Clin Transl Oncol (2017) 19:12–20
DOI 10.1007/s12094-016-1506-0

REVIEW ARTICLE

Spanish consensus for the management of patients with anaplastic cell thyroid carcinoma

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Received: 21 February 2016 / Accepted: 24 March 2016 / Published online: 5 April 2016
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Abstract Anaplastic thyroid cancer (ATC) is the most aggressive solid tumor and almost uniformly lethal in humans. The Boards of the Thyroid Cancer Group of the Spanish Society of Endocrinology and Nutrition and the Grupo Español de Enfermedades Huérfanas e Infrecuentes of the Spanish Society of Oncology requested that an independent task force draft a more comprehensive consensus statement regarding ATC. All relevant literature was reviewed, including serial PubMed searches together with additional articles. This is the first, comprehensive Spanish consensus statement for ATC and includes the characteristics, diagnosis, initial evaluation, treatment goals, recommendations and modalities for locoregional and advanced disease, palliative care options, surveillance, and long-term monitoring. Newer systemic therapies are being investigated, but more effective combinations are needed to improve patient outcomes. Though more aggressive radiotherapy has reduced locoregional recurrences, median overall survival has not improved in more than 50 years.

Keywords Anaplastic thyroid carcinoma · Poorly differentiated thyroid carcinoma · Genetic abnormalities · Distant metastases

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Introduction

Thyroid cancer is unique in that different histologic subtypes exhibit the complete spectrum of cancer behavior. Small, localized papillary thyroid cancers are common and the associated life expectancy is near normal [1]. In contrast, anaplastic thyroid cancer (ATC) is the most aggressive solid tumor known to man. Even when detected while it is still localized, the prognosis is poor. This cancer is uncommon and appears more often in people with low education level, blood group type B, and a history of goiter. Rapid evaluation and establishment of treatment goals are imperative for optimum patient management and call for a multidisciplinary approach. Unfortunately, ATC patient's survival has seen no significant improvement in nearly six decades and little progress has been made in its treatment. Nevertheless, it is important to know which patients will benefit from treatment and stand a better chance of long-term survival; e.g., younger patients with a history of nodular goiter who undergo complete resection of a single

anaplastic tumor without distant metastasis display a better likelihood for long-term survival [2, 3].

To date, no Spanish consensus exists to treat ATC patients. The Board of the Thyroid Cancer Group of the Spanish Society of Endocrinology and Nutrition (SEEN) and the Grupo Español de Enfermedades Huérfanas e Infrecuentes (GETHI) of the Spanish Society of Oncology (SEOM) asked that an independent task force be created to develop a more comprehensive ATC consensus statement to aid practitioners. They selected nine chairpersons to lead the task force and membership on the panel was based on expertise and previous contributions to this field. The topics to be addressed were assigned to two specialists (JMGS and PJF) to write the manuscript that was later reviewed and approved by all the experts. They used their knowledge of the subject, as well as a systematic search using MEDLINE (PubMed), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), for primary references, reviews, and other materials available prior to December 2015, to set down a series of recommendations. In preparing this consensus, we addressed the characteristics, diagnosis, initial evaluation, treatment goals, approaches to locoregional versus advanced/metastatic disease, management options, including palliative care/hospice, surveillance and long-term monitoring, and prognosis. Additionally, we have tried to clarify patients' preference and expectations. All drafts were reviewed and edited by the members of the panel for consistency and returned to the primary authors for review. The authors include specialist physicians in Endocrinology and Oncology. The medical opinions expressed in this consensus are those of the authors. The SEEN and SEOM Boards approved the final document.

Consensus

Epidemiology and characteristics of anaplastic thyroid carcinoma

ATC is an uncommon type of thyroid cancer; it accounts for 0.69.8 % of all thyroid cancers [4]. It has an incidence of 12 cases per million people per year and mortality of close to 100 %. It is vastly different from other histological types of thyroid cancer, especially in its tremendous invasiveness (Table 1).

Most ATCs originate in a nodular goiter or from a well or poorly differentiated thyroid carcinoma; thus, it presents in older individuals than well-differentiated tumors. Up to 80 % of all patients are over the age of 50 at diagnosis (median age of 66–72 years) and age has treatment implications.

The main features of ATC include being histologically undifferentiated and its aggressiveness, tending to display early, systemic dissemination. Consequently, 50 % of all patients have metastasis at diagnosis and 25 % do so within the following months and face a median survival time of 6 months [5, 6]. Therefore, ATC is the thyroid cancer with the worst prognosis and highest mortality. Despite its rarity, it accounts for half of all deaths from thyroid cancer and patients develop distant metastases more frequently than those with well-differentiated thyroid cancers. Moreover, most cases of ATC, displayed progression of locoregional disease and died from local complications [6]. Precisely because of its low prevalence, little research into ATC is performed.

An eightfold decrease in the incidence of ATC has been observed in the last 30 years. This is probably due to the development and availability of immunohistochemical methods that have rendered lymphomas and mixed forms of ATC more readily detected. Moreover, one of the most common pathogenic factors, the presence of nodular goiter, is less common in people of high socioeconomic status, since many undergo prophylactic surgical procedures in which well-differentiated thyroid cancers are sometimes discovered [7–9].

Pathological and genetic abnormalities in anaplastic thyroid carcinoma

Several differentiated thyroid cancers have a single known mutation, but undifferentiated ones, like ATC, have multiple mutations and genetic, epigenetic, and proteomic anomalies (DNA methylation, post-translational modifications, and chromatin remodeling) [10]. Pathology studies reveal spindle cell patterns and immunohistochemical staining is positive for keratin and negative for thyroglobulin; likewise, serum thyroglobulin is unelevated and thyroid peroxidase antibody titers are negative.

The most prevalent genetic mutations are listed in Table 2 and several altered pathways have been identified in undifferentiated anaplastic tissues, including the cell cycle, focal adhesion, mitogen-activated protein kinase, cytoskeleton, transforming growth factor β1 [10], *p53* gene mutation with an overexpression of the p53 protein. Moreover, the p53 protein plays a major role in tumor progression via the cell dedifferentiation pathway, increasing tumor aggressiveness. Its presence, therefore, entails a worse prognosis [8, 10]. The incidence of $BRAF^{V600E}$ mutations in ATC is similar to early-stage well-differentiated tumors, suggesting that some ATC may, in fact, develop from papillary thyroid carcinoma and that the *BRAF* signaling pathway may be highly relevant in this process [11].

Table 1 Differences between anaplastic thyroid carcinoma and papillary thyroid tumor

Characteristics	Anaplastic thyroid carcinoma	Papillary thyroid carcinoma
Incidence	3.8 % of all thyroid cancer	75 % of all thyroid cancer
Mortality	50 % of all deaths from thyroid cancer	<10 % cancer-related mortality
Median age at diagnosis (years)	70	40
Origin	Nodular goiter, well-differentiated thyroid carcinoma	Spontaneously, cervical radiation therapy, some genetic diseases
$BRAF^{V600E}$ mutation (%)	26	45
Concentrate ^{131}I	No	70 %
Thyroglobulin expression	No	Yes
Histological differentiation	Undifferentiated	Well-differentiated
Behavior	Aggressive	Indolent
Clinical feature	Large, rapidly growing painful cervical mass	Painless thyroid nodule
Dissemination	Distant metastases	Regional adenopathies
Metastases at diagnosis (%)	50–75	2–14
Treatment of resectable disease	Surgery and adjuvant radiotherapy and chemotherapy	Surgery
Treatment of unresectable disease	Focus on quality of life. Systemic therapy offers limited benefit	Radioiodine ablation

Table 2 Most prevalent mutations observed in anaplastic thyroid carcinoma

Mutation	Prevalence (%)
AXIN1	82
p53	55
β-Catenin	38
BRAF	26
RAS	22
PTEN	12
PIK3CA	17
microRNA expression	–

ATC also displays anomalies in the number of chromosomes or chromosomal integrity involving regions containing epidermal growth factor receptors, *MET*, *BRAF*, *K-RAS*, *CCND1*, *FOSL1*, *UBE2C*, *CDKN2A*, and PPARγ-28. Similarly, gains in copies of epidermal growth factor receptor, vascular endothelial growth factor receptor 1,2, platelet-derived growth factor receptor A, B, phosphatidylinositol-4,5-bisphosphate 3-kinase a, b, KIT, PDK1, AKT1, and MET [12, 13] have been reported. Stem cell marker's expression has been detected in ATC through immunohistochemistry and PCR [12]. However, no cancer stem cell population has been isolated yet.

MicroRNAs are scantly expressed in other cancers. Some researchers have found down-regulated microRNA in cancer that can be targets of the proteins involved in thyrocyte transformation, and epigenetic silencing of several thyroid-specific genes has also been detected. These changes can diminish the tumor's ability to concentrate ^{131}I, thereby decreasing treatment options [8]. MicroRNAs have been used to classify thyroid tumors [8, 14–16]. Specific downregulation of miR-21 induced differentiation and apoptosis in C443 and SW1736. Inversely, the treatment inhibited the epigenetic mechanisms that control differentiation and cell cycle progression. MiR-21 knockdown significantly increased expression of PDCD4, p21, sodiumiodine symporter, and thyroglobulin. All told, these findings suggest that miR-21 is involved in tumor growth, differentiation, and apoptosis; thus, miR-21 suppression is worth exploring as a possible pathway toward an effective ATC therapy. MicroRNA biogenesis and functions, p53 regulatory network, cyclin D1, and cell cycle control, together with mitochondrial activity, might be co-regulated in their functions. On the other hand, miR-99a is a member of the miR-99 family and has been reported to be down-regulated in some cancers. MiR-99a suppresses tumors and participates in inhibiting the tumorigenesis by acting on the mammalian target of rapamycin (mTOR) pathway in ATC cells and may serve as a novel prognostic and therapeutic target in ATC [16, 17].

Insight into genetic mutations has led to several newer biological agents being tested to treat ATC. Aurora kinase inhibitors, PPARγ agonists, and vascular targeting agents are some of the latest, propitious agents and, with further

research, could become alternative therapies. Further, well-coordinated, preclinical and clinical research is needed to provide more robust evidence for emerging ATC treatments.

The role of iodine has been pointed to. After iodized salt was introduced in some countries, the annual incidence of ATC decreased. One plausible explanation for why ATC is more prevalent in areas with severe iodine deficiency is that when goiter is endemic, people are less concerned about thyroid nodules or swelling. As a result, diagnosis is often delayed until after ATC has developed thereby giving initially well-differentiated thyroid cancer, time to evolve into ATC [18].

To date, no familial association has been described for ATC.

Testing necessary for anaplastic thyroid carcinoma treatment decision-making

The clinical interview should inquire about the most common symptoms presented in Table 3. Clinicians should consider and be alert to the possibility of unusual presentations, such as respiratory obstruction, gastrointestinal symptoms, or bone symptoms due to metastases. The patient should be asked about prior or concurrent differentiated thyroid carcinoma, given that around 2871 % will have a positive history.

The onset of loco-regional symptoms is quick and physical examination will typically reveal palpable hard thyroid masses that tend to be multiple, bilateral, >5 cm in 80 % of cases. Findings include an enlarging neck mass (86 %), dysphonia (33 %), dysphagia (38 %), dyspnea (27 %), pain (16 %), cough and hemoptysis (10 %), and superior vena cava syndrome (8 %) [6]. Distant metastases are found in lung (37.2 %), mediastinum (25 %), liver (10.1 %), bone (6.4 %), kidneys (5.3 %), heart and adrenals (5.2 %), and brain (4.4 %). Most patients debut with a preoperative cervical mass apparently limited to the neck, but tumors can double in size within a period of days or a few weeks.

General imaging studies may reveal an extensive disease at the time of diagnosis; thus, these studies are mandatory to determine the status and existence of distant metastases. If CT fails to detect metastases, a positron emission tomography may be indicated and, in some cases, ultrasound and whole body MRI [19–22].

All ATCs are stage IV according to the TNM staging system, and are subdivided into:

- IVA: intrathyroid tumor, without extracapsular extension
- IVB: extrathyroid tumor, without distant metastases
- IVC: presence of distant metastases

Biopsy is essential to confirm diagnosis, either by fine needle aspiration cytology or biopsy. Diagnosing ATC is generally straightforward on fine needle aspiration, as it shows frankly malignant features, including necrosis, striking nuclear pleomorphism, atypia, pleomorphic multinucleated giant cells, very large cells, and several single, non-cohesive cells, which are uncommon in more differentiated thyroid tumors. However, the distinction between ATC and well-differentiated tumors can occasionally be challenging. ATC and poorly differentiated thyroid carcinoma can initially present similar cytological features and, therefore, be mistaken for follicular thyroid cell carcinoma variants. Immunohistochemical staining methods are typically positive for cytokeratins and TP53, but negative for thyroglobulin. Ki-67 index (MIB-1) is high in samples from cytology or histology.

Laboratory testing should include: hemogram, general biochemistry including liver function, kidney function, calcium, ions, and basal thyrotropin hormone. Some authors recommend positron emission tomography/computer tomography to stage poorly differentiated carcinoma from ATC; however, more studies are needed to define their diagnostic and prognostic usefulness in this setting [20, 22].

Differences between anaplastic thyroid carcinoma and poorly differentiated thyroid carcinoma

Poorly differentiated thyroid carcinoma is a rare, independent thyroid cancer histotype. Until its recognition in 2004, the World Health Organization classified it as a

Table 3 The most common clinical symptoms in anaplastic thyroid carcinoma

Symptom	Present (median) (%)	Appears in (range) (%)
Bulky mass in the neck	86	46–100
Dysphagia	38	1–58
Dysphonia	33	16–58
Dyspnea	27	4–44
Neck pain	16	9–32
Cough and hemoptysis	10	–
Superior vena cava syndrome	8	5–12

variant of well-differentiated thyroid carcinoma. It comprises a heterogeneous group of tumors with clinical and histological features that are intermediate on the spectrum between well-differentiated and ATC, and may be a transitional form. Poorly differentiated thyroid cancer and ATC are sometimes used interchangeably by pathologists and clinicians, thereby confusing the entire issue of how to properly manage ATC.

Poorly differentiated thyroid carcinoma exhibits morphological and clinical characteristics that are intermediate between well-differentiated carcinomas and ATC. Unlike well-differentiated tumors, they have multiple activating mutations. The most widely accepted diagnostic criteria for poorly differentiated thyroid carcinoma are: (1) the presence of a solid/trabecular/insular growth pattern; (2) the absence of the conventional nuclear features of papillary carcinoma; and (3) the presence of at least one of the following: convoluted nuclei, ≥3 mitotic activities per 10 high-power fields, and tumor necrosis. The most common molecular findings are *TP5383* mutations; *BRAF* mutations may also be present, probably reflecting tumor origin in an existing papillary carcinoma. *RAS* mutations occur in up to 50 % of poorly differentiated thyroid carcinomas. ATC, as presented above, display many mutations, and genetic, epigenetic, and proteomic abnormalities [9]. Preservation of immunohistochemical markers of epithelial and thyroid differentiation, such as thyroglobulin and thyroid transcription factor 1, in poorly differentiated carcinoma can contribute to distinguishing it from ATC. One management difference is that total thyroidectomy, central node dissection, and lateral neck dissection, when appropriate, are generally recommended in patients with poorly differentiated thyroid carcinoma, but not in cases of ATC. ^{131}I therapy for patients with ^{131}I-avid distant metastases is also indicated, as is external radiotherapy directed at local residual disease, especially if the surgical team suspects residual disease or when margins are positive on histological evaluation [23, 24].

Anaplastic thyroid carcinoma prognostic factors

Survival for ACT patients ranges from 2.5 to 8.5 months, depending on the presence or absence of metastases [4, 17, 19] and the presence of metastases at diagnosis is the single most decisive factor indicating poor prognosis, with a 3.2 relative risk of mortality (range 2.0–51.1) compared to patients with localized disease. The 6-month survival rate is <20 % [1]; hence, the issue of prognosis should be comprehensively addressed, so that patients can comprehend the impact their disease will have on their quality of life.

The prognostic factors to be considered for treatment decision-making include patient's age, tumor size, and TNM stage.

A retrospective Japanese study identified the following prognostic factors as indicators of poor evolution: age ≥70 years, white blood count >10,000/mm, extrathyroid invasion and distant metastasis at diagnosis, and incomplete or no resection. Multimodal, aggressive treatment, and radiation doses of ≥40 Gy improve survival in stages IVA and IVB, i.e., locally confined tumors, but are of questionable benefit in stage IVC [25]. Another large, multicenter Japanese study also identified age of ≥70 years, presence of acute symptoms, leukocytosis, tumor ≥5 cm, T4B tumor, and distant metastasis as significant risk factors for decreased survival [25]. Long-term survival is possible for selected patients with ATC. The ATC Research Consortium of Japan classification system (extent of disease) and other prognostic factors (e.g., biologic malignancy grade) should be considered when determining treatment strategy[26].

As a result, the aggressiveness of this tumor makes prognostic variables influence the choice of treatment in non-metastatic stages, i.e., more extensive surgery, high-dose radiotherapy, combination therapy can improve survival of patients with non-metastatic ATC and adverse prognostic factors [27].

Role of aggressive therapy in anaplastic thyroid carcinoma

Although survival rates have not significantly improved in the last six decades, multimodality treatment, including surgery, radiation, chemotherapy, and probably in the near future, targeted therapy, is deemed the best strategy to enhance patient outcomes. Treatment approach should be based on recommendations from a multidisciplinary team comprised of surgeons, endocrinologists, medical oncologists, radiation oncologists, pathologists, and radiologists. Optimal management includes rapid assessment of burden of disease, accurate staging, and surgery with the goal of macroscopically complete resection combined with perioperative chemotherapy and radiotherapy.

Once the diagnosis of ATC has been confirmed, tumor stage should be ascertained, that is, extension and resectability, in addition to the patient's overall health status, co-morbidities, functional status, and, hence, operability, as they are the most relevant factors in deciding how best to treat the disease. If the tumor is confined to the thyroid, expedient action and management are essential, given the speed with which metastases appear. In stage IVA, radical surgery, and complementary treatment with radiotherapy and/or chemotherapy are the best alternatives when the aim is to increase survival.

When providing this information, both the risk and benefit of treatment goals and strategies, aggressive therapy, or palliative care must be weighed and patients' expectations and preferences contemplated so that an

informed decision can be made. Treatment strategy and tumor stage notwithstanding, median survival is <1 year; hence, symptomatic control and quality of life must take priority over any other consideration [27, 28].

Indications for radical curative surgery and perioperative multimodal treatment in ATC

Surgical resection stage IVA disease with postoperative chemoradiation remains the American Thyroid Association's (ATA) standard recommendation. ATA guidelines propose multimodal therapy in stages IVA/IVB, i.e., resectable disease, since they have better prognosis and longer survival [19]. If surgery is not possible, chemoradiotherapy should be offered [29–31]. Additionally, certain unresectable IVB stages may respond to aggressive multimodal therapy, including the different treatment regimes described below.

Total thyroidectomy that includes all regional structures and lymph nodes is the surgery of choice for localized ATC. Aggressive resection is probably not indicated for stage IVB and IVC disease, given that morbidity and operative risks outweigh the limited benefits of surgery. Most stage IVB and IVC cases are technically inoperable [31].

External radiation should be started as soon as the patient is sufficiently recovered from neck surgery, usually within 2–3 weeks. Systemic chemotherapy can begin once the patient is sufficiently recuperated from surgery, potentially within 1 week, depending on treatment goals. Perioperative treatment can consist of radiotherapy, chemotherapy, or both.

External beam radiation therapy should be administered once or twice daily (1.5 Gy per fraction) to a total dose of 45–66 Gy. A twice-daily fractionation regimen exhibits a trend toward longer survival. The use of conformal 3-dimensional radiotherapy or intensity-modulated radiotherapy did not influence survival or toxicity [32, 33]. Intensity-modulated radiotherapy is an advanced form of three-dimensional conformal radiotherapy, conforming high doses to the tumor while allowing low dose to normal tissues, thereby achieving a good therapeutic ratio [34–37].

The most promising results for combined therapy have been attained with doxorubicin with or without taxanes or cisplatin combined with external beam radiation therapy [32, 36]. Thus, induction chemotherapy with bi-weekly paclitaxel is a promising strategy for stage IVB ATC, as many responders can reach long-term survival after surgery [37, 38].

In the fosbretabulin in anaplastic cancer of the thyroid (FACT) phase II/III trial, thyroidectomy followed by fosbretabulin in combination with chemotherapy compared with carboplatin/paclitaxel without fosbretabulin, showed a non-significant trend toward improved patient survival (8.2 vs. 4.0 months; 33.3 vs. 7.7 % 1-year survival, respectively) [39].

Nevertheless, as ATC is usually refractory to conventional chemotherapy, radiotherapy, and ^{131}I therapy, new approaches are needed. Original research projects are emerging in the literature regarding genetic mutations, chromosomal instability, and identification of potential biomarkers to be used to develop new anti-ATC agents.

Therapies for metastatic anaplastic thyroid carcinoma

Research into molecular therapies (deacetylase inhibitors, tubulin binding compounds, etc.) and ATC pathogenesis continue to evolve. Care for patients with metastatic disease, stage IVC, focuses on quality of life, as systemic therapy offers very limited benefit. Treatment decision algorithm for stage IV anaplastic thyroid carcinoma is presented in Fig. 1. Chemotherapy may therefore be used in patients with good performance status, but is controversial in the elderly with a poor performance status and other comorbidities. One appropriate alternative for these cases is inclusion in a clinical trial.Likewise, debulking or radiotherapy may be necessary to prevent respiratory or esophageal obstruction.

Motesanib, sorafenib, vandetanib, sunitinib, lenvatinib, imatinib, cabozantinib, gefitinib, everolimus, axitinib, and pazopanib are targeted agents known as tyrosine kinase inhibitors that are capable of suppressing the *RET* oncogene, and vascular endothelial growth factor receptors that have been tested in ATC clinical trials, other multikinase inhibitors have also been used in advanced differentiated thyroid carcinoma.

Of the aforementioned, sorafenib [40–42], axitinib [43], gefitinib [44], imatinib [45], sunitinib [46], and the anti-microtubules fosbretabulin and combretastatin A4 phosphate [47] have reached phase II clinical trials with small sample sizes, yielding promising results with some 33–75 % disease control, whereas the objective response rate was <25 %. In the three ATC-specific phase II studies, 20, 11, and 26 participants were included; objective response rate was 10, 25, and 0 %, respectively; median overall survival was 3.9, 5, and 4.7 months, and, 6-month survival was 30, 45, and 34 % for sorafenib, imatinib, and fosbretabulin, respectively [40, 45, 47]. Several studies are underway to examine new drugs, immunotherapy, or a combination together with chemotherapy.

Paclitaxel has been the most widely cytotoxic agent studied. This anti-microtubule exhibits activity both in monotherapy [48] and in combination with new, targeting agents such as efatutazone [49] and pazopanib [50]. Two studies are currently underway that assess the efficacy of

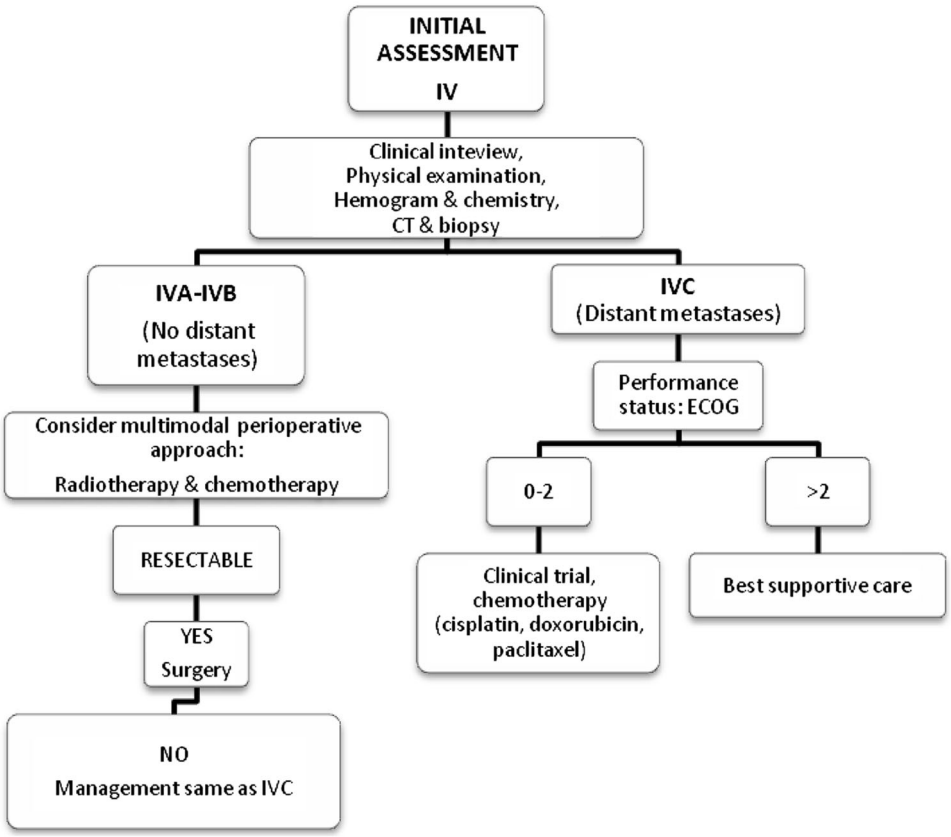

Fig. 1 Treatment decision algorithm for stage IV anaplastic thyroid carcinoma. *ATC* anaplastic thyroid carcinoma, *CT* computed tomography, *ECOG* Eastern Cooperative Oncology Group, performance status scale

fosbretabulin or combretastatin in combination with carboplatin/paclitaxel (NCT01701349, NCT00507429) [51, 52]. While the study failed to meet statistical significance in improving overall survival by adding fosbretabulin to carboplatin/paclitaxel, it is the largest, prospective, randomized trial ever conducted in ATC. The regimen is well tolerated, with adverse effects and mortality primarily related to ATC and disease progression. Everolimus is an mTOR inhibitor and acquired resistance to mTOR inhibition following acceptable response can occur due to secondary mutations in mTOR's FRB domain [53, 54].

In summary, targeted therapy has its place in ATC, but has yet to be fully elucidated and, in this direction, the vascular disrupting agent fosbretabulin appeared to show some signal. Care must be exercised in designing clinical trials to include as many eligible patients as possible in this rapidly fatal disease. Other targeted agents, including sorafenib, have been less successful, but older targeted molecules like imatinib should be revisited, perhaps in combination with histone deacetylase inhibitors.

Case reports have been published of sustained response to chemotherapy regimens such as cisplatin and doxorubicin, associated with radiotherapy, peplomycin, and granulocyte colony stimulating growth factor [55], or with valproic acid [56], docetaxel, and gefitinib [57], erlotinib (in patients significantly expressing epidermal growth factor receptor) [58], and vemurafenib [59]. In patients with $BRAF^{V600E}$ mutation, the combination of $BRAF^{V600E}$ and mTOR inhibition lays the foundation for treatment worthy of further research in *in vivo* model systems [54, 59]. There is a published case report of a patient treated with everolimus. His ATC continued to respond for 18 months; whole-exome sequencing revealed a nonsense mutation in *TSC2*, a negative regulator of mTOR, suggesting a mechanism for sensitivity to everolimus [53].

It is important to note that approximately one-third of differentiated thyroid carcinomas and all ATC do not concentrate ^{131}I; hence, radionuclides are not active as therapy in this cancer. The effect of sodium iodide symporter gene transfection on the uptake of some β- and γ-emitters in human ATC has been evaluated. The results demonstrate the possibility of using sodium iodide symporter gene transfection in ATC for both imaging and therapy, although the short retention time is considered to be the main hurdle to be overcome for its successful implementation [60].

In the near future, biological agents will probably be the standard of care for this aggressive disease, just as they are today in ^{131}I-resistant, differentiated thyroid and other refractory tumors, such as renal or liver cancer.

Palliative care to improve quality of life for anaplastic thyroid carcinoma patients

Palliative care addresses patients' and their families' physical, emotional, social, intellectual, and spiritual needs. Such services typically include one or more of the following: a medical practitioner, specifically trained in palliative medicine; a nurse practitioner, and counselors trained to deal with patients and families coping with serious illness, life-limiting illnesses with no predictable endpoint, complications of therapies, or end-of-life situations. Palliative care is inclusive of life-prolonging therapies. The treatment team should include palliative care expertise at every appropriate stage of patient management to help with pain and symptom control, as well as addressing psychosocial and spiritual issues. Palliative care services are appropriate for any ATC patient receiving treatment intended to prolong life. The treatment team should engage care for ATC patients who decline therapies intended to prolong life, yet still require symptom and pain relief for the remainder of their illness [21, 27, 28].

Regardless, palliative debulking surgery or, more frequently, radiotherapy may be necessary to relieve symptoms such as pain due to bone and brain metastases or cord compression, bleeding, or airway obstruction resulting from extrinsic compression of the thyroid tumor.

Patients with known bone metastases should also be considered as candidates for periodic treatment with intravenous perfusions of bisphosphonates or with subcutaneous administration of an inhibitor of receptor activator for nuclear factor κβ ligand (RANKL), activator of the NF-κβ ligand receptor. Nevertheless, there are currently no precise recommendations regarding treatment duration or frequency of these drugs [19].

Optimal frequency of imaging and follow-up studies in patients with remission after initial therapy

Brain, neck, chest, abdomen, and pelvis TCs should be performed every 1–3 months for the first year and every 4–6 months thereafter [19], in subjects who have undergone complete tumor resection. In cases with no clinical evidence of disease, positron emission tomography with 18-fluorodeoxyglucose scanning should be considered every 6 months' post-treatment to identify small volume disease, requiring fast treatment decisions [22].

Conclusions

In ATC, the best management practices include rapidly evaluating the burden of disease, including potential airway compromise and proper staging. The absence of distant metastases, stages IVA/IVB, is the best prognostic factor to date. Curative surgery through total thyroidectomy and aggressive tumor debulking is the most effective way to prolong survival. Radiotherapy and chemotherapy in combination with surgery has proven to impact survival.

In advanced disease, given the low survival rates and scant efficacy of systemic treatments, priority should be given to preserving quality of life and offering the patient the opportunity to participate in a clinical trial whenever possible. Doxorubicin and cisplatin are classical agents and, like paclitaxel, they are currently the most widely used. They are active alone or in combination with radiotherapy. Of the new targeting agents, the microtubule disrupting agent, combretastatin, and its prodrug, fosbretabulin, have demonstrated efficacy in phase II–III studies. Other drugs have shown poor outcomes, although imatinib may be reconsidered, perhaps in combination with histone deacetylase inhibitors.

Despite advances made in understanding the molecular pathogenesis of this aggressive cancer over the last two decades, more work is needed to identify suitable targets for successful tumor-directed therapy.

Acknowledgments The Board of the Thyroid Cancer Group of the Spanish Society of Endocrinology and Nutrition (SEEN) and the GETHI (Grupo Español de Enfermedades Huérfanas e Infrecuentes) of the Spanish Society of Oncology (SEOM) staff whose support made this review possible.

Conflict of interest The authors have nothing to disclose.

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