of neck structures by the primary tumor, causing dysphagia, voice alterations and/or hoarseness, and inspiratory stridor and cough (Abe & Lam, 2021; Chintakuntlawar et al., 2019; Remick et al., 2011). Superior vena cava syndrome, Horner's syndrome (caused by compression of the parasympathetic chain) (Amaral et al., 2020) and invasion of the carotid arteries resulting on a hematoma or stroke (Keutgen et al., 2015), can be present as well. A rapid enlargement when accompanied by pain can be caused by hemorrhage into the thyroid mass, and hemoptysis might suggest the tumor has eroded trough the trachea. (Molinaro et al., 2017). Lymph nodes are usually palpable at presentation (Brunicardi et al., 2014) with cervical node invasion being present in 29 to 40 % of patients with this kind of carcinoma (Abe & Lam, 2021; Molinaro et al., 2017).

Patients can experience constitutional symptoms, including anorexia, weight loss, and high-grade fever (Molinaro et al., 2017; Naeem et al., 2020).

At presentation, nearly 50% of patients have metastatic disease (stage IVc). This appears to have increased according to newer studies, in comparison to older ones, which is thought to be a direct consequence of advancements in radiological imaging techniques that enable more accurate detection of metastatic (Abe & Lam, 2021). Even so, about a quarter will develop distant metastasis throughout the course of the disease (Remick et al., 2011). Lung and pleural metastases are the most common form

of metastasis found in patients with this type of malignancy, being found in < 90% of patients (Haddad et al., 2022). Bone metastases occur in about 5 to 15% of cases, and they can be accompanied by bone pain, spinal cord compression or pathological bone fractures (Bible et al., 2021); they are usually lytic lesions (Haddad et al., 2022). Brain metastases are present in 1-5% of patients with ATC and are linked to a poor prognosis (Bible et al., 2021). This type of tumor can theoretically metastasize to any site, with evidence of abdominal, pancreatic, skin, liver, kidneys, heart, and adrenal glands metastases (Haddad et al., 2022).

Although anaplastic thyroid carcinoma is a non-functioning malignancy, in rare instances, patients can show signs and symptoms of thyrotoxicosis. This is thought to be attributable to the fast destruction of the thyroid tissue by the tumor, resulting in the release of thyroxine into the bloodstream (Abe & Lam, 2021). With continuous destruction of the normal thyroid tissue, patients can end up developing hypothyroidism (Murakami et al., 1989). Sometimes, the large tumor mass can result in a compromised thyroid function. For these reasons, serum thyroid function tests are encouraged to be assessed (Bible et al., 2021).

Calcium and phosphorus levels should be determined since both hypocalcemia and hypercalcemia can be encountered in patients with ATC. Tumor invasion of the parathyroids, and secondary effects of both surgery and external beam radiotherapy are potentially attributable causes of hypocalcemia (Bible et al., 2021; Heymann et al., 2005).

ATC can be responsible for many paraneoplastic manifestations. Examples include secretion of ectopic human chorionic gonadotropin (hCG) and positive tumor-immunostaining for beta-hCG, which has been shown in some studies and liked to a poor prognosis (Abe & Lam, 2021); production of parathyroid hormone-related peptide (PTHrP) and PTHrP-immunostaining can also be found, inducing hypercalcemia; leukocytosis secondary to the production of granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), or IL-6 (present in 16–30% of patients); osteomalasia caused by secretion of ectopic fibroblast growth factor 23 (FGF-23); and hypertrophic osteoarthropathy, thought to be the

consequence of platelet derived growth factor (PDGF) or vascular endothelial growth factor (VEGF) by the thyroid carcinoma (Abe & Lam, 2021; Bible et al., 2021).

Unlike differentiated thyroid cancers (DTC), ATC does not have an associated tumor marker. Detectable thyroglobulin (TG) levels might occur if there is evidence of a DTC coexisting with ATC (Chintakuntlawar et al., 2019; Rao & Smallridge, 2023). Lack of detectable TG levels support the diagnosis of ATC (Bible et al., 2021).

In the absence of treatment, most patients die of suffocation directly caused by invasion of the airway by the tumor mass (Chintakuntlawar et al., 2019). However, with the implementation of tracheostomy, allowing airway management, deaths have frequently been attributed to pulmonary metastasis and respiratory complications (Spielman et al., 2017).

5. STAGING

Staging of tumors is of great importance, as it is as a useful tool for treatment planning, prognosis based on extent of disease, facilitates the exchange of information between healthcare centers and allows for a uniformization of clinical data (Brierley et al., 2016).

Anaplastic Thyroid Cancer staging is in accordance with the 8th edition of the American Joint Committee on Cancer (AJCC) TNM Staging System Manual, published in October 2016. However, since most papers used predate the publication of this last update and its implementation (January 2018) and use clinical data collected accordingly to previous versions of the TNM system, it was decided to also include the 7th edition's version of anaplastic thyroid carcinoma's staging classification system in this section, allowing a better understanding. In table 1. there is a comparison between the two editions of AJCC's TNM classification system.

A major difference between both editions of the AJCC's staging system relies on the T (primary tumor size) classification (Tuttle et al., 2017). Previously, a diagnosis of Anaplastic Thyroid Cancer meant an immediate classification of said tumor as a T4. T4a meant the tumor was limited to the thyroid gland, and in T4b, the disease had surpassed the thyroid capsule (Edge & American Joint Committee on Cancer., 2010). However, in the newer version, it follows the same categorization as differentiated thyroid carcinomas, with T1-T3a corresponding to intrathyroidal disease only and T3b-T4b meaning extrathyroidal invasion (Abe & Lam, 2021).

In both editions, this disease is immediately recognized as stage IV cancer, owing to its lethality and aggressiveness, and is subdivided into 3 distinct groups. The way subgrouping is organized suffered a minor change from one version to another. In AJCC's 7th edition, stage IVA corresponds to disease confined to the thyroid gland and stage IVB to gross extrathyroidal extension, regardless of N, and M0 (Edge & American Joint Committee on Cancer., 2010). As for the 8th edition, stage IVA cancers are restricted to the thyroid (T1-T3a), without lymph nodes (N0) or distant metastasis (M0). Stage IVB includes extrathyroidal lesions (T3b-T4) with or without lymph nodes involvement (N0 or N1), and intrathyroidal tumors (T1-T3a) with lymph nodes

metastasis (N1), all M0. Thus, N staging now affects subgrouping in the newer edition. Stage IVC stayed the same, that is, anaplastic thyroid carcinomas with distant metastasis (M1), regardless of T or N (Abe & Lam, 2021).

It is important to mention that no molecular markers were included in the latest staging definitions, for not being thought to have sufficient independent prognostic value (Tuttle et al., 2017).

AJCC 7th edition		**AJCC 8th edition**
TNM Classification		
T	**T4a:** intrathyroidal disease	**Tx:** primary tumor cannot be assessed **T1a:** Tumor 1 cm or less in greatest dimension, limited to the thyroid **T1b:** Tumor > 1 cm but less than 2 cm in greatest dimension, limited to the thyroid **T2:** Tumor > 2 cm but less than 4 cm in greatest dimension, limited to the thyroid **T3a:** Tumor > 4 cm in greatest dimension, limited to the thyroid
	T4b: Anaplastic carcinoma with gross extrathyroidal extension	**T3b:** Tumor of any size with gross extrathyroidal extension invading strap muscles (sternohyoid, sternothyroid, or omohyoid muscles) **T4a:** Tumor extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve **T4b:** Tumor invades prevertebral fascia, mediastinal vessels, or encases carotid artery
N	**NX:** Regional lymph nodes cannot be assessed **N0:** No regional lymph node metastasis **N1a:** Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) **N1b:** Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)	**Nx:** Regional lymph nodes cannot be assessed **N0a:** No regional lymph node metastasis (one or more cytologically or histologically confirmed benign lymph nodes) **N0b:** No regional lymph node metastasis (No radiologic or clinical evidence of locoregional lymph node metastasis) **N1a:** Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinum **N1b:** Metastasis in other unilateral, bilateral or contralateral cervical (levels I, II, III, IV or V) or retropharyngeal
M	**M0:** No distant metastasis **M1:** Distant metastasis	**M0:** No distant metastasis **M1:** Distant metastasis
Staging group		
IVA: T4a, Any N , M0		T1-T3b, N0/Nx, M0
IVB: T4b, Any N, M0		T1-T3a, N1, M0 or T3b-T4, Any N, M0
IVC: Any T, Any N , M1		Any T, Any N, M1

Table 1. Comparison of AJCC's 7th and 8th edition for staging of Anaplastic Thyroid Cancer (Abe & Lam, 2021).

Onoda *et al.* compared prognoses of ATC patients' using both mentioned editions of AJCC's Staging Manual, to evaluate its revision. Patients' data was retrieved

from the Anaplastic Thyroid Carcinoma Research Consortium of Japan (ATJCC), where a total of 757 patients were used for analysis. They concluded that, for their population, there were overlaps in survival rates and no significant differences in the prognosis between T1 and T2 groups (previously T4a) and between T3b and T4 groups (previously T4b). Interestingly, patients with T3a tumors showed prognoses in between those with T2 or T3b tumors. The overall survival (OS) was significantly better in N0 patients when in comparison to N1 patients. Nodal involvement shared a significant correlation with the T category, being more commonly found alongside T3b and T4 tumors; N served as a non-independent significant indicator of prognosis – supporting the rationale for switching node-positive and M0 patients from IVA to IVB. The median OS for stage IVA patients improved with the new changes applied, and it was statistically significant. However, the median OS for stage IVB patients did not change significantly. Since both editions share the same categorization for stage IVC, no comparison between the two was possible to accomplish. Patients that migrated from 7th edition's stage IVA to the revised 8th edition's stage IVB showed a significantly worse OS when compared to the revised stage IVA. Even so, the OS of these migrated patients was better when compared to the old IVB patients (Onoda et al., 2020).

6. DIAGNOSTIC APPROACH

6.1. Definitive diagnosis

Diagnosing this entity is of great importance given its poor prognosis and necessity for aggressive treatment. It's done with the help of clinical, biochemical, radiographic, and histologic assessments. The definite diagnosis relies on confirmation with either cytologic or histopathology assessments and exclusion of causes with a more favorable prognosis and treatment (Bible et al., 2021; Podany et al., 2022) .

Fine-needle aspiration (FNA), as with any thyroid mass, is typically the first exam done to obtain tissue samples (Keutgen et al., 2015). A correct diagnosis can be achieved in more than 60% of cases of FNA, especially when the aspirate is highly cellular, and immunohistochemistry is possible. Cytological diagnosis can be very challenging, especially with small and limited samples, and due to the overlapping features with other conditions. In these cases, where the FNA is nondiagnostic, a core biopsy should be considered. However, given the prevalence of tumor necrosis and reactive inflammatory findings, such biopsies can also be nondiagnostic. Therefore, the use of ultrasound guided biopsies allows the identification of solid areas or nodal disease that might be more suitable for tissue samples. In comparison to FNA, core biopsy allows a broader range of genomic testing. In rare cases, ATC are only diagnosed after open biopsy of surgical resection (Bible et al., 2021).

6.2. Histologic and Immunophenotypic characteristics

Anaplastic thyroid carcinoma's morphology varies greatly among individuals posing a significant diagnostic challenge for pathologists due to intratumoral mixture of different histological types (Molinaro et al., 2017).

On microscopic examination, this carcinoma exhibits a highly malignant morphology. Cancerous cells have a prominent nuclear pleomorphism with irregular contours and a thick, coarse chromatin. It has a high proliferative rate with numerous mitotic figures, and sometimes atypical ones, with a tripolar shape (indicative of

abnormal mitosis and suspicious of malignancy), might be observed. It also contains marked areas of necrosis and inflammation in the stroma (Abe & Lam, 2021; Molinaro et al., 2017; Yang & Barletta, 2020). Unlike more differentiated thyroid carcinomas, the normal thyroid structure is not maintained, and neoplastic cells are not arranged to form follicles or colloids. Colloids, however, can be seen in areas of normal thyroid tissue or well-differentiated carcinomas entrapped in the tumor tissue (Molinaro et al., 2017).

Tumor-associated macrophages (TAMs), particularly M2 macrophages, frequently infiltrates ATC and execute pro-tumorigenic properties, such as facilitating dedifferentiation, proliferation, migration, invasiveness, and immunosuppression, contributing to treatment resistance and to patient's decreased survival. These macrophages are found in 22% to 95% of ATCs and form a dense network resembling a microglia-like appearance, directly connected to neoplastic cells, executing metabolic and trophic functions. Consequently, it results in a high expression of several inhibitory immune checkpoint mediators, like cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-ligand 1-2 (PD-L1/PD-L2), which are known to inhibit cytotoxic CD8+ T-cell functions. This network is specific to ATC and is not encountered in differentiated thyroid neoplasms, although it can be present in other cancers that metastasize to the thyroid (Jannin et al., 2022; Molinaro et al., 2017). The tumor can also be infiltrated by other cell types like lymphocytes and neutrophils, and more (Yang & Barletta, 2020).

Heterologous differentiation, such as malignant bone and cartilage, can be found within the tumorous mass (Abe & Lam, 2021). Frequently, ATC smears display an inflammatory neutrophilic background, which may be overwhelming and result in a wrongful diagnosis of acute thyroiditis (Talbott & Wakely, 2015).

The main histological appearances are Sarcomatoid, Pleomorphic giant cell, and Epithelioid morphology. Sarcomatoid, also called Spindle cell morphology (~50%) exhibits malignant spindle resembling high-grade pleomorphic sarcoma. Pleomorphic giant cell variant (~30-40%) shows highly pleomorphic malignant cells, with some giant cells containing multiple nuclei. As for the Epithelioid/Squamoid form (< 20%), they are

typically arranged in cohesive squamous tumor nests with abundant eosinophilic cytoplasm, with some of them showing keratinization (Molinaro et al., 2017) .

These different types can occur alone or in various combinations with each other, and the predominance of a particular cell type leads to the development of a distinct histological pattern (Lloyd et al., 2017; Molinaro et al., 2017). In up to 90% of cases, there is a differentiated thyroid neoplasm coexisting with ATC or a history of a prior DTC. (Jannin et al., 2022)

Less common histologic appearances can be observed in ATC, including rhabdoid, paucicellular, lymphoepithelioma-like, angiomatoid and osteoclastic (with non-neoplastic giant cells).

Rhabdoid phenotype demonstrates cells with abundant granular eosinophilic cytoplasm containing hyaline eosinophilic inclusions and rich in organelles, they also exhibit eccentric nuclei with prominent nucleoli. These rhabdoid inclusions are negative for desmin, thyroglobulin and calcitonin (Albores-Saavedra, Hernandez, et al., 2007; Bansal et al., 2020).

Paucicellular variant is described as an infiltrative and hypocellular tumor with large areas of fibrosis possible due to extensive areas of infarction, with foci of calcifications, presence of atypical spindle cells (that might be similar to fibroblasts or myofibroblasts) that cause obliteration of large blood vessels (which can be easier visualized by an elastic stain), mixed with collagen and lymphocytes. At the periphery of the tumor, areas of higher cellularity might be found, with increased mitotic activity and nuclear pleomorphism (Matias-Guiu et al., 2001; Wan et al., 1996). Riedel's or fibrous thyroiditis is a very rare entity characterized by chronic fibrosclerotic inflammation with macrophage and eosinophilic infiltration of the thyroid gland (Heufelder et al., 1996), although idiopathic fibrosis at other sites, like the mediastinum or the retroperitoneum might occur. It is an important differential diagnosis of this histological variant of ATC, because even though both entities share similar histological, and clinical findings, ATC's prognosis is very poor, whilst Riedel's has a favorable prognosis. They both manifest as a rapid firm thyroid mass growth in association with compression symptoms and are adjacent to neighboring structures.

Histological characteristics of this fibrous thyroiditis include sclerohyaline fibrosis and vessel obliteration of blood vessel attributable to phlebitis caused by lymphoplasmacytic infiltration around the vessel wall. Unlike ATC, cytokeratin staining does not support Riedel's diagnosis, however, some myofibroblasts might show sporadic staining (Wan et al., 1996).

Lymphoepithelioma-like anaplastic thyroid carcinoma is composed of epithelial cells that form syncytial-shape nests. These neoplastic cells have a basophilic cytoplasm with poorly defined borders and are surrounded and infiltrated by lymphocytes and plasma cells. The main differential diagnosis is with Carcinoma showing thymus-like differentiation (CASTLE) (Dominguez-Malagon et al., 2001), a neoplasm where tumor islands and fibrous septa are frequently infiltrated by a lymphocytic and plasma cell infiltrate (Youens et al., 2011), and rarely shows necrosis (Talbott & Wakely, 2015). This ATC variant also expresses epithelial membrane antigen and is negative for calcitonin, thyroglobulin and CD5, the latter being positive in thymic and lymphoepithelioma-like carcinomas, like CASTLE. (Dominguez-Malagon et al., 2001).

Histologic angiomatoid features include vascular-like spaces, some of them cavernous, lined with large epithelioid neoplastic cells, with red blood cells on their interior. Occasionally, neoplastic cells can contain intracytoplasmic and intercytoplasmic vacuoles also filled with erythrocytes (Mills et al., 1994). Immunochemistry reveals that angiomatoid anaplastic thyroid cancers express epithelial markers but lack endothelial ones. This assists in distinguishing them from other thyroid angiomatoid carcinomas, that typically express endothelial biomarkers. However, this differential diagnosis is often very challenging due to the similarity of both tumors histological and clinical features (Cutlan et al., 2000) .

The osteoclastic variant of ATC is characterized by the presence of multinucleated, non-neoplastic, osteoclast-like giant cells (OCL-GC) interspersed in an undifferentiated cell population. The tumor can also demonstrate OCL-GC and neoplastic cells coating cavernous blood-filled channels. OCL-GC can have numerous (up to 100) round to ovoid nuclei, never showing mitotic figures, and abundant, dense eosinophilic cytoplasm. They are positive for CD68, a histiocytic cell marker, which

supports their non-neoplastic nature. Furthermore, they are thought to be part of monocyte/histiocytic lineage, derived from mononuclear cell fusion. Important differential diagnosis of this variant includes papillary thyroid carcinoma with pleomorphic tumor giant-cells (PTC-PC) and giant cell tumor of thyroid cartilage (Bantumilli et al., 2022; Gaffey et al., 1991; Mathur et al., 2022). Even though background necrosis and inflammation are widely seen on ATC, it is reported to be minimal or absent with this phenotype (Talbott & Wakely, 2015).

Histological type is not thought to affect prognosis, however recent findings suggest tumors with pleomorphic giant cell variant might have a more aggressive nature (Yang & Barletta, 2020).

On macroscopic examination, the tumor is often large and extends outside the thyroid. On cut section, ATCs are typically light tan and fleshy with zones of hemorrhage and necrosis (Abe & Lam, 2021; Lloyd et al., 2017).

Immunohistochemistry is essential in the diagnosis of Anaplastic Thyroid Carcinoma since it aids in the differential diagnosis of other forms of thyroid cancers and other non-neoplastic and neoplastic diseases that show similar histological features, but express different markers. (Lloyd et al., 2017).

Thyroid-specific proteins, like thyroglobulin and thyroid-lineage markers, such as thyroid transcription factor 1 (TTF-1) are usually negative, reflecting the loss of thyroid differentiation by the neoplastic cells (Bible et al., 2021). TTF1 is only expressed in lung, diencephalon and in thyroid follicular cells, being present in the nucleus of the latter, where it helps in the regulation of thyroid gene expression of thyroglobulin, thyroid peroxidase, TSH receptor and the sodium/iodine symporter. There is controversy surrounding thyroglobulin immunoreactivity, as some tumors might be positively marked. A potential justification might be the release of thyroglobulin from entrapped non-neoplastic follicular cells and subsequently diffusion into the cytoplasm of malignant cells, resulting in a false negative reactivity (Molinaro et al., 2017). Nonetheless, it can be positive if there is a squamoid component or a coexisting differentiated tumor (Talbott & Wakely, 2015). Significant expression of both these markers indicates thyroid differentiation and implies an alternative diagnosis might be

more suitable (Bible et al., 2021). According to Nonaka et. al's research, thyroid transcription factor 2 (TTF-2) was seen in 7% of their ATC cases, they concluded it had no greater utility than thyroglobulin does, for anaplastic carcinoma (Nonaka et al., 2008).

Paired-box gene 8 (PAX-8) is another thyroid-lineage marker, and up to 79% of anaplastic thyroid cancers show a positive reaction. This percentage differs between different phenotypes, showing 100% reactivity in the epithelial variant, while in the sarcomatoid variant, only 50 to 58% are positive (Jin et al., 2016) . PAX-8 is expressed early in the thyroid gland development and can be detected in benign thyroid follicular cells, as well as in other carcinomas, such as renal cell carcinoma, ovarian carcinoma, and pancreatic neuroendocrine tumors, making them potential differential diagnosis. However, thyroid involvement is not commonly seen in these cases. (Abe & Lam, 2021; Talbott & Wakely, 2015). Thus, this marker is highly valuable in offering proof of follicular cell origin in the setting of an undifferentiated thyroid neoplasm, supporting the diagnosis of ATC, making PAX-8 antibodies the most useful ones currently available to recognize this pathology (Bible et al., 2021; Jin et al., 2016). It's also important to notice that polyclonal antibodies against the N-terminus of PAX-8 show a cross-reaction with the N-terminus of PAX-5, a B-cell lineage marker, expressed in B cells and some large B cell lymphomas (Talbott & Wakely, 2015).

This undifferentiated thyroid neoplasm usually shows a high Ki-67 proliferative rate of over 30% (that is, > 30% of nuclei are positive for Ki-67) and positive p53, expression (up to 70%), in contrast to well-differentiated thyroid carcinomas. p63 is reported to be positive in 71% of cases (Abe & Lam, 2021b; Bible et al., 2021; Talbott & Wakely, 2015). BRAF mutations are commonly seen on ATC, ranging from 40 to 70%, in different studies. Immunohistochemical detection of the most common BRAF mutation, BRAF V600E, is specific and sensitive and can support the diagnosis of ATC. This finding also suggests the potential use of targeted BRAF inhibition as a treatment option for ATC (Bible et al., 2021).

Staining for cytokeratins is helpful in supporting the epithelial nature of ATC, since its positivity strongly supports this diagnosis. However, a negative immunostaining for these markers does not exclude this carcinoma. (Molinaro et al.,

2017). Cytokeratin is reported to be positive in 47% to 100% of cases. These variations in the degree of immunoreactivity are thought to be due to technical factors (antibody type, method of antigen retrieval and number of different cytokeratins) (Fletcher, 2013; Molinaro et al., 2017). Epithelial membrane antigen (EMA) is positive in about 50% of cases, and Carcinoembryonic antigen (CEA) is positive in about 10%, both typically highlighting squamoid cells. As for Vimentin, it is positive in 50% to 100%, being specially expressed in tumors with spindle cell components. (Fletcher, 2013; Talbott & Wakely, 2015). ATC does not stain calcitonin and neuroendocrine markers. Some special cases might show focal reactivity for factor VIII-related antigen, raising suspicion for focal endothelial differentiation (Fletcher, 2013). In a study conducted by Ragazzi et. al they showed muscle actin, p63 and p16 were more positive in anaplastic thyroid cancer than in differentiated component. While the opposite was observed for TTF-1, pankeratin and PAX-8 (Abe & Lam, 2021).

6.3. Molecular testing

Even though none of the genetic alterations found in ATC are disease-specific, molecular profiling might be useful in aiding histopathologic diagnosis. According to the latest (2021) Guidelines of the American Thyroid Association for Management of Patients with Anaplastic Thyroid Cancer, it is recommended to perform molecular profiling at the time of ATC diagnosis to guide decisions related to the use of targeted therapies (Bible et al., 2021). The most common mutations should be searched in ATC specimens, these include BRAFV600E, TERT promoter, RAS and TP53 mutations, as well as targetable abnormalities such as NTRK and ALK rearrangements (Filetti et al., 2019), which are discussed in another section.

6.4. Imaging

Radiological imaging should be performed for complete tumor staging needed for prognostic and treatment purposes, such as surgery planning. These radiological interventions should be performed before treatment. However, they should not delay

any urgent therapeutic interventions and should be scheduled afterwards (Bible et al., 2021; Keutgen et al., 2015).

Neck ultrasound is useful as it offers a quick evaluation of the primary thyroid tumor, its extension and invasion, as well as involvement of central and lateral nodal chains (Bible et al., 2021; Haddad et al., 2022). The sonographic appearance is nonspecific, and it usually shows a large hypoechoic, solid mass with vascularity, irregular structure with local invasion, suggestive of a malignant lesion (Ahmed et al., 2018; Chintakuntlawar et al., 2019).

Initial radiological tumor staging should include Computed tomography (CT) scans with contrast of the neck, chest, abdomen, and pelvis. In alternative, a Magnetic Resonance Imaging (MRI) using gadolinium contrast might be performed (Bible et al., 2021).

On CT scans, anaplastic thyroid carcinoma normally resembles a relatively large mass that is isodense or slightly hyperdense relative to skeletal muscle. Most cases show extensive calcifications and necrosis, which raises the concern of a high-grade neoplasm. It is important to differentiate ATC from thyroid lymphoma and CT might show diagnostic clues to help in their differentiation. Thyroid lymphoma is rarely calcified or necrotic, whereas ATC frequently shows both features. Multinodular goiter appears on CT as multiple regions of decreased density often accompanied by dense calcifications randomly scattered throughout the thyroid. In a patient with symptoms of obstruction or a rapidly enlarging neck mass, with radiological evidence of an invasive isodence or hyperdense mass in the thyroid gland, presence of calcification and or/necrosis, paired with no indication of Hashimoto's thyroiditis, the most likely diagnosis is ATC. When ATC is suspected, multiple aspirates should be sampled from different parts of the remaining solid portion of the tumor. Lymph nodes metastasis in the majority of cases are necrotic, in contrast, cystic nodes are rarely found in ATC and are likely related to coexistent DTC lymph node disease. CT was found to be superior vs physical examination in finding lymphadenopathies (Ahmed et al., 2018; Takashima et al., 1990).

When available, 18-Fluorodeoxygluocose (^{18}FDG) PET-CT is the preferred method for evaluating distant metastases and accurately stage the tumor (Bible et al., 2021). This molecular imaging technique uses a radiotracer (^{18}FDG), which is a glucose analogue, to visualize glucose consumption in tumor cells, whose uptake is through GLUT1 expression (Kim et al., 2021). PET imaging was also found to be more sensitive and efficient than other methods in detecting therapeutic responses in ATC (Chintakuntlawar et al., 2019). According to Kim *et al.*'s findings, FDG uptake is a significant prognostic factor for survival of patients with ATC, with higher tumor uptake being linked to a poorer prognosis. PET parameters such as SUVmax (Standardized Uptake Value Maximum - used to quantify FDG uptake in PET studies), MTV (metabolic tumor volume – quantifies the volume of tumor with abnormal glucose metabolism) and TLG (total lesion glycolysis – represents the total amount of FDG uptake by the tumor cells) were more reliable and significant prognostic factors than tumor size or stage (Kim et al., 2021).

When compared to normal total body CT, ^{18}FDG PET-CT appears to be more accurate for the detection of distant metastasis (Keutgen et al., 2015). Although MRI and CT scans are both effective in identifying bone lesions in a specific area, they are less useful when used for general skeletal screening. Plain radiographs that include long bones can also be used to screen the entire skeleton, but they can be time-consuming, distressing and trigger pain among patients with symptomatic metastases (Bible et al., 2021).

If PET/CT is not available, a bone scan/bone scintigraphy can be used instead. For the assessment of brain metastasis, if clinically relevant, brain MRI and CT scans are more sensitive than FDG PET scans, with MRI being the most preferable choice. Ideally, MRI should be performed before initiating systemic therapy, as part of ATC initial staging (Bible et al., 2021).

6.5. Laboratory Evaluations

Laboratory analyses are required to characterize the physiological status of the patient. These include: complete blood count with differential, to assess hemoglobin,

adequacy of platelets and exclusion of active infection or tumor lymphokines production (indicated by leukocytosis) or immunodeficiency (indicated by leukopenia); electrolyte panel (including calcium and phosphorus), to detect electrolyte abnormalities and exclusion of calcium homeostasis alterations; coagulation studies (including PT and aPTT) for exclusion of coagulation abnormalities; blood type, in case for an eventual blood transfusion (considering the technical difficulties of surgical resection of ATC); thyroid function tests (fT4 and TSH) to assess thyroid function, and thyroglobulin, for exclusion of concomitant DTC; blood urea nitrogen, creatinine, liver function tests and blood glucose (Bible et al., 2021; Keutgen et al., 2015; O'Neill & Shaha, 2013).

6.6. Additional investigations

Fiberoptic laryngoscopy is the best method to assess vocal cord mobility, and direct tumor involvement in the larynx and upper trachea. This exam should be performed in every patient diagnosed with ATC both at presentation and whenever needed based on symptomatic changes (Bible et al., 2021).

If there are symptoms suggestive of tumor involvement of the esophagus or the trachea, esophagogastroduodenoscopy and/or bronchoscopy can be considered to visualize direct tumor invasion, respectively (Keutgen et al., 2015).

Given the tumors frequent involvement of the esophagus, patients should also undergo evaluation of nutritional status for the consideration of enteral or parenteral nutritional support (O'Neill & Shaha, 2013).

Biopsies of distant metastasis aren't usually necessary if material from the primary lesion is sufficient for a diagnosis and molecular testing. Nonetheless, it's important to consider ATC can coexist with different cancers (differentiated thyroid carcinomas and/or non-thyroid neoplasms) and these metastases might not arise from the undifferentiated carcinoma (Bible et al., 2021).

6.7. Differential diagnoses

A diagnosis of ATC should be immediately suspected in any patient that presents with a rapidly enlarging thyroid gland mass. In most cases, these masses will turn out to be either ATC or a primary thyroid lymphoma (Bible et al., 2021). Given its poor prognosis, a correct diagnosis is crucial, since it requires prompt and appropriate treatment (Chintakuntlawar et al., 2019).

Poorly differentiated thyroid cancer (PDTC): PDTC is the most frequent and difficult differential diagnosis of ATC (Bible et al., 2021). PDTC is thought to be an intermediate lesion between differentiated thyroid carcinomas (papillary and follicular) and undifferentiated (anaplastic) thyroid carcinoma, as it shows intermediate histologic and biologic features of both types of tumors. Its diagnosis follows the Turin consensus criteria, meaning it must show follicular cell derivation; a solid, trabecular, or insular pattern; absence of conventional nuclear features of papillary thyroid cancer; and at least one of the following: significant mitotic activity (≥3 mitoses per 10 high-power fields), tumor necrosis, or convoluted nuclei (Lloyd et al., 2017). Unlike ATC, PDTC exhibits limited evidence of follicular cell differentiation, such as abortive follicles in some areas, its cell population lack substantial pleomorphism or marked atypia of the nuclei, shows less prominent necrosis and its immunoreactivity for thyroglobulin and TTF-1 (Fletcher, 2013; Molinaro et al., 2017).

Differentiated thyroid neoplasms: Both benign and malignant thyroid lesions can contain atypical cells that might manifest as single or small cell groups displaying some degree of pleomorphism and marked nuclear hyperchromasia (Talbott & Wakely, 2015). Differentiated thyroid neoplasms are typically immunoreactive to pan-cytokeratins, thyroglobulin, TTF-1 and PAX-8, and exhibits a low Ki-67 proliferative rate of under 5% (Bible et al., 2021). Taken together with the information presented in the preceding immunochemistry of ATC section, these findings enable an accurate diagnosis of undifferentiated carcinoma.

Squamous cell carcinoma (SCC) of the thyroid: This is a rare thyroid disease, corresponding to less than 1% of thyroid cancer. Historically, it was classified as a variant of anaplastic thyroid carcinoma due to its similar clinical presentation and

prognosis, as well as its microscopic similarity to the squamoid variant of ATC. However, the most recent WHO Classification of tumors of Endocrine organs recognizes it as a separate identity. In some cases, a longstanding thyroid disease, like Hashimoto's thyroiditis is present. A coexistent differentiated carcinoma is indicative of ATC, whereas chronic lymphocytic thyroiditis with squamous metaplasia is more supportive of SCC. The cancer shows a Ki-67 level greater than 30% and immunoreactivity to pan-cytokeratins, like undifferentiated thyroid carcinomas, although, it's negative for PAX-8 (Bible et al., 2021; Lloyd et al., 2017).

Medullary thyroid cancer (MTC): Medullary thyroid cancer can display bizarre and highly atypical cells that bear resemblance to anaplastic thyroid carcinoma (Fletcher, 2013). Immunoreactivity for MTC markers, like calcitonin, chromogranin, synaptophysin, and CEA, are useful in the distinction of these two entities. PAX-8 can be weakly positive in some MTC cases (Bible et al., 2021; Talbott & Wakely, 2015).

Lymphoma: Lymphomas, especially diffuse large B cell lymphomas, might manifest as a rapidly enlarging thyroid mass with compressive symptoms, mimicking the presentation of ATC. This tumor can also exhibit an infiltrative nature, replacing the follicular epithelium, and invading vascular structures (Fletcher, 2013). Cross-reactivity with PAX-5 and PAX-8 antibodies can contribute to a wrongful diagnosis, as previously stated, even though lymphomas are PAX-8 negative (Talbott & Wakely, 2015). In fact, in the past, some cases of thyroid lymphoma were misdiagnosed as ATC (Abe & Lam, 2021). Lymphoid markers, such as CD45, CD20 and PAX-5 can aid in the differential diagnosis (Bible et al., 2021).

Malignant melanoma: Malignant melanoma frequently affects the thyroid gland and epithelioid, spindle and pleomorphic cells on smears may resemble ATC's morphology. SOX-10 staining is positive in about 78 to 100% of metastatic spindle cell melanomas, and negative in all thyroid carcinomas, making it a useful marker for this specific phenotype. Other melanocytic markers include Melan-A, HMB-45, and S-100 (Talbott & Wakely, 2015).

Angiosarcoma (AS): Angiosarcoma is very similar to anaplastic thyroid cancer. Both of their prognoses are similarly poor, they can have overlapping morphology,

especially with ATC angiomatoid variant, and immunochemistry, as both are often vimentin positive; ATC may express endothelial markers and angiosarcoma can even express cytokeratin. In fact, the nature of angiomatoid tumors of the thyroid has long been debated, and some pathologists even deny the existence of true primary thyroid angiosarcomas, considering them as anaplastic tumors with an angiomatoid appearance. However, in the latest WHO Classification of Tumors of Endocrine Organs, primary Angiosarcoma is acknowledged as an independent entity. Based on immunophenotypic findings, these tumors can be divided into primitive AS, if the tumor shows endothelial differentiation; epithelioid AS if the tumor also expresses CK; angiomatoid carcinoma: if the tumor expresses both endothelial and epithelial markers and thyroglobulin; and anaplastic carcinoma with an angiosarcoma-like appearance, if the tumor does not express endothelial markers (Njim et al., 2008).

Carcinoma showing thymus-like differentiation (CASTLE): Previously discussed together with lymphoepithelioma-like variant of ATC.

Other neoplasms: Other tumors that mimic ATC include parathyroid carcinoma, metastatic carcinomas from other sites and other primary thyroid sarcomas (Fletcher, 2013; Molinaro et al., 2017; Talbott & Wakely, 2015).

Benign conditions: As previously discussed in the preceding section, benign conditions, such as acute thyroiditis and Riedel's thyroiditis can be misdiagnosed as ATC.

7. CARCINOGENESIS

Thyroid carcinomas can be divided into two main groups based on their cell of origin. Follicular-cell-derived carcinomas compose the vast majority of thyroid tumors (>95%) and are subdivided in papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), poorly differentiated carcinoma (PDTC), and anaplastic thyroid carcinoma (ATC). The other main group is composed of tumors of c-cell-derived carcinomas, known as medullary thyroid carcinomas (MTC). Other rarer types of thyroid carcinomas can be found, such as thyroid lymphomas, sarcomas, etc (Lloyd et al., 2017; Tirrò et al., 2019).

Genomic studies are particularly difficult in ATC given its extensive infiltration by macrophages. As stated before, tumor-associated macrophages (TAMs) form an intimate and dense network inside the anaplastic tumor, connecting directly with neoplastic cells. Therefore, physical separation of both of these cells is not possible, even with microdissection of tissue samples (Landa et al., 2016). Consequently, its crucial to consider TAMs' genetic background when examining ATC samples (Saini et al., 2019).

Regarding thyroid cancer mutational burden, anaplastic thyroid carcinoma exhibits the higher number of mutations, followed by PDTC, and lastly, well-differentiated thyroid carcinomas (Landa et al., 2016). ATCs have an approximately sixfold increase in tumor mutational burden when compared to WDTCs (Bible et al., 2021).

Despite being considered of follicular origin, ATC does not maintain a follicular architecture, contrarily to differentiated thyroid carcinomas. Loss of expression of thyroid differentiation markers is a hallmark of this type of neoplasm. Analyses comparing transcriptomic profiles of PTC and ATC revealed repression of thyroid differentiation, with silencing of thyroid-specific genes (such as thyroglobulin, sodium iodine symporter [NIS] and thyroid-stimulating hormone receptor [TSHR], and others), and activation of epithelial-mesenchymal transition (EMT), discussed in a following section (Landa et al., 2016; Tirrò et al., 2019).

Several genomic alterations involved in ATC carcinogenesis have been found, and these include, activation and inactivation of genes, perturbations in signaling pathways, chromosomal rearrangements, copy number alterations and gene amplifications, and epigenetic modifications.

7.1. Genomic alterations in ATC

7.1.1 Genetic mutations

TP53 and TERT mutations. Inactivating TP53 mutations constitute a genetic hallmark of ATC (Haroon Al Rasheed & Xu, 2019). TP53 is a tumor suppressor transcription factor that regulates cell cycle and apoptosis (Tirrò et al., 2019). Its prevalence is roughly 58% and its often found in BRAF-mutated ATCs (Molinaro et al., 2017). Telomerase reverse transcriptase (TERT) is the most commonly mutated gene in anaplastic thyroid cancer. It encodes the reverse transcriptase component of the telomerase complex (Molinaro et al., 2017) and its promoter mutations lead to increased telomerase activity. It is present in 73% of ATCs and is considered a clonal mutation for this carcinoma. TERT mutations can co-occur with BRAF and RAS mutations (Harron Al Rasheed & Xu, 2019; Tirrò et al., 2019). Both TP53 and TERT mutations are frequently found in ATC, less commonly in PDTC and more rarely in WDTC, suggesting that both mutations are a late event in thyroid cancer progression and essential for anaplastic transformation (Bible et al., 2021; Haroon Al Rasheed & Xu, 2019). In addition, DTCs with TERT mutation are associated with a poorer prognosis (Tirrò et al., 2019).

Tumor suppressor genes. Thioredoxin-inter-acting protein (TXNIP) gene is considered a tumor-suppressor whose transcription is negatively regulated by PPAR-γ, that shows, in ATC cells lines, an increased expression leading to TXNIP down-regulation in these cells (Morrison et al., 2014; Saini et al., 2019). Interestingly, the role of PPAR-γ in tumorigenesis is controversial and highly debatable, with some studies considering PPAR-γ as a tumor-suppressor gene that conducts antitumorigenic activities with lower expression in anaplastic thyroid carcinoma (Morrison et al., 2014; Wood et al., 2011). ATM is a cell-cycle checkpoint and DNA damage response gene found in 9% of ATC cases. Tumors with this mutated gene exhibited a higher mutation

burden in comparison to non-mutated gene tumors, in line with this gene's function in DNA repair (Landa et al., 2016). RASAL1 is a tumor suppressor gene that encodes RAS GTPase-activating protein (RasGAP) and functions as a catalyzer in RAS inactivation by hydrolyzing its GTP-active to its GDP-inactive form. Both mutations (17%) and hypermethylation of this gene, leading to its silencing, have been described in ATC, and are mutually exclusive. RASAL1 inactivation was also found to be mutually exclusive with activating mutations of the RAS pathway genes (Ngeow & Eng, 2013). Mutations in other tumor suppressor genes, like RB1, MEN1, NF1 and NF2 have been found in patients with ATC (Haroon Al Rasheed & Xu, 2019).

Genes involved in the cell cycle. Mutations and copy number alterations in genes involved in the cell cycle, like CDKN2A and CDKN2B are present in about 20% of ATC specimens (Bible et al., 2021; Yang & Barletta, 2020).

DNA replication and epigenetic regulation gene mutations. 12% of cases exhibit mutations on the DNA-mismatch repair (MMR) pathway, like MSH2, MSH6 and MLH1. Tumors containing MMR alterations displayed a "hypermutator phenotype". Histone methyltransferases (HMTs) genes are altered in 24% of ATCs, including KMT2A, KMT2C, KMT2D, and SETD2. Mutations in genes that encode various components of the SWI-SNF chromatin remodeling complex were found in 36% of ATCs. Since the impairment of a single protein in this complex is usually sufficient to impair its function, mutual exclusivity of mutations was observed among this group of genes (Landa et al., 2016). Specific histone deacetylase (HDAC) subtypes are associated with different thyroid cancer characteristics and behavior (Tirrò et al., 2019).

Mutation in receptor tyrosine kinases. Mutations in receptor tyrosine kinases (RTKs), like EPHA3, EGFR, VEGFR1-3 and NOTCH1-4 were also found in a small population of anaplastic thyroid carcinomas (Landa et al., 2016).

Other gene mutations. Eukaryotic translation initiation factor 1A (EIF1AX) mutations are associated with anaplastic progression of thyroid carcinomas (Molinaro et al., 2017) and they cause a defective formation of the 43S pre-initiation complex for protein translation. It occurs in 9% of ATCs and is strongly related with RAS mutations (Tirrò et al., 2019). Isocitrate dehydrogenase 1 (IDH1) mutation is found in 11% of

ATCs. Others considered 'novel ATC genes' have been identified in recent investigations (Molinaro et al., 2017). However, due to their very low frequency, they were excluded from this review.

7.1.2. Alterations in signaling pathways

Alterations in PI3K/AKT/mTOR pathway. PI3K is connected to a receptor tyrosine kinase (RTK) and upon growth factor ligation, becomes activated and phosphorylates PIP2 in PIP3. This starts a cascade activation of PDK1 and AKT. The phosphorylated AKT, pAKT, can then activate several other effector molecules, such as mTOR and caspase-9, that act is promoting cell proliferation, migration and invasion, and negatively impact apoptosis (Saini et al., 2019). PI3KCA gene codes for the alpha-subunit of PI3K and mutations lead to activation of its protein expression. PIK3CA alterations happen in about 18% of ATC cases (Tirrò et al., 2019). PTEN is a tumor suppressor gene, and its protein catalyzes the conversion of PIP3 to PIP2, thus negatively regulating this pathway. This proteins' inactivation leads to constitutive activation of this pathway. Its frequency increases with thyroid tumor progression and is seen in 15% of ATCs.

Alterations in MAPK pathway. Following ligand biding, this pathway triggers a series of phosphorylation of RAS, RAF, MERK, ERK, which in turn translocate to the nucleus and activates genes involved in proliferation, angiogenesis, and metastasis. The most frequent alteration in BRAF is the V600E substitution, in which valine (V) is substituted by glutamic acid (E) in the 600^{th} amino acid, triggering constitutive activation of this proto-oncogene (Tirrò et al., 2019). This mutation is present in 45% of ATCs. RAS family includes three genes, NRAS, HRAS or KRAS. Mutations in either of these genes lock RAS in its active GTP-bound form, leading to constant activation of this pathway (Tirrò et al., 2019), and happen in 28% of cases. Mutations involving BRAF and RAS genes are mutually exclusive in ATC (Landa et al., 2016). They both are considered driver mutations that occur in early tumorigenesis (Haroon Al Rasheed & Xu, 2019), accordingly being most commonly found in WDTC. BRAFV600E is most frequently observed in classic PTC and tall cell variant PTC (Bible et al., 2021).

Alterations in the WNT pathway. Canonical Wnt/β-catenin pathway is a very important part of epithelial-to-mesenchymal process, operating during embryogenesis, wound healing, and carcinogenesis. Normally β-catenin is bound to a destructive complex composed of GSK3β, AXIN1, APC and CKI and it is actively marked for ubiquitin-degradation, through phosphorylation by CK1 and CSK3β. However, when Wnt molecules connect to its frizzled receptor, β-catenin dissociates from the other components of this complex, accumulates in the cytoplasm and is able to translocate to the nucleus where it regulates genes connected to cell proliferation and angiogenesis, and transcription factors involved in EMT (Saini et al., 2019). Mutation of genes encoded in this pathway, CTNNB1 (β-catenin), AXIN1 and APC, are hallmarks of less differentiated thyroid carcinomas. CTNNB1 transcription factor mutations (>60% of cases) (Tirrò et al., 2019) occur in sites of catalyzation by CK1 and GSK3β, preventing its phosphorylation by said factor, resulting in stabilization of β-catenin (Sastre-Perona & Santisteban, 2012).

Alterations in the Sonic hedgehog (SHH) pathway. SHH is a protein acting as a ligand for its Patched1 (PTCH1) receptor. This binding leads to detachment of SMO from the receptor to activate Gli1, which subsequently translocate to the cell nucleus act on genes like Snail and E-Cadherin, involved in the epithelial-to-mesenchymal transition. Although it doesn't appear to be a primary driver for ATC tumorigenesis, it contributes to anaplastic transformation. In ATC cells this pathway is induced either by a non-canonical way through the RAS/BRAF/MEK pathway or by a paracrine response to extracellular-produced SHH (Saini et al., 2019).

Alterations in the NF-κB pathway. This pathway is activated in inflammation via numerous growth factors, cytokine, and Toll-like receptors. In normal conditions, NF-kB exists in its inactive form in the cytosol, bound to its negative regulator, phosphorylate inhibitor of kB, IkB. Different kinds of kinases, depending on the type of receptor that triggered this activation, result in the phosphorylation of IkB, marking it for proteasomal degradation. The newly freed NF-kB moves to the nucleus and activates transcription factors involved in inflammation, cell, survival, growth, and proliferation. In thyroid cancer, BRAFV600E is known to directly phosphorylate IkB promoting this pathway. For example, in anaplastic thyroid carcinoma, receptor CCR6,

through the binding of its ligand, CCL20, leads to activation of this pathway and contributing to this neoplasm migration and invasion. NF-kB also enhances the oncogenic potential and resistance to drug-induced apoptosis in ATC cells (Saini et al., 2019).

Alterations in the NOTCH pathway. After binding of its ligand, Notch receptor is cleaved by γ-secretase and releases its NOTCH intracytoplasmic domain (NICD) that moves to the cell nucleus, where it acts to form a transcription complex with other factors, positively regulating the transcription of genes involved in cell differentiation (Saini et al., 2019). Interestingly, its role in thyroid cancer is controversial among published studies: while some advocate its overexpression favors thyroid carcinogenesis and a worse prognosis, others claim that it acts as a tumor suppressor and its signaling is downregulated in thyroid neoplasms. Based on these contradictions, Traversi *et al.* ensured an investigation to further evaluate the role of NOTCH signaling on thyroid carcinomas, concluding that this pathway might act as a modulator, which explains at some degree, its conflicting findings encountered among bibliography (Traversi et al., 2021). Therefore, more studies are needed to truly clarify its influence in thyroid cancer and in anaplastic transformation.

7.1.3. Gene amplifications and copy number gains

ATC cells can also exhibit gene amplifications and copy number gains, as part of their genomic changes. PIK3CA and DUSP26 gene amplification has been recognized in some ATC specimens. Additionally, copy number gains have also been discovered in genes like PIK3CA, PI3KCB, KIT, PDK1, AKTQ and MET (Saini et al., 2019).

7.1.4. Chromosomal abnormalities and gene fusions

PAX8-PPARγ fusion. Peroxisome proliferator activated receptor gamma (PPAR-γ) is a nuclear transcription factor that favors cell apoptosis by activation of caspases and downregulating cell survival genes (Tirrò et al., 2019). In ATC, PPAR-γ gene commonly suffers chromosomal rearrangement with PAX-8 gene, forming a fusion

gene that encode PAX8-PPARγ fusion protein, which induces activation of Wnt/TCF signaling leading to increased invasiveness (Saini et al., 2019).

RET/PTC rearrangements. RET/PTC fusion leads to the constitutive activation of the tyrosine kinase receptor. This chimeric receptor can either directly or indirectly activate MAPK and PI3K/AKT pathways. Rearrangements of the RET with different partner genes have been identified, being the most frequent the RET-PTC1 fusion, involving the CCDC6 gene. Even though RET rearrangements are particularly frequent in papillary thyroid cancer of young patients, and in radiation-induced thyroid tumors, they have also been identified in rare patients with ATC (Tirrò et al., 2019).

ALK rearrangements. Anaplastic lymphoma kinase (ALK) can suffer both activating mutations and gene rearrangements in anaplastic thyroid carcinomas. It typically fuses with the STRN gene, encoding the STRN-ALK chimeric protein. This leads to strong activation of MAPK, PI3K and JAK/STAT signaling pathways, assisting in disease progression and aggressiveness (Bible et al., 2021; Tirrò et al., 2019).

NTRK rearrangements. Neurotrophic tropomyosin receptor kinases (NRTK) comprise a group of 3 different tyrosine kinase receptors, TRKA, TRKB and TRKC. Fusions of their respective genes with another gene partner results in an encoded fusion protein that is constitutively turned-on leading to the activation of downstream signaling pathways, such as MAPK, Phospholipase C-γ, and PI3K, depending on the type of TRK involved (Amatu et al., 2016). However, this is a rare event found in anaplastic thyroid carcinoma (Bible et al., 2021).

Chromosomal abnormalities. ATC has a very unstable genome and can exhibit numerous losses and gains of entire chromosomes, chromosome arms, or small interstitial chromosomal regions (Bible et al., 2021).

7.1.5. Epigenetic modifications

Chromatin remodeling allows for selective activation and silencing of genes. Histone methylation, carried out by Histone methyltransferases (HMTs), leads to the suppression of certain genes. In the context of anaplastic thyroid carcinoma's

carcinogenesis, down-regulated genes include those involved in cell cycle regulation, cell adhesion, apoptosis, and thyroid differentiation (like PAX-8, TSHR and PTEN). Opposingly, histone deacetylation, implemented through histone deacetylases results in gene expression of important molecules that participate in signaling pathways, like MAPK/ERK, PI3K/AKT and EMT (Saini et al., 2019).

Micro-RNAs (miRNAs) are non-coding RNAs that regulate post-transcriptional. Alterations in these small molecules can also be seen in ATC (Molinaro et al., 2017). Some miRNAs are important in controlling epithelial-mesenchymal transition are discussed in an upcoming section.

7.2. Anaplastic origin

The true origin of anaplastic thyroid carcinogenesis has not yet been identified. Currently, the most accepted theory states that ATC originates from well-differentiated thyroid carcinomas that undergo a multistep process of dedifferentiation with several genomic alterations suffering anaplastic transformation (Capdevila et al., 2018). Several observations found in numerous studies support this hypothesis, such as: (a) the concomitant existence of foci of differentiated carcinomas within the stroma of anaplastic tumors or a previous history of DTCs, in ATC patients; (b) undifferentiated tumors containing areas of DTC exhibit a higher percentage of BRAF and RAS mutations than in those that do not contain them; (c) ATC specimens with foci of DTC carrying the BRAFV600E mutation, also carry the same mutation (Molinaro et al., 2017); (d) the existence of poorly differentiated thyroid carcinomas, that appears to exhibit an intermediate lesion between both extremity lesions (Lloyd et al., 2017); (e) increasing mutation burden ranging from differentiated thyroid carcinomas and poorly differentiated thyroid carcinomas to anaplastic thyroid carcinoma (Landa et al., 2016).

Some authors even suggest that ATC might also arise from de novo or from long-standing goiters (Saini et al., 2019).

In addition, both TP53 and TERT mutations are frequently found in ATC, less commonly in PDTC and more rarely in WDTC, suggesting that both mutations are a late event in thyroid cancer progression and essential for anaplastic transformation.

To gain a deeper understanding of ATC's origins and genomic evolution, Capdevila *et al.* compared the genomic alterations of paired ATCs and Papillary thyroid carcinomas (PTCs) occurring in the same patient. From the 3 examined pairs, they observed a large genomic discrepancy between both types of tumors, as there were very few common trunk mutations. In a second analysis, gene mutations from both ATCs, and PTCs found in public data bases were comparatively analyzed. From this comparison, they came to conclusion that the gene mutations with the highest cancer-cell fraction were not the same in both types, meaning both tumors had different driver mutations, thus both tumors were largely different (Capdevila et al., 2018). However, its small sample size and exclusion of FTCs were pointed out as limitations by Dong *et al.*, which also investigated to further comprehend ATC's origins. In their study, 5 patients with coexisting ATC and well-differentiated carcinomas were analyzed. Their data revealed to be concordant with the hypothesis that ATC shares a mutual ancestor with its concurrent WDTC, with every phylogenetic analysis revealing that a significant number of somatic mutations and copy number variations were shared (Dong et al., 2018).

7.3. Epithelial-to-mesenchymal transition

Epithelial-to-mesenchymal transition (EMT) is a multiphase process in which epithelial cells undergo molecular and cellular alterations and acquire a mesenchymal phenotype. EMT represents a hallmark of cancer progression, as it plays a pivotal role in both cancer invasiveness and metastasis. This process also occurs in physiological conditions, for instance, during embryogenesis and morphogenesis of organs, also called type I EMT; and during tissue regeneration and fibrosis, named type II EMT. When addressing EMT occurring in tumor setting, its labeled as type III EMT (Baldini et al., 2021).

During this phenomenon, cancer cells dedifferentiate, lose cell-to-cell adhesion (through proteolytic digestion of receptors involved in cell-to-cell contact), undergo cytoskeleton rearrangements (gaining a fusiform appearance), start producing adhesion molecules that contribute to cell movement and release proteases that lead to incremented digestion of extracellular matrix components. They switch expression of genes from those of epithelial phenotype (such as E-cadherin, claudin, occludin and others) to genes typical of mesenchymal phenotype (like N-cadherin, vimentin, and catenin)(Baldini et al., 2021; Shakib et al., 2019).

E-cadherin is typically encountered in epithelial cells, being expressed in normal thyroid cells, with its expression diminishing alongside the progression to undifferentiated carcinomas. Its gene, CDH1, is frequently downregulated in ATC (Shakib et al., 2019). BRAFV600E, leading to overactivation of the MEK-ERK pathway, plays a significant role in inducing EMT in malignant cells. In thyroid cancer, it is capable of promoting cell invasiveness by decreasing E-cadherin expression through a Snail-dependent mechanism (Baldini et al., 2021).

Currently, it's known that cancer cells in the majority of times do not undergo a full transition to a mesenchymal phenotype and maintain some features of their epithelial origin. EMT is thereby mostly incomplete and this ability of neoplastic cells to move along the epithelial-mesenchymal spectrum is recognized as epithelial-mesenchymal plasticity (EMP) (Baldini et al., 2021).

The induction of EMT in cancer cells is influenced by numerous factors, such as cellular and humoral components of inflammation; hypoxia and induction of hypoxia-inducible factors; extracellular stimuli, growth factors (including transforming growth factor beta [TGF-β], epithelial growth factor [EGF], fibroblast growth factor [FGF], insulin growth factor [IGF], and platelet-derived growth factor [PDGF]) and binding of Wnt to its frizzled receptor. All of these factors lead to the expression of EMT-transcription factors like Zeb1 and Zeb2, Snail1 and Snail2, and Twist1 (Baldini et al., 2021; Shakib et al., 2019).

Transforming growth factor beta (TGF-β) is a cytokine involved in numerous cellular processes, such as cell growth, proliferation, and differentiation. Although its

role in cancer progression is still not clear, TGF-β is thought to drive EMT (Latar et al., 2022). TGF-β acts as a tumor repressor in the initial stages of carcinogenesis, however, in later stages it facilitates cancer growth, EMT and metastasis. This cytokine binds to its corresponding receptor and triggers a downstream activation of their corresponding signal transducers – SMADs. Smad2/3 bind Smad4 and together they move to the cell nucleus and regulate several genes. Opposingly, Smad7 acts as an antagonist for TGF-β/Smad signaling, and its induced transcription prevents TGF-β-induced MET and invasion of cancer cells (Hao et al., 2019). Interestingly, although one would think Smad7 would not be expressed in ATC, in reality, in comparison to other studied thyroid carcinomas, this undifferentiated neoplasm exhibits higher expression of this repressor (Montemayor-Garcia et al., 2013). Cerutti *et al.´*s investigation also shows a similar finding and propose that this data might suggest that overexpression of Smad7 might be associated with a loss of its inhibitory effect on TGF-β signaling, contributing to the malignant phenotype observed in ATC (Cerutti et al., 2003).

It was found that the knockdown of FOXD3, a transcription factor associated with embryonic differentiation and tumorigenesis, lead to inhibition of apoptosis, increased growth, and proliferation, promoted invasiveness and EMT of all studied ATC cell lines. FODX3 downregulation was also associated with enhanced MAPK/ERK signaling and diminished levels of E-cadherin (Yin et al., 2017).

According to Chin *et al.*'s findings, EGFR signaling and Cyr61 play a significant role in cell migration and EMT in anaplastic thyroid tumorigenesis. EGF was discovered to enhance cell migration and induce cytoskeletal rearrangements in ATC cells. Ultimately, EGF, by binding to EGFR, leads to increased levels of Cyr61 (also called CCN1, an extracellular matrix protein involved in cell adhesion, DNA synthesis, angiogenesis, and cell survival) gene expression, as well as its protein expression and secretion through the ERK/CREB signal pathway. In their investigation, EGF culminated in the expression of vimentin and reduced levels of E-cadherin in ATC cells. Adding to this, knockdown of Cyr61 resulted in increased expression of epithelial markers, decreased expression of mesenchymal ones, and reverted the cell morphology to a round epithelial shape (Chin et al., 2016).

As previously stated, mutations affecting Wnt signaling pathway are hallmarks of less differentiated thyroid neoplasms. Wnt/β-catenin constitutive activation results in the accumulation of β-catenin in the nucleus, serving as a co-activator for transcription factors implicated in both carcinogenesis and EMT (Shakib et al., 2019). In a recent study, M2-like TAMs were found to promote dedifferentiation, proliferation, and metastasis (migration and invasion) in thyroid cancer cells through synthesis and secretion of Wnt ligands, Wnt1 and Wnt3a. These acted in a paracrine way, leading to activation of Wnt/β-catenin signaling and culminating in activation of EMT-related signals. Silencing Wnt1 or Wnt3 gene expression with the corresponding shRNA, led to interruption of tumor growth and proliferation. In the same way, upon treatment with these shRNAs, thyroid neoplastic cells showed increased expression of E-cadherin and diminished N-Cadherin and vimentin levels (Lv et al., 2021).

Zinc finger E-box-binding homeobox 1/2 (Zeb1 and Zeb2) are important transcription factors that modulate the suppression of crucial regulators of epithelial polarity proteins, therefore inducing the EMT process in neoplastic cells (Shakib et al., 2019). These factors downregulate E-cadherin synthesis by binding to E-box elements in their promoter site, activating EMT. Montemayor-Garcia *et al.* demonstrated that ATC cells, in comparison to well-differentiated thyroid neoplasms and normal thyroid tissue, had higher expression of Zeb1. They also concluded that its increase expression is associated with decreased expression of E-cadherin (Montemayor-Garcia et al., 2013).

Slug (also known as Snail2) is a member of Snail zinc finger E-box binding family, regulating cell motility and EMT initiation. It acts as a transcriptional repressor and was found to be associated with loss of E-cadherin expression in some tumors. Although it is not normally expressed in thyroid tissue, it's overexpressed in thyroid neoplastic cells, with studies showing higher expression in ATC cells when compared to well-differentiated thyroid carcinomas. Twist1 is another transcriptional factor capable of binding to E-box motifs that has been observed to be highly expressed in ATC cells. It's considered a major regulator for EMT, being involved in cell migration, invasion, and resistance to apoptosis (Shakib et al., 2019).

Other factors involved in induction of ATC's EMT are S100A13 (a calcium-binding protein thar regulates protein phosphorylation, enzyme activity, calcium homeostasis, organization of cytoskeletal component and transcription factors); TUG1 (taurine upregulated gene 1 – a member of competing endogenous RNAs that interacts with miR-145 and functions as an oncogene); BAG3 (Bcl-2-associated anthanogene 3; stimulates the nuclear accumulation of β-catenin and expression of Zeb1); miR-146b (ultimately leads to E-cadherin downregulation); and Runx2 (a master regulator in embryonic differentiation). Others involved in the inhibition of this process include TBX1 (a member of the T-box family of transcription factors, it upregulates E-cadherin and downregulates N-cadherin, vimentin, and E-cadherin repressors, thereby represses mesenchymal transition); miR-30 and miR-200 (they induce suppression of Zeb1 and Zeb2; TP53 mutation was found to be able to decrease miR-200 expression) (Shakib et al., 2019).

Tumor cells can revert back to their epithelial phenotype in a reverse process called mesenchymal-to-epithelial transition (MET), leading to cell proliferation and formation of a metastatic tumor in a secondary site (Shakib et al., 2019)

8. MANAGEMENT AND TREATMENT

Different treatment modalities are available for anaplastic thyroid carcinoma patients and are discussed in this section. Treatment was widely based on the most recent American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer, released in 2021, as they provided the most recent and thorough treatment options with well-grounded explanations, and scientific rigor.

8.1. Patient communication

Given that ATC shares such a devastating prognosis, communication with the patient and respective family and providers is utterly important. Treatment options, risks (including financial costs and mental health consequences) and benefits of procedures, and possible outcomes should be realistically communicated. Conversations about end-of-life care should be initiated at the time of diagnosis, and goals of care should be determined, either therapeutic or palliative care, in accordance with the prognosis, staging, available therapies, comorbidities and, above all, patient's wishes and expectations. A clear understanding of how to manage airway should also be discussed (Bible et al., 2021; Haddad et al., 2022)

Therapies decisions should be done at the individual level, together with an expert team composed of oncologists, radiotherapists, endocrinologists, pathologists, palliative care physicians, and surgeons (Bible et al., 2021; Oliinyk et al., 2022). Nutritional and gastroenterological expertise is also required for evaluation of nutritional status and consideration of enteral or parenteral nutritional support (O'Neill & Shaha, 2013).

8.2. Surgery

A rapid and accurate staging is necessary to determine if the patient benefits from surgical intervention and the type of surgical procedure needed. Evaluation of disease extent must be done closest to the surgical intervention, given the rapid growth of the mass and the possibility of change of clinical stage. Airway and

locoregional assessments are very important in management planning, altered vocal cord mobility, as previously stated, indicates recurrent laryngeal nerve involvement, and implies greater caution in manipulation of the contralateral nerve; also, invasion of upper aerodigestive organs by the tumor significantly raises the complexity of the surgery (Bible et al., 2021).

Patients with stage IVA or IVB ATC may be surgical candidates and resectability should be based on the structures involved; the anticipation of a complete resection (R0/R1); and if resection of involved structures results in a significant morbidity or mortality. Consequently, this means, for these patients, surgery should be recommended if complete tumor resection can be achieved with minimal morbidity (Bible et al., 2021).

Simultaneously, a fraction of patients with systemic disease (stage IVC ATC) might be eligible for surgery for locoregional disease control, with a palliative intention for alleviation of pain and prevention of local complications like those resulting from compression of neck structures (Bible et al., 2021). However, risk-benefit must be carefully evaluated in these cases. On the one hand, surgery might enhance therapeutic outcomes and facilitate local control with adjuvant RT and ChT, but on the other hand, it is associated with significant morbidity and delays the initiation of systemic therapy (Oliinyk et al., 2022).

Surgical approaches to the primary tumor in metastatic ATC patients are controversial. In an effort to learn more about its role in these patients, Oliinyk *et al.* conducted a systematic literature review together with a SEER-based study and pooled analysis. From their research, surgery was found to be associated with an improved OS in ATC stage IVC. No differences were observed between total thyroidectomy and lesser extensive surgeries (subtotal/near total thyroidectomies or lobectomies), but from their pooled analysis, a tendency towards improved OS was seen for total thyroidectomy. Negative margins are associated with a survival benefit, but their pooled analysis did not corroborate it. Debulking as palliative surgery is not recommended for these patients, and it was an independent predictor for higher overall and disease-specific mortality in ATC IVC patients. Furthermore, not only do the

potential risks outweigh the benefits, but it also delays the onset of RT and systemic therapy (Oliinyk et al., 2022).

The majority of studies show that complete resection, meaning a negative (R0) or microscopic (R1) margin, is associated with prolonged disease-free survival and overall survival, even without other combination therapies. R2 resections comprise macroscopic positive margins or debulking interventions. During surgical interventions, tumor margins can be assessed through frozen section analysis, which assists surgeons in their efforts to secure a negative margin (Bible et al., 2021).

Most studies corroborate the role of surgery in improvement of outcomes in ATC. Compared to patients without surgical intervention, patients that underwent surgery show a significantly longer median overall survival (3 months vs 8 months respectively). However, these results might suffer from selection bias, given <8% patients analyzed were stage IVC ATC, which normally is not recommended for surgery, and has a worse prognosis (Bible et al., 2021).

In a systematic review evaluating the role of surgery in ATC, Hu *et al.*, contrary to previous observations, reported no significant difference in survival among patients by resection type. Therefore, according to these findings, negative margins may not afford additional survival benefit. However, these observations should be carefully interpreted given the confounding variables, different resection definitions, and biases across the different studies reviewed (Hu et al., 2017).

The most optimal surgical treatment for resectability is total or near-total thyroidectomy with lymph node resection of the lateral and central neck compartments. This is supported by the fact that close to 20% of patients with anaplastic thyroid cancer have a coexisting differentiated-thyroid carcinoma (Bible et al., 2021).

Radical tumor resections (including upper aerodigestive organ resections or major vascular or mediational resections) are of questionable benefit, even when clear margins are achieved and are not recommended given this tumor poor prognosis (Bible et al., 2021; Hu et al., 2017). A resectable tumor is defined by a tumor in which R0 or R1 margins can be obtained, therefore, this definition is highly dependent on

surgeon's experience. Resectability of ATC should be determined by preoperative imaging (discussed in the imaging section) as well as laryngoscopy and often also esophagostomy and broncoscopy (Bible et al., 2021). Invasion of mediastinal vessels or the prevertebral fascia is considered a definitive criterion for unresectability (Hu et al., 2017).

Rarely (2 to 6% of cases), a small anaplastic component can be found incidentally after surgical resection of another non-anaplastic tumor. Unfortunately, there's no data regarding either extent of thyroidectomy or the indication of neoadjuvant therapy for these incidental cases (Bible et al., 2021).

Potential complications associated with oncologic thyroid surgery consist of permanent and transient unilateral or bilateral recurrent laryngeal nerve palsy, injuries to the superior laryngeal nerve, tracheomalacia, hypoparathyroidism and fistulae (Hu et al., 2017).

8.3. External radiation and chemotherapy

Since metastization occurs early in disease setting, and this carcinoma has a rapid progression and high mortality, association therapy (surgery plus radiotherapy and chemotherapy) is very common in patients with anaplastic carcinoma and should be started as soon as possible. Even though no appropriate studies have been conducted to evaluate the best timeframe for onset of association therapy, most professionals recommend initiation of radiotherapy 2 to 3 weeks after surgery, to allow post-operative healing and so the patient is able to lie down and tolerate immobilization. As for chemotherapy, it can normally be administered sooner, 1 week following the intervention, as it requires less post-operative healing for safe administration. Additionally, this allows preparation for RT, as chemotherapy regimens (taxanes) are usually radio-sensitizing agents. However, if the patient has undergone tracheal or esophageal resection and reconstruction, initiation of adjuvant chemotherapy and radiation therapy is recommended to be postponed 4 to 6 weeks following the surgical intervention, to allow a better healing of the surgical wound and increase tolerance for the treatment (Bible et al., 2021).

The best outcomes regarding local disease control and survival in stages IVA and IVB ATC seem to be achieved by complete/near-complete surgical resection, followed by radiotherapy, sometimes in association with chemotherapy. In fact, the combination of surgery plus high-dose radiation therapy is linked to an improved survival in ATC patients and its better than surgery or radiotherapy alone (Bible et al., 2021). Consequently, it's viable to explore more aggressive interventions in patients with early-stage tumors, intrathyroidal or minimal extrathyroidal disease (Hu et al., 2017).

Although different radiation doses (≥ 40 Gy or ≥60 Gy) have been mentioned across different references, studies seem to be consistent with the fact that higher radiation doses lead to prolonged survival in comparison to lower doses (Bible et al., 2021; Filetti et al., 2019). In opposition, palliative radiation doses are usually between 20 and 30 Gy (Oliinyk et al., 2022).

Patients with unresectable disease or have had R2 resection and don't have metastatic disease with good performance status can be offered an aggressive radiotherapy approach for local disease control. In similarity with written earlier, higher radiation doses are associated with longer survival. Patients with poor performance status, or decline an aggressive approach with higher radiation doses, low-dose radiotherapy may be useful in palliation and control of local disease and symptoms (Bible et al., 2021). Moreover, chemotherapy might also be considered in patients with an unresectable stage IVB tumor for local disease control (Filetti et al., 2019).

Concerning stage IVC ATCs, most commonly utilized therapies include cytotoxic chemotherapy, with or without radiation therapy, as well as immunotherapeutic approaches and targeted therapies, if key mutations are found (Oliinyk et al., 2022). Patients and their families should be inquired if they desire or not aggressive care. If not, patients should be directed for the best supportive care. If chosen an aggressive option patients can undergo either palliative cytotoxic chemoradiotherapy and/or radiation as well as systemic therapies (Bible et al., 2021).

Radiotherapy treatment volume in ATC patients is usually very large, posing a greater risk for toxicity as radiation is used in wider areas. Consequently, reducing treatment-associated toxicities is of great concern. Toxicity seems to be similar to other head and neck tumor treatments, and sometimes might be mistaken by symptoms of the tumor itself. Acute toxicity includes skin erythema, xerostomia, and desquamation and mucositis of the esophagus, trachea, and larynx. Late toxicity comprises skin telangiectasias and pigmentation, soft tissue fibrosis, lymphedema, esophageal and tracheal stenosis, with the latter being a rare event (Bible et al., 2021).

Intensity-modulated radiation therapy (IMRT) is the recommended approach as it minimizes radiation exposure to surrounding healthy tissues, including spinal cord, larynx, esophagus brachial plexus and salivary glands. This technique is supported by strong evidence showing its effectiveness in reducing toxicity in other head and neck cancers (Bible et al., 2021). Another possible method consists of hyperfractionated radiotherapy, in which the total dose of radiation is divided into smaller doses and is given more times a day (Molinaro et al., 2017). It increases response rate and has a shorter complete treatment time, which can theoretically reduce the risk of tumor cell repopulation. On the downside, it poses an increase physical toxicity and financial burden (Bible et al., 2021).

Cytotoxic chemotherapy has been the primary treatment for metastatic disease in ATC. Despite so, it has disappointing results, with low response rates and carries high toxicity for the patients, with corresponding loss of quality of life (Filetti et al., 2019). Trimodal treatment, however, was associated with longer survival than bimodal therapy (without chemotherapy) in patients with stage IVA and IVB, and even in patients with metastatic disease, but this incorporation of chemotherapy has been less well studied (Bible et al., 2021).

According to the American Thyroid Association, recommended regimens consist of single-agent therapy with taxanes or in combination with either anthracyclines (doxorubicin) or platins (cisplatin or carboplatin), administered weekly. Cytotoxic therapy can be used as a bridging therapy while the patients wait for the initiation of radiotherapy and/or results regarding molecular information and novel therapeutics (Bible et al., 2021).

In the light of current evidence, surgical resection is recommended to be given first in patients with resectable disease followed by additional chemoradiotherapy. However, in patients with initial unresectable disease, chemotherapy may, in rare cases, allow for resectability, and therefore, should be considered in patients with good performance status and without significant metastatic disease (Bible et al., 2021).

Unlike other thyroid tumors, radioactive iodine (RAI) is not an effective treatment option, and its use is not recommended in ATC. Despite that, in the rare event that a well-differentiated thyroid carcinoma coexists with ATC, and the anaplastic component is in complete remission and the DTC part poses a threat for the patient, RAI might be used in other to treat the DTC component (Bible et al., 2021).

8.4. Approach to special ATC metastases

Surgical excision and radiotherapy are viable options for managing brain metastasis. Complete removal of the lesions yields greater survival compared to partial removal. Surgical intervention not only enhances quality of life but also alleviates neurological symptoms. However, there's no published evidence supporting the effectiveness of systemic therapy in treating brain metastases arising from ATC. Patients experiencing mass effect should receive dexamethasone treatment. It is advised that when brain metastases are diagnosed, patients should be referred to neurosurgery and radiation oncology are recommended (Bible et al., 2021).

Symptomatic bone metastases are ideally treated with radiation therapy unless surgery becomes necessary (in cases like pathological fractures or spinal cord compression). If both radiation therapy and surgery are not suitable options, cryoablation may be considered for the management of these lesions. Vertebroplasty or other orthopedic fixations can also be considered in articulation with orthopedic surgeons and are recommended before initiation of palliative radiotherapy. The use of radiation therapy effectively reduces bone pain and pharmacological pain relief should be administered to patients. Furthermore, bisphosphonates can be prescribed as they have demonstrated efficacy in preventing, inhibiting, and delaying cancer-related skeletal complications. Denosumab, an inhibitor of RANK ligand, has also been

demonstrated to be effective in said situations. In complementation, calcium and vitamin D supplementation should be ensured as well (Bible et al., 2021).

8.5. Tracheostomy

Airway problems are very common in ATC patients. Obstruction can be mild to severe and can either be part of the initial disease presentation, develop over time or during treatment. Breathing problems can be due to extrinsic pressure on the trachea or the central part of the neck by the tumorous mass; from direct invasion of the trachea by neoplastic cells, and even cause bleeding directly into the lumen; from paralyzed vocal cords, via recurrent laryngeal nerve invasion; or from radiation therapy of the primary tumor, that causes laryngeal edema and narrowing of the lumen. Furthermore, these airway issues can be further augmented with physical exertion and upper airway infection (Xu et al., 2015).

Any manipulation of the airway, particularly during intubation, surgical intervention or even when attempting percutaneous endoscopic gastrostomy can result in an acute airway emergency. Conservative measures to treat airway distress, like high humidification of air and corticosteroids, might help, but only temporarily and become unhelpful as disease progresses (Xu et al., 2015).

Tracheostomy is not routinely recommended by physicians and should be avoided if feasible. Although it prolongs life by overcoming acute airway obstruction, it is associated with decreased long-term survival. Possible explanations involve the use of this approach in more advanced disease (hence with lower long-term survival) and by causing delay on the onset of radiotherapy. Recommendations for this approach include acute airway distress, unresectable tumors that do not benefit from debulking or dyspnea unresponsive to corticosteroids. Also, it can be considered before radiotherapy in anticipation of laryngeal or tracheal edema. There can be continuous tumor growth around the tracheostomy stoma, leading to bleeding and, ultimately, to tracheostomy tube displacement (Bible et al., 2021; Keutgen et al., 2015).

Tracheostomy negatively affects the patient well-being and body image perception. It not only affects the patients, but also the caregivers quality of life and

increases stress levels (Bible et al., 2021). Tracheostomy tube and secretions cause discomfort and patients experience swallowing problems, requiring a feeding tube or a long-term gastrostomy (Xu et al., 2015). This procedure can result in tumor plugging, erosion and bleeding upon the placement (Keutgen et al., 2015).

This procedure can be difficult if there is an extensive tumor mass in front of the trachea, or considerate bleeding, lowering visibility and correct identification of the trachea. Insertion of a tracheostomy tube is more challenging in patients with a massive tumor, since there's a bigger distance between the skin and the trachea, occupied by the thyroidal mass (Xu et al., 2015). In this context, a wider incision through the cricothyroid membrane (cricothyroidotomy) might be performed instead. For said reasons, these procedures should be performed in an operating room under general anesthesia by experienced anesthesiologists and surgeons (Bible et al., 2021).

8.6. Novel therapies

The disappointing results of conventional chemotherapy, alone or in combination with radiation therapy for progressive ATC disease, urge the need for novel therapeutics. These targeted therapies act by blocking the activity of oncogenes that normally promote tumor growth and oncogenic transformation in this tumor (Molinaro et al., 2017). Most targeted therapies consist of small-molecule or monoclonal antibodies (Gao et al., 2023). In this section, the most commonly used targeted therapies used in ATC are outlined, together with studies evaluating their efficacy and or safety in patients suffering from this disease, together with promising therapies in need of further investigation.

As previously stated, receptor tyrosine kinases are transmembrane receptors that upon binding by its ligand trigger a downstream signaling that culminates in various cellular mechanisms, like cell growth and proliferation. In anaplastic thyroid cancer, receptor tyrosine kinases are frequently altered with aberrant signaling. Tyrosine kinase inhibitors are small molecules that can compete for the ATP-binding site of the tyrosine kinase domain or can act in an allosteric manner through binding in

a different site, rather than the active site, which induces a conformational change of the protein, affecting its activity (Molinaro et al., 2017).

According to ATA guidelines patients with ATC, who are deemed healthy enough, should be considered to enroll in clinical trials, especially those focused on target mutations. BRAFV600E is the most commonly encountered productively actionable mutation seen on ATC patients. For this reason, testing for this mutation should be done early, upon diagnosis, which can be done through immunochemistry. As for patients who do not possess BRAF V600E mutation or their mutation status is unknown and have an unresectable stage IVB disease or a metastatic disease that wish to proceed an aggressive approach, they should be encouraged to participate in clinical trials, owning to the uncommon occurrence of ATC, the limited availability of supportive data in improvement of survival and quality of life from cystemic therapies, and the need to develop evidence-based therapeutic approaches for advanced ATC (Bible et al., 2021).

8.6.1. BRAF V600E-mutated ATC TKIs

Drabafenib + Trametinib. Dabrafenib is a BRAF inhibitor and Trametinib is a MEK inhibitor, both effective in the treatment of BRAF V600E mutated carcinomas (Tirrò et al., 2019). This combination is approved by the FDA for ATC patients carrying the same mutation with metastatic disease or locally advanced with unresectable disease, but it's not yet approved by the EMA (with its only indications being for the treatment of melanoma and small-cell lung cancer harboring BRAF V600E mutation). In a study of 23 eligible patients, encouraging results were seen, as this combination therapy showed a response rate of 61%. 4% of patients had a complete response and a partial one was observed in 57% of patients; the one-year overall survival was 80%. However, results might be biased due to exclusion of worse performance-status patients (Bible et al., 2021). ROAR is a phase II basket trial that studied the effects of combination therapy of dabrafenib and trametinib in patients with BRAF V600E-mutant rare cancers. This study is still ongoing; however, it is no longer enrolling new patients. ATC cohort comprehended 36 patients and from their latest analysis update,

only 6 patients remained on the study. The other patients either died (24) or withdrawn (6) from the study. This last update confirms earlier observations that this combination has a meaningful clinical activity in BRAF V600E mutated advanced or metastatic ATC. From this additional information, this combination continued to be associated with manageable toxicity (the most common adverse effect found was pyrexia, easily manageable with temporary dose interruption), good tolerance and durable responses and survival. The overall response rate was 56%, median overall survival was 14.5 months and overall survival rate was 51.7% at one-year and 31.5% at 2 years. In support of this trial, numerous retrospective studies and case reports are concordant with the findings, further supporting this treatment. A selection bias is seen in this study, since patients only patients that could swallow the combination pill could be enrolled, limiting the enrollment of patients with dysphagia, a notorious feature of advanced ATC (Subbiah et al., 2022).

Despite these positive results, chemoradiation therapy is still the current standard for stage IVB patients. This combination therapy might be considered as a neoadjuvant approach to allow resectability (Bible et al., 2021). Accordingly, this therapeutic option is advised by both ATA, and ESMO guidelines for ATC patients harboring this mutation (Subbiah et al., 2022) and ATA guidelines recommend the initiation of dabrafenib plus trametinib over systemic therapies in eligible patients with unresectable IVB ATC or IVC ATC who decline radiation therapy (Bible et al., 2021).

Acquired resistance to BRAF inhibitors might develop in consequence to secondary mutations that lead to activation of alternative pathways (Jannin et al., 2022)

Vemurafenib. Vemurafenib is a selective BRAF inhibitor. It was evaluated in a study with only 2 in a total of 7 BRAF-mutated ATC showing responses to therapy. A combination of vemurafenib with a MEK inhibitor, cobimetinib is currently undergoing study (Bible et al., 2021). Monotherapy with vemurafenib modest efficacy can be due to reactivation of related pathways via alternative mechanisms. In a phase II basket trial using vemurafenib, the overall response rate was of 29%, which is substantially lower than the overall response rate observed in the dabrafenib plus trametinib trial (Subbiah et al., 2022). Lang *et al.* reported a case of marked partial response to

monotherapy with vemurafenib in a 78-year-old man with BRAFV600E mutated ATC. The patient maintained a response for 7 months, where the disease relapsed given development of drug resistance. The patient died 10 months after initiation of therapy (Lang et al., 2023).

8.6.2. Non-mutated BRAF V600E ATC TKIs

Larotrectinib. Larotrectinib is a TRK 1-3 inhibitor approved for solid tumors with NTRK fusion (Bible et al., 2021). In a pooled subgroup analysis of 2 clinical trials, there was a reported 29% response rate in 2 ATC patients with a median OS of 14.1 months (Jannin et al., 2022). In another pooled data analysis of 3 phase I/II clinical trials, the safety and efficacy of Larotrectinib was evaluated in patients with locally advanced or metastatic thyroid carcinomas carrying a NTRK fusion. The study contained 7 patients with ATC and the overall response rate was 29%; no complete responses were observed in the ATC subgroup, 2 patients showed a partial response, 1 had stable disease and 3 had progressive disease. In 1 patient, the best response to treatment could not be determined. Median progression-free survival was 2.2 months. And 12- and 24-month PFS were both 17%. The median OS was 8.8 months (Waguespack et al., 2022).

Entrectinib. Entrectinib is a TRK 1-3 inhibitor approved for solid tumors with NTRK fusion, in addition, it also Inhibits the ALK and ROS1 tyrosine kinases (Bible et al., 2021). In a Portuguese case report, a 51-year-old female diagnosed with ATC was put on Lenvatinib while waiting for molecular results. Thereafter, a NTRK3 fusion was found. Initial response was observed with improvement of symptoms and given the stable disease the patient was maintained on Lenvatinib for a total of 12 weeks. Following disease progression, a therapeutic switch was made to entrectinib. After 6 weeks of treatment, the tumor showed marked shrinkage on imaging studies as well as in another one performed 3 weeks later, this time with no invasion of adjacent structures. By this time, the disease was considered surgical resectable, and the patient underwent total thyroidectomy with central lymphadenectomy. Treatment

with entrectinib was continued following the surgical intervention and after adjuvant RT with concomitant paclitaxel (Damásio et al., 2022).

Selpercatinib. Selpercatinib is a selective RET inhibitor with FDA approval for patients with RET fusion thyroid cancer. In the trial that led to its FDA approval, 2 ATC patients enrolled in said study and 1 patient responded for 18 months. Use of selpercatinib is therefore recommended in clinical trial setting for patients with RET fusions (Bible et al., 2021). No approvals have been obtained in ATC patients for RET inhibitors (Jannin et al., 2022).

Lenvatinib. Lenvatinib is a multikinase inhibitor of VEGFR 1-3, FGFR 1-4, PDGFR, RET, and KIT (Bible et al., 2021). Its use has been approved in Japan following a prospective trial that showed efficacy, with 24% of ATC patients responding and an OS of 10.6 months. However, in a confirmatory phase II trial by the International Thyroid Oncology Group, it was shown to have no efficacy and the study was suspended (Bible et al., 2021; Damásio et al., 2022).

Antiangiogenic drugs pose a great bleeding risk for ATC patients. Given this disease high invasion of surrounding tissues, quick tumor shrinkage can lead to bleeding and/or fistula in these patients. Therefore, patients should be warned about these potential risks (Bible et al., 2021).

8.6.3. Immunotherapy

Programmed death receptor 1 (PD-1) is an inhibitory receptor expressed in various immune cells. Interaction of this receptor with its ligand, PD-L1 or PD-L2, leads to a negative immune regulation with immune escape of tumor cells. Several studies support a high expression of PD-L1 in ATC tissues and indicate this pathway might play a significant role in this tumor (Gao et al., 2023).

Spartalizumab. Spartalizumab is an immune checkpoint inhibitor antibody with anti-PD-1/PD-2 effects (Jannin et al., 2022). In a study with 42 ATC patients, the overall response rate was 19%. 12 patients harbored BRAFV600E mutation, and the response rate in said group was only 8% (only one patient responded). The median OS was 5.9

months in the whole cohort of patients and 40% survived longer than a year. Patients with PD-L1 expression < 1% had a median OS of 1.6 months, and no patient responded to this therapy. In patients with PD-L1 expression of 1-49%, had a response rate of 18%. As for the group with > 50% of PD-L1 expression, the reported response rate was the highest with 35% (Bible et al., 2021). This drug, however, is neither FDA- or EMA-approved and is not commercially available (Jannin et al., 2022).

Pembrolizumab. Pembrolizumab is an anti-PD-1 antibody and an option for solid tumors tumors with high tumor mutation burden (TMB-H; ≥ 10 mut/Mb) (Haddad et al., 2022). In a French study that included 16 ATC patients, the observed response rate was 25% with a median duration of response of 7.3 months (Jannin et al., 2022).

The success of immune checkpoint inhibitors therapies depends on the positive expression of PD-L1 by cancer tissues (Gao et al., 2023). In consequence, these data might lead to a systematic screening of PD-L1 status for patients with ATC. In addition, it's necessary to define a specific expression score for PD-L1 expression to match its clinical benefit (Jannin et al., 2022).

ATA guidelines recommend the use of checkpoint inhibitors in metastatic ATC patients with high PD-L1 expression without other targetable alterations (Bible et al., 2021).

CTLA-4 antagonists. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is a receptor expressed on T cells. Its ligand is a costimulatory molecule, CD80/CD86, that is expressed on antigen presenting cells. This binding transmits inhibitory signals to the T cell, leading to a negative regulation of the immune response. Anti-CTLA-4 drugs inhibit this interaction, promoting an immune response. A clinical trial evaluating a combination therapy of CTLA-4 antagonists together with PD-1 antagonists in ATC patients is currently ongoing (Gao et al., 2023).

CAR-T cell therapy. Chimeric antigen receptor T (CAR-T) cells are cells that were genetically modified to express synthetic T-cell receptors that target tumor expressed antigens. These are able to recognize and kill tumor cells and many studies have confirmed its effectiveness in killing ATC cells and in xenograft mouse models. Despite great results in preclinical settings, no clinical studies with CAR-T cells have been

performed so far, and their clinical significance needs additional investigations (Gao et al., 2023).

8.6.4. Other drugs

Everolimus. Everolimus is a rapamycin analogue that binds to an intracellular protein to form an inhibitory complex with the mTOR complex, inhibiting the activity of mTOR kinase. It also reduces the expression of VEGF (Bible et al., 2021; Yuan & Guo, 2023). Data from 3 different clinical trials including ATC patients revealed a response in only one patient in each study. In the whole thyroid cancer patient cohort, only 2 patients had a dramatic response to everolimus and through examination, a mutation was found in PI3K/mTOR/AKT pathway, underlining the important of patient selection for this pathway's mutation to be important in ATC (Bible et al., 2021). Despite the disappointing results, there have been no clinical trials investigating the use of mTOR inhibitors specifically in the context of ATC with mutations in the PI3K/AKT/mTOR pathway (Jannin et al., 2022), which suggests the importance of confirming these mutations before initiating treatment with mTOR inhibitors.

Efatutazone. Efatutazone is an orally active synthetic thiazolidinedione peroxisome proliferator-activated receptor (PPAR) agonist. It has remarkable antitumor activity in preclinical models of human ATC (Molinaro et al., 2017). It was evaluated together with paclitaxel in a phase I study in 15 patients with ATC, where safety, tolerability and efficacy were assessed. Results from this study proved that efatutazone was safe and well tolerated (Molinaro et al., 2017).

Bortezomib. Bortezomib is a protease inhibitor that upregulates NOXA, a pro-apoptotic protein that interacts with anti-apoptotic proteins of the bcl-2 family, resulting in apoptosis of malignant cells. In addition, it also suppresses the NF-kB signaling pathway, resulting in downregulation of its anti-apoptotic genes. To date, no clinical trials were conducted in humans, but in a preclinical study it was shown to induce apoptosis in anaplastic cell lines and to be synergistic with doxorubicin (Molinaro et al., 2017).

Various different drugs have been tested in clinical and preclinical settings (Abe & Lam, 2021) and table 2 shows a list of other drugs used in trials with ATC patients and in preclinical studies with ATC cell lines or models.

Drug	Biological effect	Authors and publication year	Studies details and results
Tyrosine Kinase Inhibitors			
Imatinib	Oral inhibitor of ABL, c-Kit, and PDGFR[1]	Ha *et al.*, 2010	A total of 8 patients with ATC were treated with imatinib twice daily with responses assessed every 8 weeks. 2 patients had partial responses and 4 had stable disease. Progression-free survival was 36% and the 6-month OS was 45%.[1]
Sorafenib	Oral tyrosine kinase inhibitor (TKI) of BRAF, VEGFR 1-3, PDGR, c-KIT, FLT3, RET and RAF[1,3] Possesses antiangiogenic activities[1]	Savvides *et al.*, 2013	Phase II trial involving 20 patients with ATC, where sorafenib was given twice daily. 2 patients had a partial response and 5 had stable disease. 6-month PFS was 15% and 6-month OS was 30% and 1-year OS was 20%.[1]
Pazopanib	Inhibitor of VEGFR 1-3, PDGFRα/β & c-Kit, [1] Enhances the cytotoxic effects of paclitaxel in vivo and in vitro models[1]	Bible *et al.*, 2012	No effects against ATC[1] Treatment had to be discontinued due to disease progression or severe toxicity[1]
Sunitinib	Oral inhibitor of VEGFR 1-3, PDGFRα/β, c-KIT, RET and FLT3[1] Active against activated endothelial and ATC cells in vivo and in vitro[2]	Grande *et al.*, 2013	Case report of an almost complete regression of the neck tumor mass, but no effect on distant metastasis. However, the patient died 5 months after the start of the treatment due to an upper gastrointestinal bleeding. [1]
		Ravaud *et al.*, 2017	Phase II trial with 71 advanced thyroid carcinomas that included 4 ATC patients, where 1 patient showed stable disease >12 months. 2 of the ATC patients did not undergo further radiological evaluation.[5]
Crizontinib	Second generation specific ALK inhibitor[3]	Godbert *et al.*, 2014	Case report of an excellent partial response in a 71-yo patient with ALK-rearrangement ATC[1]
Larotrectinib	Selective inhibitor of TRK[1]	Cabanillas *et al.*, 2020	A total of 7 ATC patients harboring NTRK fusion were treated with an overall response rate was 29%.[1]
Axitinib	Oral potent selective inhibitor of VEGFR1-3[1]	Cohen *et al.*, 2014	Phase II trial with 2 patients with ATC where one of the patients had a partial response. [1]
Erlotinib	EGFR inhibitor with antiproliferative effects in ATC cells both in vivo and in vitro [1]	Masago *et al.*, 2011	Case report of a patient with EGFR-mutated ATC had a good clinical response remaining progression free for > 6 months. [1]

Gefitinib	Oral inhibitor of EGFR[2]	Pennell *et al.*, 2007	Phase II trial with only one patient (in a total of 5) with ATC had stable disease after 12 months of therapy. There were no partial or complete responses observed.[1]
		Fury *et al.*, 2007	Phase I trial where the only ATC patient experienced significant partial response for about 4 months but had to withdraw from the study due to a Pulmonary embolism. [1]
Cediranib	Inhibitor of VEGFR1,2[2]	Gomez-Rivera *et al.*, 2007	Cediranib blocked tumor growth and prolonged survival in murine xenograft models in a preclinical setting.[2]
Ceritinib	2nd generation ALK inhibitor that overcomes secondary resistance[3]	Guan *et al.*, 2017	Study that shows limited efficacy of this drug in ATC patients with ALK mutations and fusions.[3]
Vandetanib	Inhibitor of EGFR, VEGFR, and RET[4] Also inhibits other TK and serine/threonine kinases[4] Possesses anti-angiogenesis properties[4]	Ferrari *et al.*, 2018	This study shows vandetanib induced apoptosis and inhibited proliferation, migration, and invasion ability of ATC cells. [4]
Anlotinib	Multikinase inhibitor of VEGFR, FGFR, c-KIT and PDGFR[4]	Gui *et al.*, 2021	Case report of a 67-year-old patient that received a combination therapy of anlotinib and sintilimab. The patient exhibited a partial response for 18.3 months. [4]
Apatinib	Inhibitor of VEGFR2, c-KIT and RET[4]	Zhao *et al.*, 2022	Phase II clinical trial that evaluated the efficacy and safety of apatinib for ATC and PDTC. The overall response rate was 41.2% and disease control rate was 88.2%. However, 64.7% of patients experienced grade 3 or higher adverse effects motivating dose reduction. It also showed that low dose apatinib plus melittin worked synergistically and can reduce the incidence of adverse effects. [4]
Monoclonal antibodies			
Cetuximab	Human-murine chimeric monoclonal antibody against EGFR [1]	Kim *et al.*, 2006	Monotreatment with cetuximab inhibited the growth and progression of ATC xenografs in mice models. [2]
Bevacizumab	IgG1 monoclonal antibody against VEGF[4]	Prichard *et al.*, 2007	Bevacizumab alone or in combination with cetuximab inhibited tumor cell growth and angiogenesis in murine orthotopic models of ATC.[4]
Other drugs			
Palbociclib	Inhibitor of CDK4/6, preventing it from forming a complex with cyclin D	Wong *et al.*, 2019	Treatment with Palbociclib in xenograft ATC models strongly inhibited ATC proliferation, but it was susceptible to developing resistance. When in combination with a PI3K/mTOR inhibitor they acted synergistically even in ATC cells that did not carry PI3K mutations. [4]

Fosbretabulin	Fosbretabulin is also known as Combrestastatin A4 phosphate (CA4P) is a synthetic prodrug of the active molecule combrestatin A4. [2] It is a vascular-disrupting agent that inhibits tubulin polymerization and selectevly acts in neovascular endothelial cells, destabilizing spindles and induces apoptosis of the neovasculature of the tumor leading to decreased blood flow[2]	Dowlati *et al.*, 2002	Phase I trial with one patient found a durable complete response, however it was associated with significant cardiovascular adverse effects. [1]
		Mooney *et al.*, 2009	Phase II study where 26 patients showed no objective responses. 7 patients exhibited stable disease. Median survival time was 4,7 months and 34% and 23% of patients were alive at 6 and 12 months, respectively. [1,2]

Table 2. Other drugs used in trials with ATC patients and in preclinical studies with ATC cell lines or models. **Sources:** [1](Lang et al., 2023); [2](Molinaro et al., 2017); [3](Tirrò et al., 2019); [4](Yuan & Guo, 2023); [5](Abe & Lam, 2021)

9. CONCLUSIONS

Anaplastic thyroid carcinoma is a rare and lethal disease that affects the elderly more commonly, having an estimated median survival time between 3 and 6 months. In recent decades its incidence has shown a global declining trend.

Suspicion should be raised in cases of a longstanding goiter that exhibits a rapid increase in size over a period of weeks. Symptoms are most commonly due to compression of cervical structures by the primary tumor and can lead to asphyxiation, being the most common cause of death in patients without treatment. Distant metastases are very frequent at initial presentation and most cases of local disease develop into a systemic disease in the course of its natural history. Given this tumor's poor prognosis, a prompt diagnosis should be established, and a multidisciplinary team made of endocrinologists, oncologists, surgeons, palliative care experts and radiologists should come together in an effort to thoughtfully guide the patient throughout the whole process. In addition, patients should be offered palliative care and comfort measures if they desire.

Recent molecular studies and next generation sequencing have allowed a clearer view on anaplastic tumor carcinogenesis, identification of altered signaling pathways and important mutations that are thought to influence this tumor's prognosis. Together, this allowed the speculation of possible molecular target therapies that target these genetic alterations. Current studies with these drugs show satisfactory and promising results, however, more studies are needed to further characterize their safety and efficacy. Alongside this tumor's rarity and its concerning prognosis, patients should be encouraged to engage in clinical trials in an attempt to fully understand their genomic alterations and to find the best treatment approaches, considering the urge for new treatments.

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