U.PORTO

FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2017/2018

Ana Sofia Gonçalves de Figueiredo

Melhoria na Abordagem do Carcinoma Anaplásico da Tiroide: novas perspetivas

New Perspectives for Anaplastic Thyroid Carcinoma Approach Improvement

março, 2018

Ana Sofia Gonçalves de Figueiredo

Melhoria na Abordagem do Carcinoma Anaplásico da Tiroide: novas perspetivas

New Perspectives for Anaplastic Thyroid Carcinoma Approach Improvement

Mestrado Integrado em Medicina

Área: Cirurgia Geral

Tipologia: Monografia

Trabalho efetuado sob a Orientação de:

Mestre Patrícia Andrea Ferreira

Trabalho organizado de acordo com as normas da revista:

Endocrine, Metabolic & Immune Disorders - Drug Targets

março, 2018

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Ana Sofia Gonçalves de Figueiredo, abaixo assinado, nº mecanográfico 201204432, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 12/03/2018

Assinatura conforme cartão de identificação:

Ana Sofia Gonçalves de Figueiredo

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Ana Sofia Gonçalves de Figueiredo

NÚMERO DE ESTUDANTE | E-MAIL

201204432 | sofiafigueiredo.94@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Cirurgia Geral

TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

New Perspectives for Anaplastic Thyroid Carcinoma Approach Improvement

ORIENTADOR

Mestre Patrícia Andrea Ferreira

COORIENTADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 12 / 03 / 2017

Assinatura conforme cartão de identificação: Ana Sofia Gonçalves de Figueiredo

Dedicatória

Um obrigada especial aos meus pais e a minha irmã pelo apoio incondicional e pela companhia na realização deste caminho pela arte da Medicina. Obrigada por me ajudarem a alcançar os meus sonhos.

New Perspectives for Anaplastic Thyroid Carcinoma Approach Improvement

Figueiredo, Ana Sofia[a], Andrea-Ferreira, Patrícia, MSc[*b]
[a]*Faculty of Medicine, University of Porto, Porto, Portugal;* [b]*Department of General Surgery, Centro Hospitalar São João, Porto, Portugal, Faculty of Medicine, University of Porto, Porto, Portugal.*

Abstract: Anaplastic thyroid carcinoma is rare but it represents the deadliest type of thyroid cancer, characterized by a rapid course. Diagnosis is usually made on a late stage, when more than half of the patients have distant metastasis. Thus, treatment options are mainly palliative and lack of efficacy. With the mutational landscape investigation and the discovery of new targets, new directed treatments are also being tried.
Considering the current tendency to be more conservative at multinodular goiter approach and some differentiated thyroid carcinomas treatment, it is very important to understand which may evolve to anaplastic cancers.
Our main purpose is to review the current information on anaplastic thyroid aetiology and risk factors which may contribute to an earlier diagnosis, and also to give new perspectives about the most recent treatment options and future directions, in particular, multikinase inhibitors, BRAF inhibitors and other directed agents aiming to stabilize the tumour growth and enable radical surgery with curative intent.

Keywords: anaplastic thyroid carcinoma, aetiology, prognostic factors, risk factors, treatment, new approaches.

1. INTRODUCTION

Anaplastic thyroid carcinoma (ATC) is a rare and lethal form of thyroid cancer. It presents with a quick progression and overall survival remains very poor. Diagnosis is usually late and local or distant metastases are frequently present (50-75%) [1], so most of the patients only receive medical treatment with palliative intent. It is therefore imperative to perform a rapid evaluation and discussion of treatment goals with a multidisciplinary team.

Several attempts have been made to identify ATC risk factors, but its aetiology essentially remains unknown. Nevertheless, the most known prognostic factors are age, sex, local tumour extension and the presence of distant metastases [2].

During the last few years, new data about its tumorigenesis suggest that ATC can develop after goitre, arise from dedifferentiation of pre-existent well-differentiated thyroid cancer (WDTC), or can develop *de novo* [3]. Recent studies relate ATC with additional mutations gain, beyond the ones usually related to most thyroid cancers, $BRAF^{V600E}$ and RAS. Identified genetic mutations are TERT promoter mutation, TP53 mutation, along with alterations in PIK3CA-PTEN-AKT-mTOR pathway, SWI-SNF complex, histone-methyltransferases, and mismatch repair genes [4].

This review aims to summarize the most recent information about ATC, risk factors and treatment, as well as to create a Portugal Universal Form to collect ATC data from all hospitals to facilitate future analyses and understanding (more information on "Apêndice").

*Address correspondence to this author at the Department of General Surgery, Faculty of Medicine, Porto University, P.O. Box: 4200-319, Porto, Portugal; E-mails: pandferreira@med.up.pt; mimed12099@med.up.pt

2. METHODS

The data used in this review was searched with "anaplastic thyroid carcinoma" as query in database MEDLINE via Pubmed®, between 01/01/2000 and 25/09/2017. From the initial search (n=1855) were selected 276 articles which title contained "Anaplastic Thyroid Carcinoma", "Anaplastic Thyroid Cancer" or "Anaplastic Carcinoma of the Thyroid". All abstracts were read resulting in 51 articles (included in this bibliography). Additionally, 17 articles were manually selected from the bibliographic analyses of the included articles.

3. EPIDEMIOLOGY AND HISTOLOGY

Anaplastic thyroid cancer is a rare form of cancer, more common in women, which accounts for 1-4% of all thyroid malignancies in Europe [5-6]. Currently, the incidence of ATC is decreasing in several countries due, in part to the early detection of small tumours related to the wide use of ultrasonography, the increase of dietary iodine and the higher detectability rate of lymphomas and mixed forms of ATC [2, 7].

The age of presentation is more advanced than in differentiated thyroid cancer, with a median age at initial diagnosis ranging from sixth to seventh decade [1-2, 8]. Besides its rarity, it has a median survival of 5 months, 1-year survival of 20% and 5-year survival varying from 5 to 14%, depending on the study [5, 8-9].

WHO defines ATC as a *highly aggressive thyroid malignancy composed of undifferentiated follicular thyroid cells* [10]. Other characteristics are necrosis, haemorrhage and

invasiveness, occupying and replacing most of the parenchyma and infiltrating the surrounding soft tissues and adjacent structures of the neck. Histologically it's divided in three major growth patterns: spindle cell, pleomorphic giant cell and squamoid. These patterns are not related with patient's outcome, except for the paucicellular variant (another rare histological variant) that has been related to a more indolent course affecting young patients [11-12].

3.1. Aetiology

ATC has an extremely high proliferative rate, easily invades the surrounding neck structures and metastasize to other organs [13]. The most common type of carcinoma to coexist with ATC is papillary thyroid carcinoma (PTC), particularly the aggressive tall cell variant, followed by oncocytic type of follicular thyroid carcinoma (FTC)[2]. Besides that, anaplastic transformation may also take place in a metastatic focus[11], again suggesting that ATC can develop from WDTC, through dedifferentiation, a complex process of multiple gains and deletions in several chromosomal regions. However, some ATC seem to arise *de novo*, suggesting a direct pathway between normal follicular cells and ATC cells [9]. This fact raises an important question "Is there a way to predict which are PTC/ FTC that will evolve to ATC?".

4. CLINICAL PRESENTATION AND STAGING

The most frequent presentation of ATC is a rapidly growing neck mass causing mechanical compression, hoarseness, dysphagia, dyspnoea, cervical pain and in fewer cases is related do cough, haemoptysis and superior vena cava syndrome [1, 14]. In Table 1, we can confirm that ATC is more frequent in the elderly, with a 60% women ratio.

In the past all diagnosed tumours were considered as stage IV. Intrathyroidal lesions (T4a), N0, M0 were categorized as a stage IVA and primary tumours with extrathyroidal extension, with or without locoregional metastasis, M0 were categorized as a stage IVB; in stage IVC the tumour had distant metastases[12]. Now, in TNM (8th edition) system staging ATC will use the same T definitions as differentiated thyroid cancer. Nevertheless, the stage groups stayed the same with intrathyroidal disease classified as stage IVA, while the presence of lymph node metastases or gross extrathyroidal extension is stage IVB and distant metastases are classified as IVC disease[15]. At diagnosis, stage IVA patients represent 10.2%, stage IVB 40.2% and IVC 45.8%, according to several studies [6].

Fine needle aspiration biopsy is the most important diagnostic tool, although it may be unsuccessful due to extensive necrosis. In that case, a core biopsy might be needed [6, 16]. The main differential diagnoses are: poorly differentiated thyroid carcinoma (PDTC), well differentiated thyroid carcinomas with uncommon patterns, Riedel thyroiditis (mimics paucicellular variant) and medullar thyroid carcinoma (sometimes present features of dedifferentiation), in which cases immunohistochemistry may also be helpful. Distinguishing ATC from other thyroid neoplasms is crucial because the chances of survival and treatment options are drastically different. For instance, anaplastic tumour cells don't concentrate radioactive iodine as well as differentiated thyroid carcinomas [2].

In addition, primary evaluation should include laboratory tests: complete blood count with platelets, electrolytes, glucose and biochemistry with liver and kidney functions. Free thyroxine and thyrotropin serum levels should also be measured because thyroid function may be compromised by the tumour [17].

Due to ATC rapid progression, 40% of the patients have

Authors	N	Female (%)	Age (y)	Previous or concomitant DTC (%)	Tumour size (cm)	Confined to thyroid (%)	WBC count ≥10 000mm^3 (%)	Distant metastasis (%)
McIver *et al.*	134	60	67	4,5	6,6 (1,5-16)	2		46
Kihara *et al.*	19	63	73	42,0	5,7 (3,6-10,5)	16	16	47
Goutsouliak *et al.*	75	68	74	2,6				16
Kebebew *et al.*	516	67	71		6,4 (1,0-15,0)	7,5		43
Akaishi *et al.*	100	80	68	13,0	≤5 – 79% >5 – 21%	11	33	58
Sugitani *et al.*	677	62	69	30,0	≤5 – 5% >5 – 64%	20	33	43
Sun *et al.*	60	53	58		<6 – 52% ≥6 – 48%	7	37	27
Paunovic *et al.*	150	64		57,6				33
Wendler *et al.*	100	52	71	17,0		9		54
Baek *et al.*	329	64	69		≤5 – 45% >5 – 54%	22,2	24,9	31
Glaser *et al.*	3552	60			≤6 – 37% >6 – 32%	8,9		47

Table 1 Characteristics of patients with ATC

extra thyroidal extension and lymph node metastasis at initial presentation, also supported by Table 1. Extensive local invasion might occur in up to 70-76% of the patients, affecting muscle, trachea, oesophagus and larynx. The most frequent metastatic sites are lung (25%- 78%), cervical lymph nodes (51-83%) mediastinum (25%), pleura (29-31%), adrenal glands (24-33%), liver (10-23%), brain (8-23%) and bone (6-23%)[17-18]. For that reason, we need to perform complete body imaging exams, such as computerized tomography (CT), positron emission tomography (PET), and in some cases whole body magnetic resonance (MRI) [19].

The airway compromise can result in suffocation, pointed, along with distant metastasis, as the main causes of death in these patients [2, 6].

5. RISK FACTORS

Risk factors for ATC are not fully understood, but several authors discovered newsworthy connections over the past decade. A long-standing goitre, the prior existence of differentiated thyroid cancer and age over 65 years are recognised as the main risk factors [9, 12]. More than 80% of patients have long history of goitre and DTC is associated with ATC in 7% to 89% of the patients, according to different studies [2].

Besides that, ATC is twice as common in areas with endemic goitre [3]. However, the definition of long standing goitre is not clear, some authors point to an average of 18 years standing goiter [20], while others only state the history of thyroid mass for more than 9 months [21]. On the other hand, other studies verified the presence of goiter for more than 10 and 20 years [22], showing it as an independent factor for survival, not a risk factor [18, 23]. It's important to understand which longstanding goiters presents at risk and how should they be monitored.

Interestingly, new investigations show low education level, type B blood group, history of nonthyroidal malignancies, late menarche, early first pregnancy and diabetes as independent risk factors for ATC[9, 20]. In molecular research TERT promoter mutation was independently associated as a risk factor for ATC; in fact, TERT mutation is related with anaplastic transformation of papillary carcinoma [24]. The molecular progress may allow, in the future, the evaluation of a patient's risk profile based on his genetic mutations. Nowadays a few identified mutations are already being studied to identify which of them increase the risk of ATC.

6. PROGNOSTIC FACTORS

Several studies have suggested that younger age is related with a better prognosis and overall survival (OS) in patients with ATC, as demonstrated in Table 2 [12, 25]. Most of the studies found age <70 years as a good prognostic factor [8, 26-28], except *Kebebew et al.* that identified age<60 years as independent predictor of lower cause-specific mortality [29].

Smaller tumour size (<5-6 cm), disease confined to

Author	Age	Gender	WBC> 10000mm^3	Extra-thyroid invasion	Confined to thyroid	Tumour multicentricity	Tumour size >5 cm	Distant metastasis	No metastasis	Surgical ressection	No ressection
Akaishi *et al.*[26] (n=100)	>70y 1.03* (1.01-1.05)	1.40 (0.77-2.48)	2.04* (1.26-3.24)	3.02* (1.17-10.39)				1.94* (1.18-3.25)			3.99* (2.37-6.66)
Kebebew *et al.* [29] (n=516)	<60y 0.482* (0.268-0.867)	1.089 (0.746-1.590)			0.572* (0.366-0.893)		1.245* (0.854-1.816)	1.492* (1.113-2.000)		0.779 (0.312-1.946)	
Sugitani *et al.*[27] (n=677)	>70y 1.28* (1.04-1.58)	1.09 (0.88-1.36)	1.48* (1.18-1.87)	1.47* (1.11-1.96)			1.42* (1.12-1.81)	1.83* (1.48-2.27)		0.35* (0.28-0.43)	
Sun *et al.*[30] (n=60)	>55 1.829 (0.984-3.397)	0.879 (0.469-1.646)	1.869* (1.069-3.269)	1.78 (0.486-6.665)			>6cm 1.075 (0.566-2.044)	0.607 (0.129-2.845)		1.219 (0.823-1.804)	
Paunovic *et al.*[22] (n=150)	<50y 0.68* (0.49-0.95)	1.22 (0.82-1.72)				4.76* (1.76-12.50)		2.56* (1.43-4.54)		0.43* (0.29-0.63)	
Wendler *et al.*[8] (n=100)	>70y 1.048* (1.015-1.082)							2.718* (1.384-5.342)			2.201* (1.186-4.086)
***Baek et al.*[28] (n=329)**	>70y 1.493* (1.134-1.965)		*	1.648* (1.074-2.527)			*	1.561* (1.136-2.146)		0.505* ** (0.339–0.659)	
Glaser *et al.*[25] (n=3552)	>65 1.42* (1.26-1.60)			1.36* (1.13-1.62)			>6cm 1.36* (1.23-1.55)		0.62* (0.55-0.70)		1.76* (1.52-2.03)

Table 2: Prognostic factor: multivariate analyses

Relative risk; 95% confidence interval; p<0.05 is represented with *.

**The group treated with surgery and adjuvant RT/concurrent QT had a RR of 0.340, p<0.01

thyroid gland and the absence of distant metastasis at diagnosis were significantly associated with improved OS. In a retrospective review of 677 patients, white blood cell (WBC) count of +10,000mm3, acute symptoms and distant metastasis were risk factors for poorer survival [27]. In another study, *Akaishi et al.* reported similar results [26]. In fact, almost all studies present on Table 2 found distant metastasis as a bad prognostic factor, excepting for *Sun et al.* probably related with the smaller sampler size.

Concerning the treatment related factors of prognosis, multimodal treatment (combining surgery, radiotherapy and chemotherapy) is the recommendation of American Thyroid Association [12]. The complete tumour resection is the best surgical treatment [21, 26, 28], more specifically *Scott M. Glaser et al.* found that negative margin status improved survival, with an absolute 2-year survival of 27% for the patients with negative margin status versus 11% for the patients with positive/unknown margin status [25]. The data published by *Sugitani et al.* and *Smallridge et al.* identified the use of a high dose of radiation >40Gy as a factor that significantly prolonged survival [9, 27].

7. MOLECULAR BIOMARKERS

7.1. Gene alterations and signalling pathways

Several studies have shown the possibility to evaluate the mutational tumour profile preoperatively through fine needle biopsy aspirates analysis. This strategy could allow the increase of precision targeted therapy, according to the most significant pathway mutations present [31].

The molecular mechanisms responsible for the clinical aggressiveness are not well known, but $BRAF^{v600E}$, ERK1/2-MEK1/2, PI3K-AKT, TP53 are commonly mutated in ATC[32].

The prototypic progression to ATC can be considered as a process of dedifferentiation of WDTC, such as PTC or FTC. The $BRAF^{v600E}$ mutation is the most frequent in PTC, while NRAS/KRAS/HRAS variants are more common in FTC. The prognostic significance of RET/PTC is still uncertain, but tumours harbouring these alterations rarely progress to undifferentiated thyroid cancer [31].

Two important signalling pathways in thyroid cancer, PI3K-Akt pathway and the MAP kinase cascade (Ras-Raf-MEK-ERK), are regulated by the RAS oncogene family [31]. RAS mutations can occur in both benign and malign tumours, and are found in 42,6% of all ATC patients, NRAS more frequently than HRAS [9, 33]. For this reason, this mutation doesn't seem enough for itself to cause ATC. In contrast, some authors showed increased frequency of distant metastases in patients harbouring thyroid tumours with *RAS* mutation [31].

The $BRAF^{v600E}$ point mutation (13.8% - 38%), leaves BRAF and MAPK signalling pathway (Raf-MEK-ERK) constitutively activated, to induce changes in tumour microenvironment through extracellular matrix protein (ECM), promote tumour invasion and metastasis. $BRAF^{v600E}$ mutation was demonstrated to decrease NIS membrane localization and NIS gene expression, which mediates the active iodine uptake in thyroid follicular cells [33-34].

Somatic mutations in the promoter of TERT (human telomerase reverse transcriptase) gene have been described as recurrent in several cancers, including melanomas, CNS tumours and thyroid cancers [11]. TERT promoter gene mutation is found in up to 54% of all ATCs, and the prevalence seems to increase with dedifferentiation, fluctuating from 11,4% in PTC, 17,3% in FTC to 40,1% in ATC [33]. Enhanced TERT promoter activity, significantly increasing cell proliferation, has been related with two mutations, C228T and C250T. The C228T mutation has been associated with $BRAF^{v600E}$ mutation, providing aggressiveness to papillary thyroid cancer and a possible genetic mechanism involved in tumour progression [13]. *Oishi et al.* concluded that a papillary carcinoma harbouring TERT promoter mutation is at higher risk for anaplastic transformation [24]. BRAF appears to be frequently associated with TERT mutation suggesting an effect on patient´s prognosis, although more studies are needed to clarify this issue [35].

Gain of function mutations in the PI3K3CA gene is found in 25-40% of anaplastic cancers, however it's rare in typical PTC (<3%). In contrast, PI3K3CA gene mutation is frequent in poorly differentiated thyroid carcinoma and in PTC with distant metastasis (31%) suggesting a late stage mutation in dedifferentiation process [11, 24]. The PI3K-Akt pathway is a very important intracellular signalling pathway for mammals, acting in the phosphorylation of downstream target proteins, like caspase 9, forkhead, Par-4, Bad, p21 and mTOR. This pathway could be related with tumour development, promote tumour metastasis through the increase activity of NF-kB and promote tumour growth by the VEGF gene expression [36]. Nonetheless, unlike BRAF and TERT mutations, PI3K3CA mutation was only present in half of the antecedent papillary cancer, becoming a less useful alteration to evaluate patient's risk.

ATC also harbours mutation in CTNNB1 gene (25-60%), which is a major component of E-cadherin cell-cell adhesion complexes and constitutively activates *Wnt* pathway [11, 32].

In a retrospective study of 144 cases, TP53 mutation was found in 54,4%, representing the most frequently anomaly observed[33]. TP53 gene mutations are frequent in several human cancers, reported as the most common genetic alteration in malignant cells. Loss of TTF-1 expression and PAX-8, strongly expressed in WDTC, is a hallmark of anaplastic carcinoma [33]. High PPARy levels are also found in ATC, against the low levels found in DTC [13].

In an exome-wide analysis of the mutational landscape of ATC, were found mutations in genes related to malignancy not previously associated to thyroid tumorigenesis, such as mTOR, NF1, NF2, MLH1, MLH3, MSH5, MSH6, ERBB2, EIF1AX and USH2A. Somatic recurrent mutations were also found in TP53, RAS-family genes, PIK3CA and BRAF ($BRAF^{v600E}$ and RAS were mutually exclusive)[32]. *Weinberger et al.* analysed the gene expression microarray of

three different studies, and discovered an important role for M-phase cell cycle genes in ATC, along with 6 novel upregulated genes (*TMEM158, CXCL5, E2F7, DLGAP5, MME, ASPM)* and 3 downregulated genes (*SFTA3*, *LMO3*, and *C2orf40)*, which had not been specifically implicated in ATC [37]. The increase in genetic and molecular knowledge about the dedifferentiation process has introduced new targeted-therapy drugs, targeting specific pathways [38].

7.2. Epigenetic alterations and miRNAs deregulation

Strict controlled epigenetic regulation is essential for normal tissue growth, development and maintenance. Deregulation of epigenetic controls may influence the origin/ progression of several disease processes, including cancer. The Aurora group, found overexpressed in ATC, act as the regulators of mitotic events; in fact, Aurora kinase inhibition has been shown to significantly reduce the growth of ATC cells *in vivo*. Enhancer of Zeste homolog 2 (EZH2) is a histone lysine-methyltransferase, overexpressed in ATC. This overexpression contributed to altered histone methylation, transcriptional silence of PAX8, leading to an aggressive behaviour of the tumour [13, 39]. Several histone modifications were found: overexpression of histone-deacetylases (HDAC) affect the ERK1/2-MEK1/2 and PI3K-Akt pathways through the altered expression of cell cycle control proteins and the histone-methyltransferase KMT2A, KMT2C, KMT2D and SETD2 overexpression, involved in chromatin accessibility [39]. *Landa et al*. suggested the participation of SWI/SNF chromatin remodelling complex in the aggressive behaviour of advanced thyroid tumours [24, 40].

Modifications in micro-RNA expression are also present in ATC, interfering with gene expression and tumour progression [2]. The micro-RNA family miR-30, implicated in supressing tumour migration and metastasis *in vivo* and *in vitro*, has been found to have reduced expression in ATC. Furthermore, miR-200 family has a crucial role in the control of epithelial-mesenchymal transition, being a useful way to distinguish ATC from WDTC [2, 13, 39]. Let-7 family has the potential to overexpress TTF-1, altering NIS gene expression, and miR-138 is being pointed as potentially related with TERT transcript [39].

8. TREATMENT

Multimodal treatment consists in surgery and external beam radiotherapy with radiosensitizing chemotherapy [16]. Complete surgical resection is generally recommended for stage IVA patients and systemic therapy (clinical trials and/or palliative treatment) is usually advocated for stage IVC patients [41]. Systemic chemotherapy and radiotherapy may be considered in three clinical settings: (I) as neoadjuvant therapy for locoregional ATC downstaging; (II) as adjuvant therapy after complete surgical resection or for low-volume locoregional and distant residual disease; and (III) as palliative therapy [42].

8.1. Surgery

At presentation, 10% of patients have intrathyroidal tumour, 40% have extrathyroidal invasions and/or lymph node metastasis and the rest present with metastatic disease. Complete surgical resection with therapeutic lymph node dissection remains de cornerstone for prolonging ATC patient's survival. According to ATA guidelines, surgery should be performed if grossly negative margins (R1) are achievable [12].

Several authors correlate maximal debulking, negative margin status and total thyroidectomy with a statistically significant better survival rate [8, 21, 23, 41, 43]. *Goffredo et al.* analysed 335 patients undergoing surgery and found a median overall survival among operated vs non-operated patients, of 9.7 vs 3.0 months for stage IVA, 4.2 vs 3.4 months for stage IVB and 3.4 vs 1.7 for stage IVC ($p<0.001$) [44]. Nevertheless, the most important aspect in the management of ATC treatment is to select patients who might benefit from surgery-based treatment, which are mainly stage IVA and some selected stage IVB patients, with grossly negative margins (R1) achievable [29, 45]. In stage IVB tumours, neoadjuvant preoperative radiotherapy can sometimes be considered to downstage locally irresectable disease and subsequently enable complete resection [12]. *Baek et al*., also suggests that surgery-based multimodal treatment should only be performed in patients with age under 70 years, no acute clinical symptoms and no distant metastasis[28].

The most common complications of ATC resections are haemorrhage, vocal cord paralysis, chylous fistulae, surgical site infection, dysphagia, salivary fistulae and hypoparathyroidism [42].

In stage IVC patients, palliative resection of the tumour should be considered to avoid airway compromise or oesophageal obstruction, and provide better quality of life [42].However, airway compromise recurrence may occur and tracheostomy should be performed in life-threatening asphyxia. Tracheal stent presents as a less invasive palliative option than tracheostomy, relieving dyspnoea and improving the quality of life of patients, but has a minimal impact in survival. Besides that, tracheostomy is surgically challenging in these patients, deteriorates quality of life and requires extensive care [46-47]. Selective embolization of thyroid arteries may become an interesting option of palliative treatment for patients with intractable bleeding, pain or signs of local compression [48].

8.2. Radiotherapy

External Beam Radiation (EBR) is given with the aim of improving overall survival and local control; unfortunately due to the high level of toxicity, rapid mass progression and quick development of metastatic disease the results are unsatisfactory [49]. When available, patients should be irradiated with intensity modulated radiotherapy (IMRT) instead of conventional radiotherapy [50]. Hyperfractionated radiation consists in multiple small radiation doses that allow

more than one radiation treatment a day, reducing toxicity and decreasing the time of the treatment needed for a course of radiation, which is important in tumours that grow rapidly[51]. *Tennvall et al*. found a strong correlation between local control and accelerated radiotherapy[52]. Although unresectable ATC remains a challenge for treatment, *Todd A. Pezzi et al.* demonstrated that higher doses of radiotherapy were associated with improved survival, in patients treated <45Gy the median survival was 4.24 months compared with 6.77 months in patients that received from 45 to 59.9Gy[53]. *K So et al.* also reported a good locoregional control in 70% of ATC patients treated with radiotherapy (>50 Gy) with or without surgery or chemotherapy, and 66,7% of locoregional control in patients treated with palliative intent (<40 Gy) [54].

8.3. Chemotherapy

The most effective class of agents in systemic therapy are taxanes (paclitaxel or decetaxel), the anthracyclines (doxorubicin) and the platins (cisplatin and carboplatin)[2].

One of the most studied chemotherapy agents is doxorubicin, but no significant survival benefit has been observed [23, 52]. Other recent studies point the use of taxanes as radio-sensitizing agents, in a multimodal treatment, as a more effective chemotherapeutic agent than those traditionally used in a selected group of patients [51, 55-56]. *Ain et al.* reported a 53% response rate with continuous infusion of paclitaxel [57]. *Higashiyama et al.* described a 33% response rate in stage IVB and 25% in stage IVC patients, treated with paclitaxel weekly administration [58]. *Troch et al*. reported the promising results of a small series of 6 patients treated to 60Gy with docetaxel [56].

8.4. Novel agents

8.4.1. Multikinase Inhibitors

A phase II trial, in 20 patients with advanced disease treated with daily sorafenib resulted in overall median progression-free survival of 1.9 months with a median and a 1-year survival of 3.9 months and 20%, respectively [59]. On the other hand, *Yasuhiro Ito et al.* concluded that sorafenib is ineffective in ATC treatment [60]. Similar to sorafenib, pazopanib - a multikinase inhibitor including VEGFR, PDGFR and c-kit - demonstrated no activity in ATC [16].

Tahara M. et al. reported a single arm, phase II trial, using lenvatinib - a multikinase inhibitor that targets the vascular endothelial growth factor receptor 1–3, fibroblast growth factor receptor 1–4, platelet-derived growth factor receptor-alpha, and RET and KIT proto-oncogenes. Although the small number of patients, only 17, the results were promising, with a median progression free survival of 7.4 months and median OS of 10.6 months [61]. Lenvatinib is currently approved in Japan for ATC treatment.

8.4.2. BRAF inhibitors

In one patient with BRAF V600E mutated ATC, therapy with vemurafenib improved her condition rapidly with nearly complete tumour regression [62]. Another patient, which tumour is BRAF V600E and programmed death-ligand 1 (PD-L1) positive, was in complete radiographic and clinical remission for 20 months after treatment with vemurafenib and nivolumab [63]. De novo mutations of BRAF to vemurafenib were associated to rapid rebound of MAP kinase ERK signalling.

The combination therapy of dabrafenib and trametinib in subjects with $BRAF^{V600E}$-mutated is still ongoing, with significantly improved outcomes (NCT02034110).

8.4.3. mTOR inhibitors

Some clinical trials using everolimus in thyroid cancer are currently ongoing. Further, *Wagle N. et al.* reported the case of a patient with a sustained response to everolimus for 18 months, followed by tissue resistance with tumour progression[64].

8.4.4. PPARy agonists

A phase I study using efatutazone in combination with paclitaxel was well tolerated, one patient achieved partial response and half maintained stable disease. A randomized phase II study is ongoing [65].

8.4.5. Other Targeted Therapies

Although it is rare, some ATC harbour oncogenic mutations in the ALK gene. In these patients, a huge decrease of lesions volume was reported with crizotinib – ALK inhibitor [66].

Combretastatin A-4 phosphate, a microtubule destabilizing agent that can alter endothelial-cell and stromal-cell biology, has demonstrated preclinical single-agent activity. On this basis, a randomized trial was conducted with fosbretabulin (combretastatin A4 phosphate) showing a trend toward improved overall survival when added to carboplatin - 5,2 months versus carboplatin alone - 4 months [67].

Selinexor inhibits exportin-1 (XPO1) a nuclear export receptor involved in transport of many tumour suppressor proteins and is overexpressed in human cancers. A recent study showed that selinexor inhibited growth in ATC human xenografts, providing rationale for further investigation [68].

9. CONCLUSION

ATC is a rare form of cancer with a dismal prognosis and few understanding about its origin. The discovery of risk factors or early events in ATC transformation or ATC *de novo* may help to increase patient's outcome.

Now none of the known mutations can predict ATC development. The crucial thing, in the future, is to find/select a group of highly prevalent mutated genes in ATC, which can serve to predict or suspect the evolution from DTC to ATC.

Treatment options are still very limited, even with multimodal treatment. The knowledge of each patient

mutational landscape can create a new precise treatment model using directed molecular therapies.

LIST OF ABBREVIATIONS

ATC: Anaplastic Thyroid Carcinoma

DTC: Differentiated Thyroid Carcinoma

PTC: Papillary Thyroid Carcinoma

FTC: Follicular Thyroid Carcinoma

PDTC: Poorly Differentiated Thyroid Carcinoma

WDTC: Well Differentiated Thyroid Carcinoma

OS: Overall Survival

PFS: Progression Free Survival

WHO: World Health Organization

TNM: classification of malignant tumours; T- size of the tumour; N – regional lymph nodes invasion; M - metastasis

CONFLICT OF INTEREST

The authors report no conflicts of interest.

REFERENCES

1. Gomez Saez, J. M.; Jimenez-Fonseca, P.; Santamaria Sandi, J.; Capdevila Castillon, J.; Navarro Gonzalez, E.; Zafon Llopis, C.; Ramon, Y. C. A. T.; Riesco Eizaguirre, G.; Grande Pulido, E.; Galofre Ferrater, J. C., Spanish consensus for the management of patients with anaplastic cell thyroid carcinoma. *Endocrinologia y nutricion : organo de la Sociedad Espanola de Endocrinologia y Nutricion* **2015,** *62* (3), e15-22.
2. Molinaro, E.; Romei, C.; Biagini, A.; Sabini, E.; Agate, L.; Mazzeo, S.; Materazzi, G.; Sellari-Franceschini, S.; Ribechini, A.; Torregrossa, L.; Basolo, F.; Vitti, P.; Elisei, R., Anaplastic thyroid carcinoma: from clinicopathology to genetics and advanced therapies. *Nature reviews. Endocrinology* **2017**.
3. Steggink, L. C.; van Dijk, B. A.; Links, T. P.; Plukker, J. T., Survival in anaplastic thyroid cancer in relation to pre-existing goiter: a population-based study. *American journal of surgery* **2015,** *209* (6), 1013-9.
4. Xu, B.; Ghossein, R., Genomic Landscape of poorly Differentiated and Anaplastic Thyroid Carcinoma. *Endocrine Pathology* **2016,** *27* (3), 205-212.
5. Dal Maso, L.; Tavilla, A.; Pacini, F.; Serraino, D.; van Dijk, B. A. C.; Chirlaque, M. D.; Capocaccia, R.; Larrañaga, N.; Colonna, M.; Agius, D.; Ardanaz, E.; Rubió-Casadevall, J.; Kowalska, A.; Virdone, S.; Mallone, S.; Amash, H.; De Angelis, R., Survival of 86,690 patients with thyroid cancer: A population-based study in 29 European countries from EUROCARE-5. *European Journal of Cancer* **2017,** *77*, 140-152.
6. Smallridge, R. C., Approach to the patient with anaplastic thyroid carcinoma. *The Journal of clinical endocrinology and metabolism* **2012,** *97* (8), 2566-72.
7. Konturek, A.; Barczynski, M.; Stopa, M.; Nowak, W., Trends in Prevalence of Thyroid Cancer Over Three Decades: A Retrospective Cohort Study of 17,526 Surgical Patients. *World journal of surgery* **2016,** *40* (3), 538-44.
8. Wendler, J.; Kroiss, M.; Gast, K.; Kreissl, M.; Allelein, S.; Lichtenauer, U.; Blaser, R.; Spitzweg, C.; Fassnacht, M.; Schott, M.; Führer, D.; Tiedje, V., *Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: Results of a multicenter study in Germany*. 2016; Vol. 175, p 521-529.
9. Smallridge, R. C.; Copland, J. A., Anaplastic Thyroid Carcinoma: Pathogenesis and Emerging Therapies. *Clinical Oncology* **2010,** *22* (6), 486-497.
10. Tumours, W. I. C. o., *WHO Classification of Tumours of Endocrine Organs*. 4th Edition ed.; 2017; Vol. Volume 10.
11. Ragazzi, M.; Ciarrocchi, A.; Sancisi, V.; Gandolfi, G.; Bisagni, A.; Piana, S., Update on anaplastic thyroid carcinoma: morphological, molecular, and genetic features of the most aggressive thyroid cancer. *Int J Endocrinol* **2014,** *2014*, 790834.
12. Smallridge, R. C.; Ain, K. B.; Asa, S. L.; Bible, K. C.; Brierley, J. D.; Burman, K. D.; Kebebew, E.; Lee, N. Y.; Nikiforov, Y. E.; Rosenthal, M. S.; Shah, M. H.; Shaha, A. R.; Tuttle, R. M., American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid : official journal of the American Thyroid Association* **2012,** *22* (11), 1104-39.
13. Smith, N.; Nucera, C., Personalized therapy in patients with anaplastic thyroid cancer: targeting genetic and epigenetic alterations. *The Journal of clinical endocrinology and metabolism* **2015,** *100* (1), 35-42.
14. Ain, K. B., Anaplastic thyroid carcinoma: behavior, biology, and therapeutic approaches. *Thyroid : official journal of the American Thyroid Association* **1998,** *8* (8), 715-26.
15. Tuttle, R.; Haugen, B.; Perrier, N., Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer: What Changed and Why? *Thyroid: official journal of the American Thyroid Association* **2017,** *27* (6), 751.
16. Cabanillas, M. E.; Zafereo, M.; Gunn, G. B.; Ferrarotto, R., Anaplastic Thyroid Carcinoma: Treatment in the Age of Molecular Targeted Therapy. *Journal of oncology practice* **2016,** *12* (6), 511-8.
17. Ranganath, R.; Shah, M. A.; Shah, A. R., Anaplastic thyroid cancer. *Current opinion in endocrinology, diabetes, and obesity* **2015,** *22* (5), 387-391.
18. Besic, N.; Gazic, B., Sites of metastases of anaplastic thyroid carcinoma: autopsy findings in 45 cases

from a single institution. *Thyroid : official journal of the American Thyroid Association* **2013,** *23* (6), 709-13.
19. Cabanillas, M. E.; McFadden, D. G.; Durante, C., Thyroid cancer. *The Lancet* **2016,** *388* (10061), 2783-2795.
20. Zivaljevic, V.; Slijepcevic, N.; Paunovic, I.; Diklic, A.; Kalezic, N.; Marinkovic, J.; Zivic, R.; Vekic, B.; Sipetic, S., Risk Factors for Anaplastic Thyroid Cancer. *International Journal of Endocrinology* **2014,** *2014*, 6.
21. Mohebati, A.; Dilorenzo, M.; Palmer, F.; Patel, S. G.; Pfister, D.; Lee, N.; Tuttle, R. M.; Shaha, A. R.; Shah, J. P.; Ganly, I., Anaplastic thyroid carcinoma: a 25-year single-institution experience. *Annals of surgical oncology* **2014,** *21* (5), 1665-70.
22. Paunovic, I. R.; Sipetic, S. B.; Zoric, G. V.; Diklic, A. D.; Savic, D. V.; Marinkovic, J.; Zivaljevic, V. R., Survival and Prognostic Factors of Anaplastic Thyroid Carcinoma. *Acta Chirurgica Belgica* **2015,** *115* (1), 62-67.
23. Haigh, P. I.; Ituarte, P. H.; Wu, H. S.; Treseler, P. A.; Posner, M. D.; Quivey, J. M.; Duh, Q. Y.; Clark, O. H., Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. *Cancer* **2001,** *91* (12), 2335-42.
24. Oishi, N.; Kondo, T.; Ebina, A.; Sato, Y.; Akaishi, J.; Hino, R.; Yamamoto, N.; Mochizuki, K.; Nakazawa, T.; Yokomichi, H.; Ito, K.; Ishikawa, Y.; Katoh, R., Molecular alterations of coexisting thyroid papillary carcinoma and anaplastic carcinoma: identification of TERT mutation as an independent risk factor for transformation. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* **2017**.
25. Glaser, S. M.; Mandish, S. F.; Gill, B. S.; Balasubramani, G. K.; Clump, D. A.; Beriwal, S., Anaplastic thyroid cancer: Prognostic factors, patterns of care, and overall survival. *Head Neck* **2016,** *38 Suppl 1*, E2083-90.
26. Akaishi, J.; Sugino, K.; Kitagawa, W.; Nagahama, M.; Kameyama, K.; Shimizu, K.; Ito, K.; Ito, K., Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. *Thyroid : official journal of the American Thyroid Association* **2011,** *21* (11), 1183-9.
27. Sugitani, I.; Miyauchi, A.; Sugino, K.; Okamoto, T.; Yoshida, A.; Suzuki, S., Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. *World journal of surgery* **2012,** *36* (6), 1247-54.
28. Baek, S.-K.; Lee, M.-C.; Hah, J. H.; Ahn, S.-H.; Son, Y.-I.; Rho, Y.-S.; Chung, P.-S.; Lee, Y.-S.; Koo, B. S.; Jung, K.-Y.; Lee, B.-J., Role of surgery in the management of anaplastic thyroid carcinoma: Korean nationwide multicenter study of 329 patients with anaplastic thyroid carcinoma, 2000 to 2012. *Head & Neck* **2017,** *39* (1), 133-139.
29. Kebebew, E.; Greenspan, F. S.; Clark, O. H.; Woeber, K. A.; McMillan, A., Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer* **2005,** *103* (7), 1330-5.
30. Sun, C.; Li, Q.; Hu, Z.; He, J.; Li, C.; Li, G.; Tao, X.; Yang, A., Treatment and prognosis of anaplastic thyroid carcinoma: experience from a single institution in China. *PloS one* **2013,** *8* (11), e80011.
31. Penna, G. C.; Vaisman, F.; Vaisman, M.; Sobrinho-Simões, M.; Soares, P., Molecular Markers Involved in Tumorigenesis of Thyroid Carcinoma: Focus on Aggressive Histotypes. *Cytogenetic and Genome Research* **2016,** *150* (3-4), 194-207.
32. Kunstman, J. W.; Juhlin, C. C.; Goh, G.; Brown, T. C.; Stenman, A.; Healy, J. M.; Rubinstein, J. C.; Choi, M.; Kiss, N.; Nelson-Williams, C.; Mane, S.; Rimm, D. L.; Prasad, M. L.; Hoog, A.; Zedenius, J.; Larsson, C.; Korah, R.; Lifton, R. P.; Carling, T., Characterization of the mutational landscape of anaplastic thyroid cancer via whole-exome sequencing. *Human molecular genetics* **2015,** *24* (8), 2318-29.
33. Bonhomme, B.; Godbert, Y.; Perot, G.; Al Ghuzlan, A.; Bardet, S.; Belleannee, G.; Criniere, L.; Do Cao, C.; Fouilloux, G.; Guyetant, S.; Kelly, A.; Leboulleux, S.; Buffet, C.; Leteurtre, E.; Michels, J. J.; Tissier, F.; Toubert, M. E.; Wassef, M.; Pinard, C.; Hostein, I.; Soubeyran, I., Molecular Pathology of Anaplastic Thyroid Carcinomas: A Retrospective Study of 144 Cases. *Thyroid : official journal of the American Thyroid Association* **2017,** *27* (5), 682-692.
34. Hsu, K.-T.; Yu, X.-M.; Audhya, A. W.; Jaume, J. C.; Lloyd, R. V.; Miyamoto, S.; Prolla, T. A.; Chen, H., Novel Approaches in Anaplastic Thyroid Cancer Therapy. *The Oncologist* **2014,** *19* (11), 1148-1155.
35. Vinagre, J.; Almeida, A.; Populo, H.; Batista, R.; Lyra, J.; Pinto, V.; Coelho, R.; Celestino, R.; Prazeres, H.; Lima, L.; Melo, M.; da Rocha, A. G.; Preto, A.; Castro, P.; Castro, L.; Pardal, F.; Lopes, J. M.; Santos, L. L.; Reis, R. M.; Cameselle-Teijeiro, J.; Sobrinho-Simoes, M.; Lima, J.; Maximo, V.; Soares, P., Frequency of TERT promoter mutations in human cancers. *Nature communications* **2013,** *4*, 2185.
36. Jin, S.; Borkhuu, O.; Bao, W.; Yang, Y.-T., Signaling Pathways in Thyroid Cancer and Their Therapeutic Implications. *Journal of Clinical Medicine Research* **2016,** *8* (4), 284-296.
37. Weinberger, P.; Ponny, S. R.; Xu, H.; Bai, S.; Smallridge, R.; Copland, J.; Sharma, A., Cell Cycle M-Phase Genes Are Highly Upregulated in Anaplastic Thyroid Carcinoma. *Thyroid : official journal of the American Thyroid Association* **2017,** *27* (2), 236-252.
38. Samimi, H.; Fallah, P.; Naderi Sohi, A.; Tavakoli, R.; Naderi, M.; Soleimani, M.; Larijani, B.; Haghpanah, V., Precision Medicine Approach to Anaplastic Thyroid Cancer: Advances in Targeted Drug Therapy Based on Specific Signaling Pathways. *Acta medica Iranica* **2017,** *55* (3), 200-208.
39. Sasanakietkul, T.; Murtha, T. D.; Javid, M.; Korah, R.; Carling, T., Epigenetic modifications in poorly differentiated and anaplastic thyroid cancer. *Molecular and cellular endocrinology* **2017**.
40. Landa, I.; Ibrahimpasic, T.; Boucai, L.; Sinha, R.; Knauf, J. A.; Shah, R. H.; Dogan, S.; Ricarte-Filho, J. C.; Krishnamoorthy, G. P.; Xu, B.; Schultz, N.; Berger, M. F.;

Sander, C.; Taylor, B. S.; Ghossein, R.; Ganly, I.; Fagin, J. A., Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *The Journal of clinical investigation* **2016,** *126* (3), 1052-66.
41. Sugitani, I.; Hasegawa, Y.; Sugasawa, M.; Tori, M.; Higashiyama, T.; Miyazaki, M.; Hosoi, H.; Orita, Y.; Kitano, H., Super-radical surgery for anaplastic thyroid carcinoma: a large cohort study using the Anaplastic Thyroid Carcinoma Research Consortium of Japan database. *Head Neck* **2014,** *36* (3), 328-33.
42. Keutgen, X. M.; Sadowski, S. M.; Kebebew, E., Management of anaplastic thyroid cancer. *Gland Surgery* **2015,** *4* (1), 44-51.
43. Brignardello, E.; Palestini, N.; Felicetti, F.; Castiglione, A.; Piovesan, A.; Gallo, M.; Freddi, M.; Ricardi, U.; Gasparri, G.; Ciccone, G.; Arvat, E.; Boccuzzi, G., Early surgery and survival of patients with anaplastic thyroid carcinoma: analysis of a case series referred to a single institution between 1999 and 2012. *Thyroid : official journal of the American Thyroid Association* **2014,** *24* (11), 1600-6.
44. Goffredo, P.; Thomas, S. M.; Adam, M. A.; Sosa, J. A.; Roman, S. A., Impact of Timeliness of Resection and Thyroidectomy Margin Status on Survival for Patients with Anaplastic Thyroid Cancer: An Analysis of 335 Cases. *Annals of surgical oncology* **2015,** *22* (13), 4166-74.
45. McIver, B.; Hay, I. D.; Giuffrida, D. F.; Dvorak, C. E.; Grant, C. S.; Thompson, G. B.; van Heerden, J. A.; Goellner, J. R., Anaplastic thyroid carcinoma: A 50-year experience at a single institution. *Surgery* **2001,** *130* (6), 1028-1034.
46. Rajeev, P.; Ezzat, T.; Slade, M.; Sadler, G. P.; Mihai, R., Tracheal stenting has minimal impact on survival in anaplastic thyroid carcinoma. *World journal of surgery* **2013,** *37* (11), 2589-93.
47. Varadharajan, K.; Mathew, R.; Odutoye, B.; Williamson, P.; Madden, B., Use of tracheal stenting in the palliation of anaplastic thyroid carcinoma: tertiary centre experience. *The Journal of laryngology and otology* **2015,** *129* (6), 568-71.
48. Dedecjus, M.; Tazbir, J.; Kaurzel, Z.; Lewinski, A.; Strozyk, G.; Brzezinski, J., Selective embolization of thyroid arteries as a preresective and palliative treatment of thyroid cancer. *Endocrine-related cancer* **2007,** *14* (3), 847-52.
49. Brierley, J. D.; Tsang, R. W., External beam radiation therapy for thyroid cancer. *Endocrinology and metabolism clinics of North America* **2008,** *37* (2), 497-509, xi.
50. Bhatia, A.; Rao, A.; Ang, K. K.; Garden, A. S.; Morrison, W. H.; Rosenthal, D. I.; Evans, D. B.; Clayman, G.; Sherman, S. I.; Schwartz, D. L., Anaplastic thyroid cancer: Clinical outcomes with conformal radiotherapy. *Head Neck* **2010,** *32* (7), 829-36.
51. Brierley, J. D., Update on external beam radiation therapy in thyroid cancer. *The Journal of clinical endocrinology and metabolism* **2011,** *96* (8), 2289-95.
52. Tennvall, J.; Lundell, G.; Wahlberg, P.; Bergenfelz, A.; Grimelius, L.; Åkerman, M.; Hjelm Skog, A. L.; Wallin, G., Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. *British Journal of Cancer* **2002,** *86* (12), 1848-1853.
53. Pezzi, T. A.; Mohamed, A. S. R.; Sheu, T.; Blanchard, P.; Sandulache, V. C.; Lai, S. Y.; Cabanillas, M. E.; Williams, M. D.; Pezzi, C. M.; Lu, C.; Garden, A. S.; Morrison, W. H.; Rosenthal, D. I.; Fuller, C. D.; Gunn, G. B., Radiation therapy dose is associated with improved survival for unresected anaplastic thyroid carcinoma: Outcomes from the National Cancer Data Base. *Cancer* **2017,** *123* (9), 1653-1661.
54. So, K.; Smith, R. E.; Davis, S. R., Radiotherapy in anaplastic thyroid carcinoma: An Australian experience. *Journal of medical imaging and radiation oncology* **2017,** *61* (2), 279-287.
55. Foote, R. L.; Molina, J. R.; Kasperbauer, J. L.; Lloyd, R. V.; McIver, B.; Morris, J. C.; Grant, C. S.; Thompson, G. B.; Richards, M. L.; Hay, I. D.; Smallridge, R. C.; Bible, K. C., Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy. *Thyroid : official journal of the American Thyroid Association* **2011,** *21* (1), 25-30.
56. Troch, M.; Koperek, O.; Scheuba, C.; Dieckmann, K.; Hoffmann, M.; Niederle, B.; Raderer, M., High efficacy of concomitant treatment of undifferentiated (anaplastic) thyroid cancer with radiation and docetaxel. *The Journal of clinical endocrinology and metabolism* **2010,** *95* (9), E54-7.
57. Ain, K. B.; Egorin, M. J.; DeSimone, P. A., Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group. *Thyroid : official journal of the American Thyroid Association* **2000,** *10* (7), 587-94.
58. Higashiyama, T.; Ito, Y.; Hirokawa, M.; Fukushima, M.; Uruno, T.; Miya, A.; Matsuzuka, F.; Miyauchi, A., Induction chemotherapy with weekly paclitaxel administration for anaplastic thyroid carcinoma. *Thyroid : official journal of the American Thyroid Association* **2010,** *20* (1), 7-14.
59. Savvides, P.; Nagaiah, G.; Lavertu, P.; Fu, P.; Wright, J. J.; Chapman, R.; Wasman, J.; Dowlati, A.; Remick, S. C., Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid. *Thyroid : official journal of the American Thyroid Association* **2013,** *23* (5), 600-4.
60. Ito, Y.; Onoda, N.; Ito, K. I.; Sugitani, I.; Takahashi, S.; Yamaguchi, I.; Kabu, K.; Tsukada, K., Sorafenib in Japanese Patients with Locally Advanced or Metastatic Medullary Thyroid Carcinoma and Anaplastic Thyroid Carcinoma. *Thyroid : official journal of the American Thyroid Association* **2017,** *27* (9), 1142-1148.
61. Tahara, M.; Kiyota, N.; Yamazaki, T.; Chayahara, N.; Nakano, K.; Inagaki, L.; Toda, K.; Enokida, T.; Minami, H.; Imamura, Y.; Sasaki, T.; Suzuki, T.; Fujino, K.; Dutcus, C. E.; Takahashi, S., Lenvatinib for Anaplastic Thyroid Cancer. *Frontiers in Oncology* **2017,** *7*, 25.

62. Rosove, M. H.; Peddi, P. F.; Glaspy, J. A., BRAF V600E inhibition in anaplastic thyroid cancer. *The New England journal of medicine* **2013,** *368* (7), 684-5.
63. Kollipara, R.; Schneider, B.; Radovich, M.; Babu, S.; Kiel, P. J., Exceptional Response with Immunotherapy in a Patient with Anaplastic Thyroid Cancer. *Oncologist* **2017,** *22* (10), 1149-1151.
64. Wagle, N.; Grabiner, B. C.; Van Allen, E. M.; Amin-Mansour, A.; Taylor-Weiner, A.; Rosenberg, M.; Gray, N.; Barletta, J. A.; Guo, Y.; Swanson, S. J.; Ruan, D. T.; Hanna, G. J.; Haddad, R. I.; Getz, G.; Kwiatkowski, D. J.; Carter, S. L.; Sabatini, D. M.; Janne, P. A.; Garraway, L. A.; Lorch, J. H., Response and acquired resistance to everolimus in anaplastic thyroid cancer. *The New England journal of medicine* **2014,** *371* (15), 1426-33.
65. Smallridge, R. C.; Copland, J. A.; Brose, M. S.; Wadsworth, J. T.; Houvras, Y.; Menefee, M. E.; Bible, K. C.; Shah, M. H.; Gramza, A. W.; Klopper, J. P.; Marlow, L. A.; Heckman, M. G.; Von Roemeling, R., Efatutazone, an Oral PPAR-γ Agonist, in Combination With Paclitaxel in Anaplastic Thyroid Cancer: Results of a Multicenter Phase 1 Trial. *The Journal of Clinical Endocrinology & Metabolism* **2013,** *98* (6), 2392-2400.
66. Godbert, Y.; Figueiredo, B. H. d.; Bonichon, F.; Chibon, F.; Hostein, I.; Pérot, G.; Dupin, C.; Daubech, A.; Belleannée, G.; Gros, A.; Italiano, A.; Soubeyran, I., Remarkable Response to Crizotinib in Woman With Anaplastic Lymphoma Kinase–Rearranged Anaplastic Thyroid Carcinoma. *Journal of Clinical Oncology* **2015,** *33* (20), e84-e87.
67. Sosa, J. A.; Elisei, R.; Jarzab, B.; Balkissoon, J.; Lu, S. P.; Bal, C.; Marur, S.; Gramza, A.; Yosef, R. B.; Gitlitz, B.; Haugen, B. R.; Ondrey, F.; Lu, C.; Karandikar, S. M.; Khuri, F.; Licitra, L.; Remick, S. C., Randomized safety and efficacy study of fosbretabulin with paclitaxel/carboplatin against anaplastic thyroid carcinoma. *Thyroid : official journal of the American Thyroid Association* **2014,** *24* (2), 232-40.
68. Garg, M.; Kanojia, D.; Mayakonda, A.; Ganesan, T. S.; Sadhanandhan, B.; Suresh, S.; S, S.; Nagare, R. P.; Said, J. W.; Doan, N. B.; Ding, L. W.; Baloglu, E.; Shacham, S.; Kauffman, M.; Koeffler, H. P., Selinexor (KPT-330) has antitumor activity against anaplastic thyroid carcinoma in vitro and in vivo and enhances sensitivity to doxorubicin. *Scientific reports* **2017,** *7* (1), 9749.

Anexo(s)

Normas da revista “Endocrine, Metabolic & Immune Disorders - Drug Targets”

INSTRUCTIONS FOR AUTHORS

ONLINE MANUSCRIPT SUBMISSION:

An online submission and tracking service via Internet facilitates a speedy and cost-effective submission of manuscripts. The full manuscript has to be submitted online via Bentham's Content Management System (CMS) at http://jms.eurekaselect.com/journals/emiddt / **View Submission Instructions**. Alternatively, you may submit the full paper to emi@benthamscience.org

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The principal/corresponding author will be required to submit a Copyright Letter along with the manuscript, on behalf of all the co-authors (if any). The author(s) will confirm that the manuscript (or any part of it) has not been published previously or is not under consideration for publication elsewhere. Furthermore, any illustration, structure or table that has been published elsewhere must be reported, and copyright permission for reproduction must be obtained.

For all online submissions, please provide soft copies of all the materials (main text in MS Word or Tex/LaTeX), figures/illustrations in TIFF, PDF or JPEG, and chemical structures drawn in ChemDraw (CDX)/ISISDraw (TGF) as separate files, while a PDF version of the entire manuscript must also be included, embedded with all the figures/illustrations/tables/chemical structures, *etc*.

It is imperative that before submission, authors should carefully proofread the files for special characters, mathematical symbols, Greek letters, equations, tables, references and images, to ensure that they appear in proper format.

References, figures, tables, structure, *etc* should be referred to in the text at the appropriate place where they are first discussed. Figure legends/captions should also be provided.

A successful electronic submission of a manuscript will be followed by a system-generated acknowledgement to the principal/corresponding author. Any queries therein should be addressed to info@benthamscience.org.

Editorial Policies:

The editorial policies of Bentham Science Publishers on publication ethics, peer-review, plagiarism, copyrights/ licenses, errata/corrections and article retraction/ withdrawal can be viewed at Editorial Policy.

Copyright Letter:

It is mandatory that a signed copyright letter also be submitted along with the manuscript by the author to whom correspondence is to be addressed, delineating the scope of the submitted article declaring the potential competing interests, acknowledging contributions from authors and funding agencies, and certifying that the paper is prepared according to the '**Instructions for Authors**'. All inconsistencies in the text and in the reference section, and any typographical errors must be carefully checked and corrected before the submission of the manuscript. The article contains no such material or information that may be unlawful, defamatory, fabricated, plagiarized, or which would, if published, in any way whatsoever, violate the terms and conditions as laid down in the copyright agreement. The

authors acknowledge that the publishers have the legal right to take appropriate action against the authors for any such violation of the terms and conditions as laid down in the copyright agreement.

MANUSCRIPTS PUBLISHED:

The Journal publishes peer-reviewed mini- and full-length review articles, research papers, and drug clinical trial studies written in English. Single topic/thematic issues may also be considered for publication.

Single Topic Issues:

These special issues are peer-reviewed and may contain invited or uninvited review/mini-review articles. A Single Topic Issue Editor will offer a short perspective and co-ordinate the solicitation of manuscripts between 3-5 (for a mini-thematic issue) to 6-10 (for full-length thematic issue) from leading scientists. Authors interested in editing a single topic issue in an emerging topic of outstanding developments in endocrine, metabolic and immune disorders may submit their proposal to the Editor-in-Chief at emiddt@benthamscience.org for consideration.

Conference Proceedings:

For proposals to publish conference proceedings in this journal, please contact us at email: proceedings@benthamscience.org.

MANUSCRIPT LENGTH:

Review Articles:

The total number of words for a published comprehensive review article article is from 8000 to 40000 words, and for mini-review articles from 3000 to 6000 words.

Systematic Reviews:

Systematic Reviews include systematic updates in review protocols, methods, research, and results from all relevant fields for any studies and updates on already published issues.

Research Articles:

The total number of words for a published research article is from 4000 to 8000 words.

Randomized Drug Clinical Trial Studies:

The maximum total page length for a drug clinical trial study published in the journal is four journal pages. Each journal page is on average 900 words.

Case Reports:

Case reports should describe new observations of findings or novel/unique outcomes relevant to the filed. The total number of words for a published case report is 1500 to 2000 words.

There is no restriction on the number of figures, tables or additional files *e.g.* video clips, animation and datasets, that can be included with each article online. Authors should include all relevant supporting data with each article (Refer to Supplementary Material section).

MANUSCRIPT PREPARATION:

The manuscript should be written in English in a clear, direct and active style. All pages must be numbered sequentially, facilitating in the reviewing and editing of the manuscript.

MICROSOFT WORD TEMPLATE:

It is advisable that authors prepare their manuscript using the template available on the Web, which will assist in preparation of the manuscript according to Journal's Format. (http://benthamscience.com/journal-files/template-files/emiddt-template.doc)

Our contracted service provider Eureka Science can, if needed, provide professional assistance to authors for the improvement of English language and figures in manuscripts.

SECTIONS IN MANUSCRIPTS:

Manuscripts submitted for research and review articles in the journal should be divided into the following sections:

- Title
- Title Page
- Structured Abstract
- Graphical Abstract
- Keywords
- Text Organization
- Conclusion
- List of Abbreviations (if any)
- Consent for Publication
- Conflict of Interest
- Acknowledgements
- References
- Appendices
- Figures/Illustrations (if any)
- Chemical Structures (if any)
- Tables (if any)
- Supportive/Supplementary Material (if any)

Title:

The title of the article should be precise and brief and must not be more than 120 characters. Authors should avoid the use of non-standard abbreviations. The first letter of each word should be in capital letters except for articles, conjunctions and prepositions.

Authors should also provide a short 'running title'. Title, running title, by line, correspondent footnote and keyword should be written as presented in original manuscripts.

Title Page:

Title page should include paper title, author(s) full name and affiliation, corresponding author(s) names complete affiliation/address, along with phone, fax and email.

Structured Abstract:

The abstract of an article should be its clear, concise and accurate summary, having no more than 250 words, and including the explicit sub-headings (as in-line or run-in headings in bold). Use of abbreviations should be avoided and the references should not be cited in the abstract. Ideally, each abstract should include the following sub-headings, but these may vary according to requirements of the article.

- Background
- Objective
- Method
- Results
- Conclusion

Graphical Abstract:

A graphic must be included with each manuscript for use in the Table of Contents (TOC). This must be submitted separately as an electronic file (preferred file types are EPS, PDF, TIFF, Microsoft Word, PowerPoint and CDX, *etc*.). A graphical abstract, not exceeding 30 words along with the illustration, helps to summarize the contents of the manuscript in a concise pictorial form. It is meant as an aid for the rapid viewing of the journals' contents and to help capture the readers' attention. The graphical abstract may feature a key structure, reaction, equation, *etc*. that the manuscript elucidates upon. It will be listed along with the manuscript title, authors' names and affiliations in the contents page, typeset within an area of 5 cm by 17 cm, but it will not appear in the article PDF file or in print.

Graphical Abstracts should be submitted as a separate file (must clearly mention graphical abstract within the file) online *via* Bentham's Content Management System by selecting the option "supplementary material".

Keywords:

6 to 8 keywords must be provided.

Text Organization:

The main text should begin on a separate page and should be divided into title page, abstract and the main text. The text may be subdivided further according to the areas to be discussed, which should be followed by the List of Abbreviations (if any), Conflict of Interest, Acknowledgements and Reference sections. For review, the manuscript should be divided into title page, abstract and the main text. The text may be subdivided further according to the areas to be discussed, which should be followed by the Acknowledgements and Reference sections. For Research Articles the manuscript should begin with the title page and abstract followed by the main text, which must be structured into separate sections as **Introduction, Material and Methods, Results, Discussion, Conclusion, Conflict of Interest, Acknowledgements and References**. The Review Article should mention any previous important recent and old reviews in the field and contain a comprehensive discussion starting with the general background of the field. It should then go on to discuss the salient features of recent developments. The authors should avoid presenting material which has already been published in a previous review. The authors are advised to present and discuss their observations in brief. The manuscript style must be uniform throughout the text and 10 pt Times New Roman fonts should be used. The full term for an abbreviation should precede its first appearance in the text unless it is a standard unit of measurement. The reference numbers should be given in square brackets in the text.

Italics should be used for Binomial names of organisms (Genus and Species), for emphasis and for unfamiliar words or phrases. Non-assimilated words from Latin or other languages should also be italicized *e.g.per se, et al., etc*.

SECTION HEADINGS:

Section headings should be numbered sequentially, left aligned and have the first letter capitalized, starting with the introduction. Sub-section headings however, should be in lower-case and italicized with their initials capitalized. They should be numbered as 1.1, 1.2, *etc.*

INTRODUCTION:

The Introduction section should include the background and aims of the research in a comprehensive manner.

MATERIALS AND METHODS:

This section provides details of the methodology used along with information on any previous efforts with corresponding references. Any details for further modifications and research should be included.

EXPERIMENTAL:

Repeated information should not be reported in the text of an article. A calculation section must include experimental data, facts and practical development from a theoretical perspective.

RESULTS:

Results should be precise.

DISCUSSION:

This should explore the significance of the results of the work, present a reproducible procedure and emphasis the importance of the article in the light of recent developments in the field. Extensive citations and discussion of published literature should be avoided.

The Results and Discussion may be presented together under one heading of "Results and Discussion". Alternatively, they may be presented under two separate sections ("Results" section and "Discussion" Sections). Short sub-headings may be added in each section if required.

CONCLUSION:

A small paragraph summarizing the contents of the article, presenting the final outcome of the research or proposing further study on the subject, may be given at the end of the article under the Conclusion section.

Authentication of Cell Lines:

The NIH acknowledges the misidentification and/or cross-contamination of cell cultures *e.g.* HeLa cells being used in a research study as a serious problem. In order to ensure that validation of the work and proper utilization of resources. It is a prerequisite that correct reagents be used in studies dealing with established human (tumor) cell lines that have been cultured for more than 4 years up to the date of submission of the manuscript. Cell lines such as short-term cultures of human tumors, murine cell lines (as a catalog of DNA profiles is not yet available) and tumor cell lines established in the course of the study that is being submitted, are presently exempt from this rule. To minimize

the risk of working with misidentified and/or contaminated cell lines, tests such as isoenzyme analysis, karyotyping/cytogenetic analysis and, more recently, molecular techniques of DNA profiling may be carried out to authenticate cell cultures. These tests may help confirm or establish the identify profile for a cell line. Bentham Science recommends that all cell lines be authenticated prior to submitting a paper for review. Authors are therefore required to provide authentication of the origin and identity of the cells by performing cell profiling either in their own laboratory or by outsourcing an approved laboratory or cell bank. Authentication is required when a new line is established or acquired, before freezing a cell line, if the performance of the line is not consistent or results are unexpected, if using more than one cell line, and before publication of the study.

The cell lines profile should be cross-checked with the profile of the donor tissue of other continuous cell lines such as provided by the authentic data bank such as www.dsmz.de/fp/cgi-bin/str.html, ATCC®, *etc*.

Standard Protocol on Approvals, Registrations, Patient Consents & Animal Protection:

All clinical investigations must be conducted according to the Declaration of Helsinki principles. For all manuscripts reporting data from studies involving human participants, formal review and approval by an appropriate institutional review board or ethics committee is required. For research involving animals, the authors should indicate whether the procedures followed were in accordance with the standards set forth in the eighth edition of *Guide for the Care and Use of Laboratory Animals* (grants.nih.gov/grants/olaw/guide-for-the-care-and-use-of-laboratory-animals_prepub.pdf; published by the National Academy of Sciences, The National Academies Press, Washington, D.C.).

Research Involving Animals:

Research work on animals should be carried out in accordance with the NC3Rs ARRIVE Guidelines. For *In Vivo* Experiments, visit https://www.nc3rs.org.uk/arrive-guidelines

Authors must clearly state the name of the approval committee, highlighting that legal and ethical approval was obtained prior to initiation of the research work carried out on animals, and that the experiments were performed in accordance with the relevant guidelines and regulations stated below.

- US authors should cite compliance with the US National Research Council's "Guide for the Care and Use of Laboratory Animals"
- The US Public Health Service's "Policy on Humane Care and Use of Laboratory Animals" and "Guide for the Care and Use of Laboratory Animals"
- UK authors should conform to UK legislation under the Animals (Scientific Procedures) Act 1986 Amendment Regulations (SI 2012/3039).
- European authors outside the UK should conform to Directive 2010/63/EU.
- Research in animals must adhere to ethical guidelines of The Basel Declaration and the International Council for Laboratory Animal Science (ICLAS) has also published ethical guidelines.
- The manuscript must clearly include a declaration of compliance with relevant guidelines (e.g. the revised Animals (Scientific Procedures) Act 1986 in the UK and Directive 2010/63/EU in Europe) and/or relevant permissions or licences obtained by the IUCN Policy Statement on Research Involving Species at Risk of Extinction and the Convention on the Trade in Endangered Species of Wild Fauna and Flora.

Research Involving Plants:

All experimental research on plants (either cultivated or wild), must comply with international guidelines. The manuscript must clearly include a declaration of compliance of field studies with relevant guidelines and/or relevant permissions or licences obtained by the IUCN Policy Statement on Research Involving Species at Risk of Extinction and the Convention on the Trade in Endangered Species of Wild Fauna and Flora.

Registration of Systematic Reviews:

Bentham Science Publishers supports retrospective registration of systematic reviews, in a suitable registry (such as PROSPERO). The registered systematic review must include the registration number as the last line of the manuscript abstract.

Consent for Publication:

If the manuscript has an individuals' data, such as personal detail, audio-video material etc., consent should be obtained from that individual. In case of children, consent should be obtained from the parent or the legal guardian.

A specific declaration of such approval and consent-to-disclose form must be made in the copyright letter and in a stand-alone paragraph at the end of the Methods section especially in the case of human studies where inclusion of a statement regarding obtaining the written informed consent from each subject or subject's guardian is a must. The original should be retained by the guarantor or corresponding author. Editors may request to provide the original forms by fax or email.

All such case reports should be followed by a proper consent prior to publishing.

Randomized Drug Clinical Trial Studies:

Randomized drug clinical trial studies are biomedical or health-related interventional and/or observational research studies conducted in phases in human beings who are randomly allocated to receive or not receive a preventive, therapeutic, or diagnostic intervention that follows a pre-defined protocol. The study is intended to determine the safety and efficacy of approaches to disease prevention, diagnosis and treatment.

Authors of randomized controlled trials are encouraged to submit trial protocols along with their manuscripts. All clinical trials must be registered (before recruitment of the first participant) at an appropriate online public trial registry that must be independent of for-profit interest (*e.g.*,www.clinicaltrials.gov). If you wish the editor(s) to consider an unregistered trial, please explain briefly why the trial has not been registered.

- All randomized clinical trials should include a flow diagram and authors should provide a completed randomized trial checklist (see CONSORT Flow Diagram and Checklist; www.consort-statement.org) and a trial protocol.
- Studies of diagnostic accuracy must be reported according to STARD guidelines; (http://www.stard-statement.org)
- Observational studies (cohort, case-control, or cross-sectional designs) must be reported according to the STROBE statement, and should be submitted with their protocols; (www.strobe-statement.org).
- Genetic association studies must be reported according to STREGA guidelines; (www.medicine.uottawa.ca)
- Systematic reviews and meta-analyses must be reported according to PRISMA guidelines; (www.prisma-statement.org)
- To find the reporting guidelines see (http://www.equator-network.org)

Important points to remember while submitting clinical trials:

- Each manuscript should clearly state an objective or hypothesis; the design and methods (including the study setting and dates, patients or participants with inclusion and exclusion criteria, or data sources, and how these were selected for the study); the essential features of any interventions; the main outcome measures; the main results of the study; a comment section placing the results in context with the published literature and addressing study limitations; and the conclusions. Data included in research reports must be original.
- Trial registry name, registration identification number, and the URL for the registry should be included at the end of the abstract and also in the space provided on the online manuscript submission form. If your research

article reports the results of a controlled health care intervention, list the trial registry, along with the unique identifying number (Please note that there should be no space between the letters and numbers of your trial registration number). Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (*e.g.*, phase 1 trials), are exempted.

- All reports of randomized trials should include a section entitled "Randomization and Masking", within the Methods section.
- The manuscript must include a statement identifying the institutional and/or licensing committee that has approved the experiments, including any relevant details.
- The SI system of units and the recommended international non-proprietary name (rINN) for drug names must be used. Kindly ensure that the dose, route, and frequency of administration of any drug you mention are correct.
- Please ensure that the clinical trials sponsored by pharmaceutical companies follow the guidelines on good publication practice: (http://www.gpp-guidelines.org)

The editors reserve the right to reject manuscripts that do not comply with the above-mentioned requirements. The author will be held responsible for false statements or failure to fulfill the above-mentioned requirements.

Greek Symbols and Special Characters:

Greek symbols and special characters often undergo formatting changes and get corrupted or lost during preparation of manuscript for publication. To ensure that all special characters used are embedded in the text, these special characters should be inserted as a symbol but should not be a result of any format styling (*Symbol* font face) otherwise they will be lost during conversion to PDF/XML

Authors are encouraged to consult reporting guidelines. These guidelines provide a set of recommendations comprising a list of items relevant to their specific research design. Chemical equations, chemical names, mathematical usage, unit of measurements, chemical and physical quantity & units must conform to SI and Chemical Abstracts or IUPAC.

All kinds of measurements should be reported only in International System of Units (SI).

List of Abbreviations:

If abbreviations are used in the text either they should be defined in the text where first used, or a list of abbreviations can be provided.

Conflict of Interest:

Financial contributions and any potential conflict of interest must be clearly acknowledged under the heading 'Conflict of Interest'. Authors must list the source(s) of funding for the study. This should be done for each author.

Acknowledgements:

All individuals listed as authors must have contributed substantially to the design, performance, analysis, or reporting of the work and are required to indicate their specific contribution. Anyone (individual/company/institution) who has substantially contributed to the study for important intellectual content, or who was involved in the article's drafting the manuscript or revising must also be acknowledged.

Guest or honorary authorship based solely on position (*e.g.* research supervisor, departmental head) is discouraged.

The specific requirements for authorship have been defined by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Examples of authors' contributions are: 'designed research/study', 'performed

research/study', 'contributed important reagents', 'collected data', 'analyzed data', 'wrote paper', *etc*. This information must be included in the submitted manuscript as a separate paragraph under the heading 'Acknowledgements'. The corresponding author is responsible for obtaining permission from all co-authors for the submission of any version of the manuscript and for any changes in the authorship.

References:

References must be listed in the ACS Style only. All references should be numbered sequentially [in square brackets] in the text and listed in the same numerical order in the reference section. The reference numbers must be finalized and the bibliography must be fully formatted before submission.

See below few examples of references listed in the ACS Style:

Journal Reference:

- **[1]** Bard, M.; Woods, R.A.; Bartón, D.H.; Corrie, J.E.; Widdowson, D.A. Sterol mutants of *Saccharomyces cerevisiae*: chromatographic analyses. *Lipids*, **1977**, *12*(8), 645-654.
- **[2]** Zhang, W.; Brombosz, S.M.; Mendoza, J.L.; Moore, J.S. A high-yield, one-step synthesis of o-phenylene ethynylene cyclic trimer via precipitation-driven alkyne metathesis. *J. Org. Chem.*, **2005**, *70*, 10198-10201.

Book Reference:

- **[3]** Crabtree, R.H. The *Organometallic Chemistry of the Transition Metals*, 3rd ed.; Wiley & Sons: New York, 2001.

Book Chapter Reference:

- **[4]** Wheeler, D.M.S.; Wheeler, M.M. D. Stereoselective Syntheses of Doxorubicin and Related Compounds In: *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B. V: Amsterdam, **1994**; Vol. *14*, pp. 3-46.

Conference Proceedings:

- **[5]** Jakeman, D.L.; Withers, S.G. E. In: *Carbohydrate Bioengineering: Interdisciplinary Approaches*, Proceedings of the 4th Carbohydrate Bioengineering Meeting, Stockholm, Sweden, June 10-13, 2001; Teeri, T.T.; Svensson, B.; Gilbert, H.J.; Feizi, T., Eds.; Royal Society of Chemistry: Cambridge, UK, **2002**; pp. 3-8.

URL(WebPage):

- **[6]** National Library of Medicine. Specialized Information Services: Toxicology and Environmental Health. sis.nlm.nih.gov/Tox/ToxMain.html (Accessed May 23, **2004**).

Patent:

- **[7]** Hoch, J.A.; Huang, S. Screening methods for the identification of novel antibiotics. U.S. Patent 6,043,045, March 28, **2000**.

Thesis:

- **[8]** Mackel, H. *Capturing the Spectra of Silicon Solar Cells*. PhD Thesis, The Australian National University: Canberra, December **2004**.

E-citations:

- **[9]** Citations for articles/material published exclusively online or in open access (free-to-view), must contain the accurate Web addresses (URLs) at the end of the reference(s), except those posted on an author's Web site (unless editorially essential), *e.g.* 'Reference: Available from: URL'.

Some important points to remember:

- All references must be complete and accurate.
- All authors must be cited and there should be no use of the phrase *et al*. (the term "*et al*." should be in italics).
- Date of access should be provided for online citations.
- Journal names should be abbreviated according to the Index Medicus/MEDLINE.
- Punctuation should be properly applied as mentioned in the examples given above.
- Superscript in the in-text citations and reference section should be avoided.
- Abstracts, unpublished data and personal communications (which can only be included if prior permission has been obtained) should not be given in the references section. The details may however appear in the footnotes.
- The authors are encouraged to use a recent version of EndNote (version 5 and above) or Reference Manager (version 10) when formatting their reference list, as this allows references to be automatically extracted.

Appendices:

In case there is a need to present lengthy, but essential methodological details, use appendices, which can be a part of the article. An appendix must not exceed three pages (Times New Roman, 10 point fonts, 900 max. words per page).The information should be provided in a condensed form, ruling out the need of full sentences. A single appendix should be titled APPENDIX, while more than one can be titled APPENDIX A, APPENDIX B, and so on.

Figures/Illustrations:

All authors must strictly follow the guidelines below for preparing illustrations for publication in ***Endocrine, Metabolic and Immune Disorders-Drug Targets***. If the figures are found to be sub-standard, then the manuscripts will be rejected and the authors offered the option of figure improvement professionally by ***Eureka Science***. The costs for such improvement will be charged to the authors.

Illustrations should be embedded in the text file, and must be numbered consecutively in the order of their appearance. Each figure should include only a single illustration which should be cropped to minimize the amount of space occupied by the illustration.

If a figure is in separate parts, all parts of the figure must be provided in a single composite illustration file.

Photographs should be provided with a scale bar if appropriate, as well as high-resolution component files.

Scaling/Resolution:

Line Art image type is normally an image based on lines and text. It does not contain tonal or shaded areas. The preferred file format should be TIFF or EPS, with the color mode being Monochrome 1-bit or RGB, in a resolution of 900-1200 dpi.

Halftone image type is a continuous tone photograph containing no text. It should have the preferred file format TIFF, with color mode being RGB or Grayscale, in a resolution of 300 dpi.

Combination image type is an image containing halftone , text or line art elements. It should have the preferred file format TIFF, with color mode being RGB or Grayscale, in a resolution of 500-900 dpi.

Formats:

For illustrations, the following file formats are acceptable:

- **Illustrator**
- **EPS** (preferred format for diagrams)
- **PDF** (also especially suitable for diagrams)
- **PNG** (preferred format for photos or images)
- **Microsoft Word** (version 5 and above; figures must be a single page)
- **PowerPoint** (figures must be a single page)
- **TIFF**
- **JPEG** (conversion should be done using the original file)
- **BMP**
- **CDX** (ChemDraw)
- **TGF** (ISISDraw)

Bentham Science does not process figures submitted in GIF format.

For TIFF or EPS figures with considerably large file size restricting the file size in online submissions is advisable. Authors may therefore convert to JPEG format before submission as this results in significantly reduced file size and upload time, while retaining acceptable quality. JPEG is a 'lossy' format. However, in order to maintain acceptable image quality, it is recommended that JPEG files are saved at High or Maximum quality.

Zipit or Stuffit tools should not be used to compress files prior to submission as the resulting compression through these tools is always negligible.

Please refrain from supplying:

1. Graphics embedded in word processor (spreadsheet, presentation) document.
2. Optimized files optimized for screen use (like GIF, BMP, PICT, WPG) because of the low resolution.
3. Files with too low a resolution.
4. Graphics that are disproportionately large for the content.

Image Conversion Tools:

There are many software packages, many of them freeware or shareware, capable of converting to and from different graphics formats, including PNG.

General tools for image conversion include Graphic Converter on the Macintosh, Paint Shop Pro, for Windows, and ImageMagick, available on Macintosh, Windows and UNIX platforms.

Bitmap images (*e.g.* screenshots) should not be converted to EPS as they result in a much larger file size than the equivalent JPEG, TIFF, PNG or BMP, and poor quality. EPS should only be used for images produced by vector-drawing applications such as Adobe Illustrator or CorelDraw. Most vector-drawing applications can be saved in, or exported as, EPS format. If the images were originally prepared in an Office application, such as Word or PowerPoint, original Office files should be directly uploaded to the site, instead of being converted to JPEG or another format of low quality.

Color Figures/Illustrations:

- The cost for color figures/plates/illustrations is **US$ 515** per article for up to 3 colour pages and subsequently **US$ 205.00** per page for any additional colour pages.
- Color figures should be supplied in CMYK and not RGB colors.

Note for authors: To maintain publication quality, figures submitted in colour will be published in colour only.

Chemical Structures:

Chemical structures MUST be prepared in ChemDraw/(CDX) and provided as separate file.

Structure Drawing Preferences:

[As according to the ACS style sheet]

Drawing Settings:	
Chain angle	120°
Bond spacing	18% of width
Fixed length	14.4 pt (0.500cm, 0.2in)
Bold width	2.0 pt (0.071cm, 0.0278in)
Line width	0.6 pt (0.021cm, 0.0084in)
Margin width	1.6 pt (0.096cm)
Hash spacing	2.5 pt (0.088cm, 0.0347in)
Text settings:	
Font	Times New Roman
Size	8 pt
Under the Preference Choose:	
Units	points
Tolerances	3 pixels
Under Page Setup Use:	
Paper	US letter
Scale	100%

Tables:

- Data Tables should be submitted in Microsoft Word table format.
- Each table should include a title/ caption being explanatory in itself with respect to the details discussed in the table. Detailed legends may then follow.
- Table number in bold font *i.e*. Table **1**, should follow a title. The title should be in small case with the first letter in caps. A full stop should be placed at the end of the title.
- Tables should be embedded in the text exactly according to their appropriate placement in the submitted manuscript.
- Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell are displayed as black lines.
- Tables should be numbered in Arabic numerals sequentially in order of their citation in the body of the text.
- If a reference is cited in both the table and text, please insert a lettered footnote in the table to refer to the numbered reference in the text.
- Tabular data provided as additional files can be submitted as an Excel spreadsheet.

Supportive/ Supplementary Material:

We do encourage to append supportive material, for example a PowerPoint file containing a talk about the study, a PowerPoint file containing additional screenshots, a Word, RTF, or PDF document showing the original instrument(s) used, a video, or the original data (SAS/ SPSS files, Excel files, Access Db files, *etc*.) provided it is inevitable or endorsed by the journal's Editor.

Supportive/Supplementary material intended for publication must be numbered and referred to in the manuscript but should not be a part of the submitted paper. In-text citations as well as a section with the heading "Supportive/ Supplementary Material" before the "References" section should be provided. Here, list all Supportive/ Supplementary Material and include a brief caption line for each file describing its contents.

Any additional files will be linked into the final published article in the form supplied by the author, but will not be displayed within the paper. They will be made available in exactly the same form as originally provided only on our Web site. Please also make sure that each additional file is a single table, figure or movie (please do not upload linked worksheets or PDF files larger than one sheet). Supportive/ Supplementary material must be provided in a single zipped file not larger than 4 MB.

Authors must clearly indicate if these files are not for publication but meant for the reviewers'/ editors' perusal only.

PERMISSION FOR REPRODUCTION:

Bentham Science has collaborated with the Copyright Clearance Center to meet our customer's licensing, besides rights & permission needs.

The Copyright Clearance Center's RightsLink® service makes it faster and easier to secure permission from Bentham Science's journal titles. Simply visit Journals by Title and locate the desired content. Then go to the article's abstract and click on "Rights and Permissions" to open the RightsLink's page. If you are unable to locate the content you wish to use or you are unable to secure the rights you are seeking, please e-mail us at permissions@benthamscience.org

Published/reproduced material should not be included unless written permission has been obtained from the copyright holder, which should be forwarded to the Editorial Office in case of acceptance of the article for publication.

AUTHORS AND INSTITUTIONAL AFFILIATIONS:

The names of the authors should be provided according to the previous citations or as the authors would want them to be published along with the institutional affiliations, current address, telephone, cell & fax numbers and the email address. Email address must be provided with an asterisk in front of the name of the principal author. The corresponding author(s) should be designated and their complete address, business telephone and fax numbers and e-mail address must be stated to receive correspondence and galley proofs.

PAGE CHARGES:

No page charges will be levied to authors for the publication of their article. However, the authors may decide for some paid-for editorial services such as open access publication and/or a faster overall publication for their article(s).

LANGUAGE AND EDITING:

Manuscripts submitted containing language inconsistencies will not be published. Authors must seek professional assistance for correction of grammatical, scientific and typographical errors. Professional team available at Eureka Science may assist you in the English language editing of your article. Please contact Eureka Science for a language editing quote at e-mail: info@eureka-science.com stating the total number of words of the article to be edited.

언어 및 편집:

영문 오타가 많은 원고는 출판되지 않을 것입니다. 영문 오타를 없애겠다는 조건으로 받은 원고는 영어 편집 전문회사인 유럽 공동 기술개발 기구로부터 가격 견적서가 보내 질 것입니다. 영어 작문에 어려움이 있는 비영어권 국가의 저자들은 원고를 학술지에 제출하기 전에 영어 편집회사와 접촉할 것을 권합니다. 영어

편집 견적서를 받기 위해서 교정될 원고의 단어수를 적은 메일을 유럽 공동 기술개발 기구 메일인 info@eureka-science.com 로 보내시기 바랍니다.

语言和编辑:

含有很多英文印刷错误的提交稿将不予发表。接受发表的稿件其英文写作应是正确的；专业的语言编辑公司（尤里卡科学，可对稿件的英文润色提供报价。建议非英语国家、且英文写作欠佳的作者在投稿前先与语言编辑公司联系。请与尤里卡科学联系 info@eureka-science.com.

EDITION ET LANGUE:

Les manuscrits soumis avec plusieurs erreurs typographiques en Anglais ne seront pas publiés en l'état. Les manuscrits sont acceptés pour publication à la condition que l'anglais utilisé soit corrigé après la soumission et seront envoyés pour examen à Eureka Science, une société d'édition de langue professionnelle. Les auteurs en provenance de pays où la langue est différente de l'anglais et qui ont de médiocres compétences en anglais écrit, sont priés de contacter la société d'édition de langue avant de soumettre leur manuscrit à la revue. Merci de contacter Eureka Science à info@eureka-science.com pour un devis en indiquant le nombre total de mot de l'article à éditer.

PROOF CORRECTIONS:

Authors will receive page proofs of their accepted paper before publications. To avoid delays in publication, proofs should be checked immediately for typographical errors and returned within **48 hours**. Major changes are not acceptable at the proof stage. If unable to send corrections within **48 hours** due to some reason, the author(s) must at least send an acknowledgement on receiving the galley proofs or the article will be published exactly as received and the publishers will not be responsible for any error occurring in the published manuscript in this regard.

The corresponding author will be solely responsible for ensuring that the revised version of the manuscript incorporating all the submitted corrections receives the approval of all the co-authors of the manuscript.

REPRINTS:

Printed reprints and e-prints may be ordered from the Publisher prior to publication of the article. First named authors may also order a personal online subscription of the journal at 50% off the normal subscription rate by contacting the subscription department at e-mail: subscriptions@benthamscience.org.

OPEN ACCESS PLUS:

Bentham Science also offers authors the choice of "Open Access Plus" publication of articles at a fee of **US$ 1,250** per article. This paid service allows for articles to be disseminated to a much wider audience, on the terms of the *Creative Commons Attribution 4.0 International Public License* (CC-BY 4.0) (https://creativecommons.org/licenses/by/4.0/legalcode). Authors are asked to indicate whether or not they wish to pay to have their article made more widely available on this "Open Access Plus" basis. Where an author does not opt-in to this paid service, then the author's article will be published only on Bentham Science's standard subscription-based access, at no additional cost to the author.

Authors who select the "Quick Track" publication option (see below) and also wish to have their article made available on an "Open Access Plus" basis will be entitled to a **50% discount** on the "Open Access Plus" publication fee.

For more information please contact us at e-mail: openaccess@benthamscience.org

REVIEWING AND PROMPTNESS OF PUBLICATION:

All papers submitted for publication are immediately subjected to editorial scrutiny, usually in consultation with members of the journal Editorial Advisory Board and outside independent reviewers. Every effort will be made to peer review submitted papers quickly. Papers which are delayed by authors in revision for more than 30 days will have to be re-submitted as a new submission. Papers accepted for publication are typeset and proofs are dispatched to authors for any corrections prior to final publication.

QUICK TRACK PUBLICATION:

For this journal an optional fast publication fee-based service called QUICK TRACK is available to authors for their submitted manuscripts.

QUICK TRACK allows online publication within 2 weeks of receipt of the final approved galley proofs from the authors. Similarly the manuscript can be published in the next forthcoming PRINT issue of the journal. The total publication time, from date of first receipt of manuscript to its online publication is 12 weeks, subject to its acceptance by the referees and modification (if any) by the authors within one week.

Authors who have availed QUICK TRACK services in a BSP journal will be entitled for an exclusive 30% discount if they again wish to avail the same services in any Bentham journal.

For more information please contact the Editorial Office by e-mail at emiddt@benthamscience.org.

COPYRIGHT:

Authors who publish in Bentham Science print & online journals will transfer copyright to their work to **Bentham Science Publishers**. Submission of a manuscript to the respective journals implies that all authors have read and agreed to the content of the Copyright Letter or the Terms and Conditions. It is a condition of publication that manuscripts submitted to this journal have not been published and will not be simultaneously submitted or published elsewhere. Plagiarism is strictly forbidden, and by submitting the article for publication the authors agree that the publishers have the legal right to take appropriate action against the authors, if plagiarism or fabricated information is discovered. By submitting a manuscript the authors agree that the copyright of their article is transferred to the publishers if and when the article is accepted for publication. Once submitted to the journal, the author will not withdraw their manuscript at any stage prior to publication.

SELF-ARCHIVING

By signing the Copyright Letter the authors retain the rights of self-archiving. Following are the important features of self-archiving policy of Bentham Science journals:

1. Authors can deposit the first draft of a submitted article on their personal websites, their institution's repositories or any non-commercial repository for personal use, internal institutional use or for permitted scholarly posting.
2. Authors may deposit the ACCEPTED VERSION of the peer-reviewed article on their personal websites, their institution's repository or any non-commercial repository such as PMC, arXiv after **12 MONTHS of publication** on the journal website. In addition, an acknowledgement must be given to the original source of publication and a link should be inserted to the published article on the journal's/publisher's website.
3. If the research is funded by NIH, Wellcome Trust or any other Open Access Mandate, authors are allowed the archiving of published version of manuscripts in an institutional repository after the mandatory embargo period. Authors should first contact the Editorial Office of the journal for information about depositing a

copy of the manuscript to a repository. Consistent with the copyright agreement, Bentham Science does not allow archiving of FINAL PUBLISHED VERSION of manuscripts.

4. The link to the original source of publication should be provided by inserting the DOI number of the article in the following sentence: "The published manuscript is available at EurekaSelect via http://www.eurekaselect.com/openurl/content.php?genre=article&doi= [insert DOI]
5. There is no embargo on the archiving of articles published under the OPEN ACCESS PLUS category. Authors are allowed deposition of such articles on institutional, non-commercial repositories and personal websites immediately after publication on the journal website.

PLAGIARISM PREVENTION:

Bentham Science Publishers uses the iThenticate software to detect instances of overlapping and similar text in submitted manuscripts. iThenticate software checks content against a database of periodicals, the Internet, and a comprehensive article database. It generates a similarity report, highlighting the percentage overlap between the uploaded article and the published material. Any instance of content overlap is further scrutinized for suspected plagiarism according to the publisher's Editorial Policies. Bentham Science allows an overall similarity of 20% for a manuscript to be considered for publication. The similarity percentage is further checked keeping the following important points in view:

Low Text Similarity:

The text of every submitted manuscript is checked using the Content Tracking mode in iThenticate. The Content Tracking mode ensures that manuscripts with an overall low percentage similarity (but which may have a higher similarity from a single source) are not overlooked. The acceptable limit for similarity of text from a single source is 5%. If the similarity level is above 5%, the manuscript is returned to the author for paraphrasing the text and citing the original source of the copied material.It is important to mention that the text taken from different sources with an overall low similarity percentage will be considered as a plagiarized content if the majority of the article is a combination of copied material.

High Text Similarity:

There may be some manuscripts with an overall low similarity percentage, but a higher percentage from a single source. A manuscript may have less than 20% overall similarity but there may be 15 % similar text taken from a single article. The similarity index in such cases is higher than the approved limit for a single source. Authors are advised to thoroughly rephrase the similar text and properly cite the original source to avoid plagiarism and copyright violation.

Types of Plagiarism:

We all know that scholarly manuscripts are written after thorough review of previously published articles. It is therefore not easy to draw a clear boundary between legitimate representation and plagiarism. However, the following important features can assist in identifying different kinds of plagiarized content. These are:

- Reproduction of others words, sentences, ideas or findings as one's own without proper acknowledgement.
- Text recycling, also known as self-plagiarism. It is an author's use of a previous publication in another paper without proper citation and acknowledgement of the original source.
- Paraphrasing poorly: Copying complete paragraphs and modifying a few words without changing the structure of original sentences or changing the sentence structure but not the words.
- Verbatim copying of text without putting quotation marks and not acknowledging the work of the original author.
- Properly citing a work but poorly paraphrasing the original text is considered as unintentional plagiarism. Similarly, manuscripts with language somewhere between paraphrasing and quoting are not acceptable. Authors should either paraphrase properly or quote and in both cases, cite the original source.

- Higher similarity in the abstract, introduction, materials and methods, and discussion and conclusion sections indicates that the manuscript may contain plagiarized text. Authors can easily explain these parts of the manuscript in many ways. However, technical terms and sometimes standard procedures cannot be rephrased; therefore Editors must review these sections carefully before making a decision.

Plagiarism in Published Manuscripts:

Published manuscripts which are found to contain plagiarized text are retracted from the journal website after careful investigation and approval by the Editor-in-Chief of the journal. A 'Retraction Note' as well as a link to the original article is published on the electronic version of the plagiarized manuscript and an addendum with retraction notification in the journal concerned.

E-PUB AHEAD OF SCHEDULE:

Bentham Science Publishers are pleased to offer electronic publication of accepted papers prior to scheduled publication. These peer-reviewed papers can be cited using the date of access and the unique DOI number. Any final changes in manuscripts will be made at the time of print publication and will be reflected in the final electronic version of the issue. Articles ahead of schedule may be ordered by pay-per-view at the relevant links by each article stated *via* the **E-Pub Ahead of Schedule**

Disclaimer:

Articles appearing in E-Pub Ahead-of-Schedule sections have been peer-reviewed and accepted for publication in this journal and posted online before scheduled publication. Articles appearing here may contain statements, opinions, and information that have errors in facts, figures, or interpretation. Accordingly, **Bentham Science Publishers**, the editors and authors and their respective employees are not responsible or liable for the use of any such inaccurate or misleading data, opinion or information contained of articles in the E-Pub Ahead-of-Schedule.

Member of Cope

Apêndice(s)

Proposta de Registo Hospitalar Nacional de Dados

e-mail: carcinomaanaplasicotiroide@gmail.com

(base de dados fica acessível em modo Excel no Google Drive)

password: carcinomaanaplasicotiroide2018

preenchimento base de dados:
https://docs.google.com/forms/d/e/1FAIpQLScqUcZ_9XxhfSY8Kz7pARPMF-EuwAmYg3FC32wR6uvHAiuVtg/viewform?c=0&w=1

BASE DE DADOS CARCINOMA ANAPLÁSICO DA TIRÓIDE

Nº de processo:

Género

1-Masculino

2-Feminino

Data nascimento:

Ano de diagnóstico:

Raça:

1-caucasiana

2-negra

3-asiatica

Patologias crónicas:

1-Diabetes Mellitus

2-Antecedentes neoplásicos

3- Doenças auto-imunes

4- Outras

Patologia Tireoideia Prévia:

1-Hipertireoidismo

2-Hipotireoidismo

3-Bócio multinodular

4-Carcinoma diferenciado

Possíveis fatores de risco:

1-Medicação habitual com levotiroxina

2- Exposição profissional a químicos

3- Bócio multinodular

4- Baixo nível educacional

5- Menarca tardia

6- Primeira gestação em idade jovem

7- Tipo sanguíneo do grupo B

8- Carcinoma diferenciado da tiroide (coexistente ou prévio)

9- Antecedentes de neoplasias malignas não tireoideias

10- Diabetes Mellitus

11- Idade superior a 65 anos

12- Mutação TERT

13- Leucocitose

Principal sintoma de apresentação:

1-Tumefação cervical

2-Assintomático (achado acidental)

3-Disfonia

4-Disfagia

Paralisia pré-operatória de corda vocal

0 - Não

1 - Sim

Ecografia

0 – Sem ecografia

1 – Nódulo <4cm

2 – Nódulo > ou igual a 4cm

3 - Outro

Invasão extra tiroideia em ecografia:

0- Ausente

1- Presente

N+ (invasão ganglionar):

0- Ausente

1- Presente

Dimensão nódulo em eco:

Valor de TSH:

Valor de T3:

Valor de T4:

Anticorpos anti-tiroideus:

0- Negativos

1- Positivos

Tomografia Computorizada

0- Não realizou

1- Realizou

Resultado de citologia/histologia:

Metastização à distância:

0- Não

1- Mediastino

2- Pulmões

3- Pleura

4- Ossos

5- Outro

Mutações:

1- p53

2- BRAF V600E

3- TERT promotor

4- Família RAS

Tratamento multimodal:

0 - Não

1- Sim

Cirurgia

1- Não operado

2- Tireoidectomia total (TT)

3- Tiroidectomia total + esvaziamento compartimento central (ECC)

4- Tiroidectomia total + esvaziamento Comp lateral (ECL)

5- TT + ECC + ECL unilateral

6- TT + ECC + ECL bilateral

7- Traqueostomia
8- Colocação de Stent
9- Outra

Margens Cirurgicas
0-R0
1-R1
2-R2

Invasão linfovascular:
0 – Ausente
1 – Presente
2- Desconhecida

Gânglios linfáticos
0- Negativos
1- Positivos
2- Não examinados

Presença de outras neoplasias na peça:
0- Não
1- Sim

Radioterapia (dose):0- Não realizou
1- <45Gy
2- >45 Gy

Quimioterapia (selecionar todos os utilizados)
0- Não Realizou
1- Paclitaxel
2- Docetaxel
3- Doxorrubicina
4- Cisplatina
5- Carboplatina

Novos alvos terapêuticos:
1- Sorafenib (inibidor multicinases)
2- Lenvatinib (inibidor multicinases)
3- Pazopanib (inibidor multicinases)
4- Vemurafenib (inibidor BRAF)
5- Everolimus (inibidor mTOR)
6- Efatutazona (agonista do PPARy)

Data de falecimento:

Agradecimentos

Agradeço a todos os que em algum momento me ajudaram a alcançar este objetivo.
Um agradecimento especial à minha orientadora, a Mestre Patrícia Andrea Ferreira, por todo o apoio, em particular pela disponibilidade desde o primeiro momento. Agradeço todas as dicas e sugestões, desde a escolha do tema ao finalizar desta monografia.
Muito Obrigada!