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Review article

Anaplastic thyroid carcinoma

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ABSTRACT

Anaplastic thyroid carcinoma (ATC) is a rare but significant malignancy due to its high mortality rate. Rendering an accurate diagnosis is crucial given the prognostic implications and treatment ramifications. Based on the prognostic significance of the extent of invasion of the primary tumor, T staging for ATC changed in the most recent edition of the American Joint Committee on Cancer (AJCC) staging manual. In the past 5 years there has been a rapid increase in our understanding of the molecular basis of ATC which has provided the basis for targeted therapy for some ATC patients. In this review, ATC prognostic factors, histologic and immunotypic features, staging updates, and molecular alterations, with an emphasis on those that may impact treatment, will be discussed.

Introduction

Anaplastic thyroid carcinoma (ATC) accounts for only 1% of all thyroid carcinomas in the United States, but is responsible for approximately a quarter of thyroid-cancer related deaths.[1,2] Although there is a fairly wide age range, the mean age at diagnosis is 65-70.[3–6] Similar to papillary thyroid carcinoma (PTC), ATC demonstrates a female predominance, though the difference in incidence between genders is less pronounced than it is for PTC (ATC female to male ratio is 1.5-2:1). The vast majority of patients present with a neck mass; a smaller subset of patients present due to hoarseness, dyspnea, dysphagia, weight loss, or symptoms (such as pain) secondary to metastatic disease.[7] ATC are large tumors, with a mean size of 5-6 cm.[5,6,8,9] Only a minority of ATC patients have tumors limited to the thyroid at diagnosis (less than 10%), with most patients presenting with tumors with extrathyroidal extension (~70%), lymph node metastases (40-45%), or distant metastases (approaching 50%).[3–6,9–11] Strap muscles are most frequently involved by locally invasive tumor followed by trachea, esophagus, and larynx.[4] The most frequent site of distant metastases are the lungs[8]; however, ATC can spread to virtually any site, including bone and brain.[12] ATC is known as a rapidly fatal disease based on reported median survival rates of 3 to 6 months.[3,6,7,13] Moreover, the one- and two-year survival rates of ATC patients are 20% and 10%, respectively.[4,5,7,14] Most patients die due to distant metastatic disease, though approaching a quarter die as a result of local disease progression.[7,11] In this review, ATC prognostic factors, histologic and immunotypic features, staging updates, and molecular alteration will be discussed.

Prognostic factors in anaplastic thyroid carcinoma

ATC is a rare disease; however, there have been several large studies that have evaluated prognostic factors in these tumors. For example, Kebebew and colleagues and Chen and colleagues both utilized the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to study prognostic factors in 516 and 261 ATC patients, respectively.[3,5] Glaser and colleagues evaluated 3,552 ATC patients with records maintained as part of the National Cancer Data Base.[4] There is also a large Japanese study that evaluated 677 ATC patients from the ATC Research Consortium of Japan,[11] and large single institution studies from Slovenia, South Korea, Japan, and the United States with cohorts of 100 patients or more.[6,7,9,15,16] These studies have demonstrated that younger age at diagnosis, absence of leukocytosis,[7,11,16] smaller tumor size,[3,4,11,15] tumor confined to the thyroid,[3–5,7,11,15] gross total resection,[7,9] and absence of distant metastases at diagnosis[3–5,7,11,15] are associated with improved survival in multivariate analysis.

Although most all ATC patients die of disease regardless of treatment strategy, completeness of surgical resection, surgery plus high-dose external beam radiation therapy (EBRT), and multimodal therapy (surgery, EBRT, and chemotherapy) have been reported to improve survival.[3–5,7,14] For example, Akaishi and colleagues reported 6-month, 1-year, and 2-year survival rates of 68%, 53% and 43% for patients with complete resection compared to 45%, 17%, and 4% for patients who had debulking surgery.[7] Kebebew and colleagues found that combined use of surgery and EBRT was an independent predictor of improved survival in multivariate analysis. However, interestingly, in subgroup analysis, they showed that combined surgical resection with EBRT improved survival in patients with locally advanced regional disease or distant metastases, but did not improve survival in patients with

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intrathyroidal ATC.[5] Mohebati and colleagues evaluated 95 ATC patients treated at Memorial Sloan-Kettering Cancer Center and showed that multimodal treatment improved survival in multivariate analysis.[14] They reported that the 1-year disease-specific survival for patients treated with surgery and chemoradiation was significantly better than for patients who were treated with surgery and EBRT only (52.6% versus 8.3%). Similarly, in a study by Rao and colleagues evaluating the outcome of 54 patients treated at MD Anderson Cancer Center, they found that the median overall survival for patients undergoing multimodal therapy was 22.1 months, with a median overall survival for their entire cohort of 11.9 months.[8] However, as pointed out by Mohebati and colleagues, retrospective studies evaluating multimodal therapy suffer from confounding factors and selection bias, and thus it is difficult to definitively establish the clinical impact of multimodal treatment in the absence of randomized prospective trials. Finally, it is worth mentioning that Glaser and colleagues showed that facility treatment volume (with a cutoff of more than 5 ATC patients treated per year) was associated with improved survival in multivariate analysis, highlighting the importance of experience in treating this aggressive malignancy.[4]

Histologic and immunophenotypic characteristics of anaplastic thyroid carcinoma

ATC is characterized by marked pleomorphism, a high proliferative rate, and invasive/infiltrative growth, with most tumors demonstrating extensive vascular invasion and significant extrathyroidal extension. Additionally, coagulative tumor necrosis is common, and frequently abundant. ATC demonstrates a few main histologic appearances: spindle cell, pleomorphic giant cell, and epithelioid, or squamoid (Fig. 1). Frequently tumors are heterogeneous and have more than one morphology present within the tumor.[9] Although ATC virtually always has areas of one of these common patterns, it is important to note that rarer histologic appearances can occur, such as ATC demonstrating a rhabdoid cytomorphology (Fig. 2a) or paucicellular variant of ATC.[17–21] Paucicellular variant can be mistaken for Riedel thyroiditis due to its low cellularity and relatively bland cytomorphology.[17,21] Although the histologic pattern of ATC is generally not thought to affect prognosis,[9] a recent study reported that tumors with a pleomorphic giant cell morphology pursued a more aggressive clinical course.[8] Very rarely, ATC may be encapsulated and noninvasive; a finding that may be associated with a prolonged survival.[9,22]

Roughly half of ATC have an associated component of differentiated thyroid carcinoma or arise in the setting of a history of differentiated thyroid carcinoma; however, the percentage varies between studies.[8,9,12,13] Interestingly, Han and colleagues showed that the percentage of ATC with a differentiated component has increased over time, going from 10% of ATC diagnosed from 1995-1999, 35% of those diagnosed from 2000-2004, and 48% of those diagnosed from 2005 to 2010.[13] The differentiated component can be PTC, follicular thyroid carcinoma, or Hurthle cell carcinoma. In the study by Rao and colleagues, approximately 30% of their ATC cohort had concurrent differentiated thyroid carcinoma and approaching 20% had a history of differentiated thyroid carcinoma (with a history of PTC in 90% of these cases).[8] About a quarter to a third of ATC occur in patients with a history of goiter.[6,23] In many cases ATC obliterates the thyroid parenchyma; however, it can also entrap non-neoplastic follicles or infiltrate through a more differentiated component of the tumor. ATC is often associated with marked inflammation. There is a heavy macrophage (M2) infiltrate in ATC, and there can also be abundant tumor infiltrating lymphocytes and neutrophils. In a small number of cases, osteoclast-like giant cells (derived from histiocytoid mononuclear cells) are present within the tumor (Fig. 2b).[24,25]

Rendering a diagnosis of ATC is usually straightforward; however, in a subset of cases the diagnosis may be more challenging. Although most ATC are pleomorphic, some ATC with a spindle cell squamous or spindle cell morphology can be deceptively bland (Fig. 3). Additionally, ATC can be missed when it comprises only a small percentage of the tumor or is present in lymph nodes only (either at the time of the initial thyroidectomy or as recurrent disease). In cases with focal ATC, the

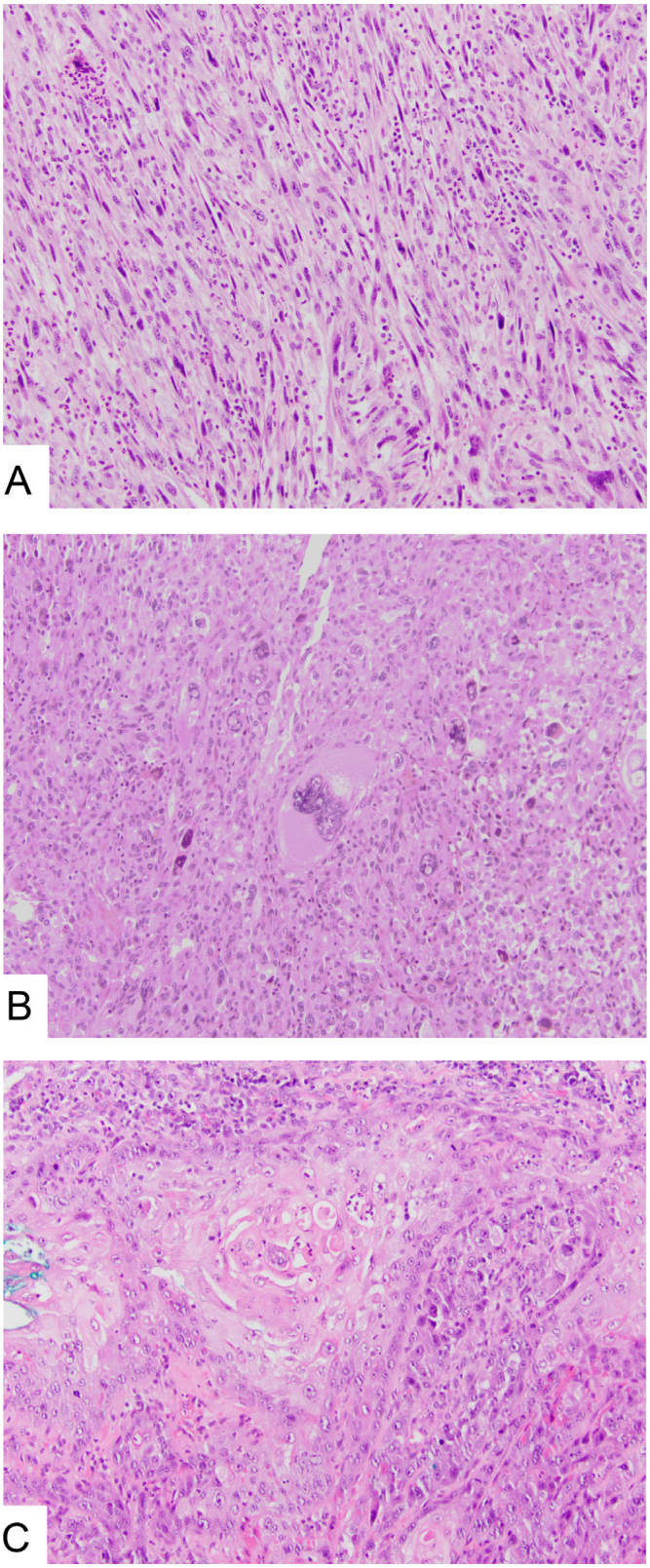

Fig. 1. Anaplastic thyroid carcinoma with a spindle cell morphology (A), pleomorphic giant cell morphology (B), and squamous morphology (C).

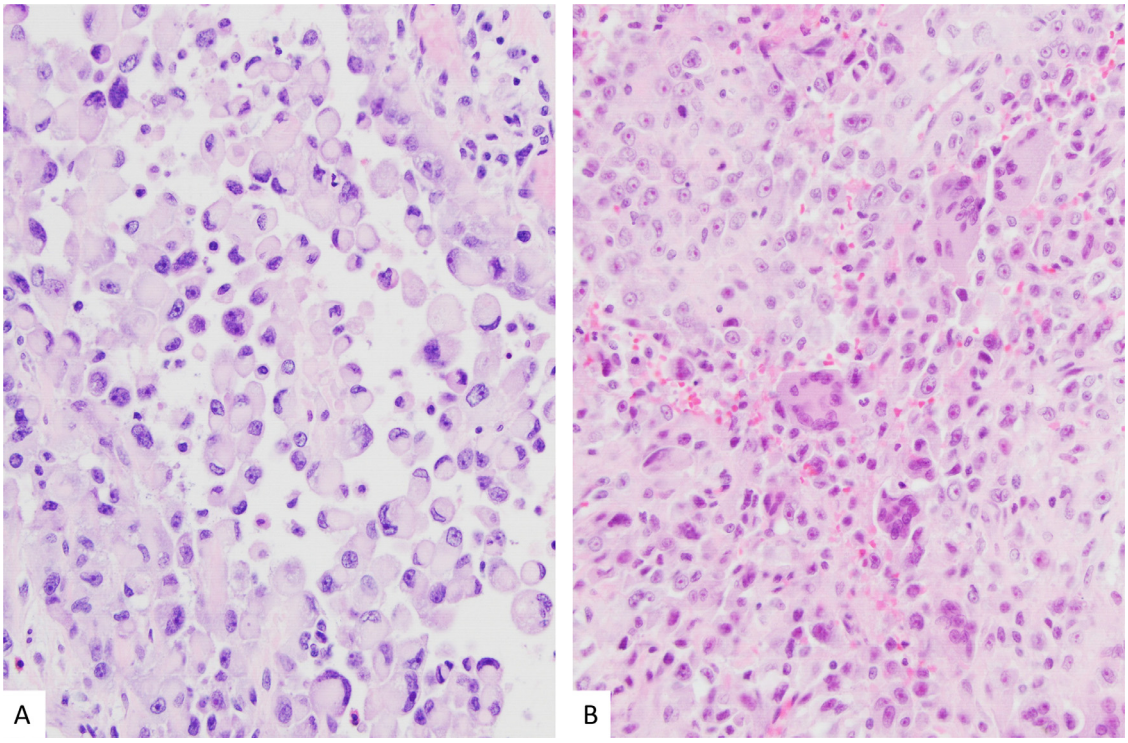

Fig. 2. Anaplastic thyroid carcinoma (ATC) with a rhabdoid cytomorphology (A). ATC with osteoclast-like giant cells (derived from histiocytoid mononuclear cells).

diagnosis is often clinically unexpected due to a less overtly aggressive clinical presentation and because the prior fine needle aspiration usually samples the differentiated component of the tumor. In order to not miss focal progression to ATC, aggressive PTC subtypes (such as hobnail variant and tall cell variant) should be carefully evaluated for areas with loss of nuclear features of PTC, increased cytologic atypia, and increased mitotic activity. Special attention should be paid to the periphery of the tumor where the focal ATC component often arises. Also, generous sampling of aggressive differentiated tumors is advised.

There are few entities that might be considered in the differential diagnosis for ATC, including poorly differentiated thyroid carcinoma, head and neck squamous cell carcinoma, NUT carcinoma, sarcoma, and undifferentiated carcinoma of another primary site. Compared with poorly differentiated thyroid carcinoma, ATC is considerably more pleomorphic, has a higher mitotic rate, and more atypical mitoses (Fig. 4). Another diagnostic consideration if the tumor has a squamoid morphology is head and neck squamous cell carcinoma. Indeed, Gopal and colleagues showed that in their cohort of spindle cell squamous ATC (an ATC frequently associated with tall cell variant), some cases were misinterpreted as laryngeal squamous cell carcinoma.[26] A history of PTC or the presence of a coexisting PTC would be useful in the distinction. Additionally, immunohistochemistry (IHC) can virtually always differentiate a squamoid ATC from a head and neck squamous cell carcinoma (discussed below). Another rare tumor that could potentially be mistaken for ATC is NUT carcinoma. NUT carcinoma, characterized by rearrangement of the nuclear protein in testis (*NUTM1*) gene on chromosome 15q14, is a rare and aggressive malignancy.[27] Although it was initially thought to predominantly present in midline structures of the head, neck, and thorax in young patients, increasingly, it is recognized that it can occur at any age and at most any site.[28] In a study by Landa and colleagues, they identified one NUT carcinoma that had been diagnosed as ATC.[29] In addition to the distinct molecular finding, the patient was the youngest in their cohort (34 years old), and (after extensive surgery and EBRT) was still alive 10 years after surgery, suggesting that this tumor is best classified as a NUT carcinoma rather than an ATC. Finally, ATC can be difficult to differentiate from other aggressive malignancies, such as sarcomas or undifferentiated carcinomas of other primary sites, on the basis of morphology alone.

IHC can be helpful in supporting an ATC diagnosis.[30] ATC is negative for thyroglobulin and is usually negative for TTF-1, though focal/weak TTF-1 staining can be seen in 10-30% of cases.[9,10,31,32] PAX8 expression is frequently maintained, with studies demonstrating PAX8 expression in roughly 35-80% of cases.[10,31–33] Keratin expression is seen in most ATC (with a higher rate of positivity for keratin cocktails detecting low molecular weight keratins such as CAM5.2).[9,10,32,34] P53 overexpression is seen in over half of ATC,[9] and the Ki67 proliferative index is virtually always over 30%.[10,35,36] Roughly one third of ATC harbor a *BRAF* V600E mutation (discussed below).[29,37–45] IHC for BRAF V600E demonstrates a strong concordance with *BRAF* status assessed by molecular assays in PTC.[46] Strong BRAF V600E staining also correlates with mutation status in ATC; however, weak staining for BRAF V600E (or cases with high background staining) has reduced specificity.[9,42,47] Demonstrating a loss of thyroglobulin and TTF-1 expression, p53 overexpression, and a Ki67 proliferative index of over 30% would all support an ATC diagnosis. This is even true if the differential diagnosis includes poorly differentiated thyroid carcinoma, since poorly differentiated thyroid carcinoma generally shows maintained thyroglobulin and TTF-1 expression, lacks p53 overexpression, and has a Ki67 proliferative index between 10 and 30%.[31,48,49] Keratins may be used to support a diagnosis of ATC in tumors with a spindled morphology. PAX8 is extremely helpful in distinguishing squamoid ATC and head and neck squamous cell carcinoma since almost all ATC with a squamous morphology show PAX8 expression whereas PAX8 expression is essentially absent in head and neck squamous cell carcinoma (Fig. 5).[33] BRAF V600E is also often positive in ATC with squamous differentiation, and thus can be used to aid in the diagnosis (Fig. 5).[9,50] Finally, when evaluating ATC, mismatch repair (MMR) IHC could also be considered since 10-15% of ATC are MMR-deficient, which potentially has prognostic and treatment implications (discussed below) (Fig. 6).[29,40,51] Wong and colleagues found that MMR-deficient (MMR-d) tumors were not histologically distinguishable for MMR-intact ATC, though MMR-d ATC did lack an associated well differentiated thyroid carcinoma

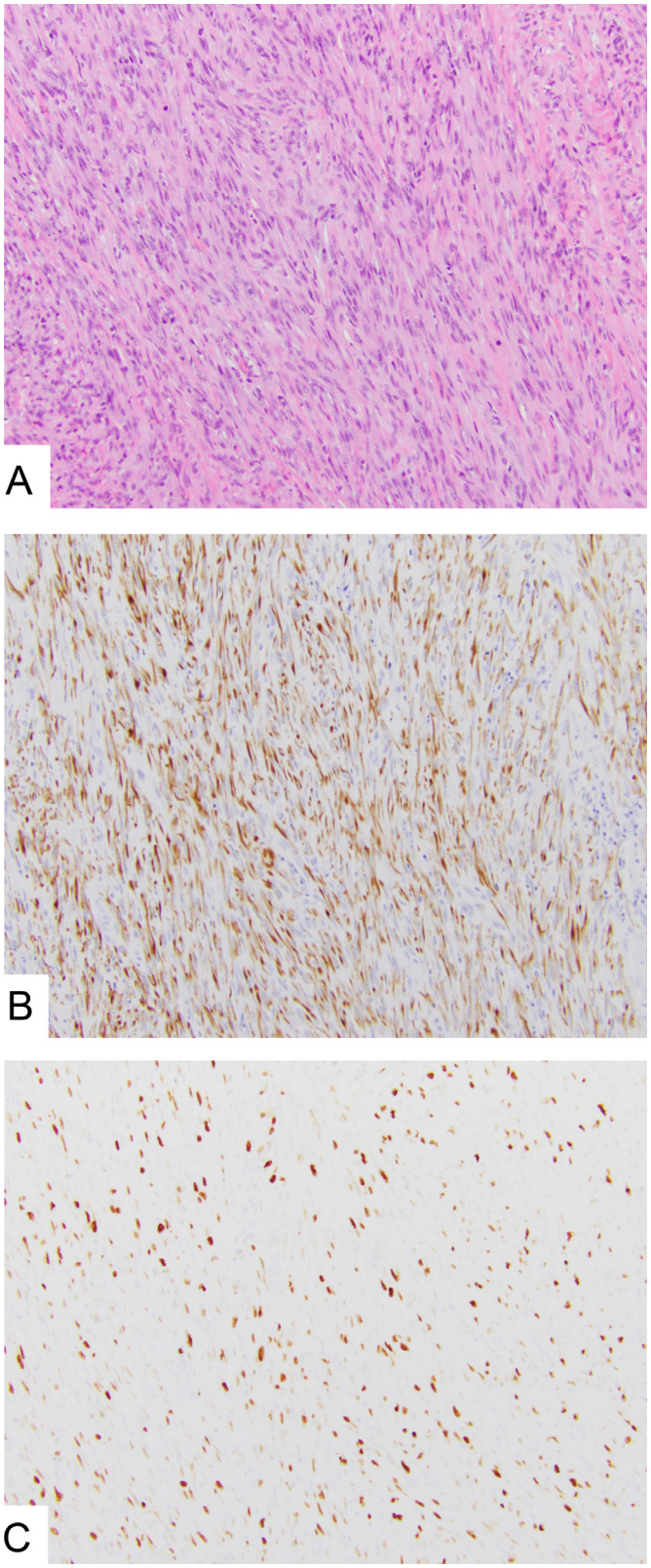

Fig. 3. Anaplastic thyroid carcinoma comprised of relatively bland spindled cells (A). CAM5.2 is positive in most ATC and can be used to confirm a diagnosis of carcinoma (B). The tumor has a Ki67 proliferative index above 30%, consistent with an ATC diagnosis (C).

component (some tumors had areas of tumor with a poorly differentiated morphology).[51]

American Joint Committee on Cancer (AJCC) staging and College of American Pathologists (CAP) guidelines on anaplastic thyroid carcinoma

T staging for ATC has changed in the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual.[52] Unlike previous versions which staged all ATC as T4, the T stage for ATC now uses the same criteria as are used differentiated thyroid carcinomas. This change is based on data showing that patients with intrathyroidal ATC at diagnosis (~10% of patients) have improved survival on multivariate analysis compared to patients with tumors with extrathyroidal extension.[3–5,7,11,14,15] For example, Chen and colleagues reported that patients with disease confined to the thyroid had 2 and 5-year survival rates of 33% and 23%, respectively, and had a median survival of 9 months; whereas, patients with tumors with extrathyroidal extension (in the absence of distant metastases) had 2 and 5-year survival rates of 16% and 10%, respectively, and had a median survival of 6 months.[3] Some studies have also shown that tumor size is a prognostic factor in multivariate analysis,[3,4,11] though the cut-off value has varied between studies (ranging from 5 cm to 7 cm). All ATC are still categorized as stage group IV (IVA: intrathyroidal, IVB: gross extrathyroidal extension or lymph node metastasis, and IVC: distant metastasis). Akaishi and colleagues reported 6-month, 1-year, and 2-year survival rates of 100%, 73%, and 62% for Stage IVA tumors, 6-month, 1-year, and 2-year survival rates of 50%, 25%, and 11% for Stage IVB tumors and 6-month, 1-year, and 2-year survival rates of 22%, 8% and 0% for Stage IVC tumors. Similarly, Sugitani and colleagues reported median survival times of 236 days, 147 days, and 81 days for patients with Stage IVA, IVB, and IVC disease, respectively. In a study by Rao and colleagues evaluating patients treated at MD Anderson Cancer Center (with many receiving multimodal therapy), survival was relatively favorable for patients with IVA disease (overall median survival was not reached), it was 12.3 months for patients with IVB disease, and 7.5 months for patients with IVC disease.

The College of American Pathologists (CAP) Guidelines indicate that ATC should be characterized as comprising a major component of the tumor or a minor component without extrathyroidal extension.[53] This is based on the above referenced studies for intrathyroidal ATC and on studies demonstrating that tumors with a minor ATC component or "incidental ATC" (i.e. tumors with a small anaplastic component in a differentiated thyroid carcinoma) have improved survival compared to tumors in which the ATC component comprises the majority of the tumor (conventional ATC).[11,13,16,23,36] However, the definition of what comprises a minor ATC component is not established and differs between studies. Sugitani and colleagues defined incidental ATC as "a largely differentiated tumor accompanied by a minute (1-2 cm) region of ATC" and reported a median survival of 395 days for such cases compared with 113 days for conventional ATC. In a study from Seoul, Han and colleagues evaluated the survival of 95 ATC patients and found that roughly one quarter of their cohort had tumors with a minor ATC component.[13] They found that 15 of the 95 patients in their cohort lived for over 2 years, 9 of whom had a tumor with an ATC component that was < 1cm. Lee and colleagues reported that the number of ATC with a small ATC component (<10% of the tumor), has increased over time, with 13% of ATC diagnosed between 1985 and 1994 demonstrating a minor ATC component compared to 50% diagnosed from 2005-2013.[16] While they found no difference in survival between patients with pure ATC, ATC with a component of differentiated thyroid carcinoma, and ATC arising in the setting of a history of DTC, the disease specific survival was significantly better for patients with tumors with a minor ATC component. They reported 1-year, 2-year, and 5-year survival rates of 34%, 29%, and 14% for the combined group of patients with pure ATC, ATC with a component of differentiated thyroid carcinoma, and

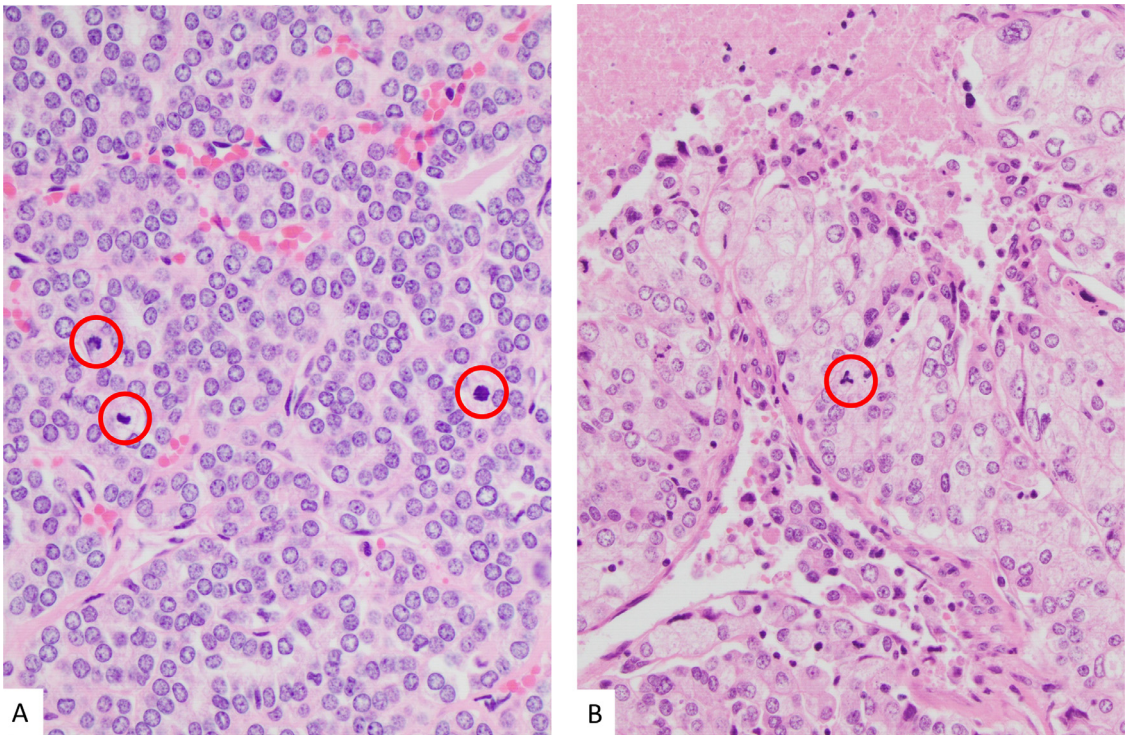

Fig. 4. Poorly differentiated thyroid carcinoma (A) may considered in the differential diagnosis of anaplastic thyroid carcinoma (ATC) (B). In contrast to ATC, poorly differentiated thyroid carcinoma is a relatively monomorphic tumor with a mitotic rate that is higher than that seen with well differentiated thyroid carcinoma (mitoses highlighted by red circles) (A). This ATC has an epithelioid morphology but demonstrates more pleomorphism than is typically seen with poorly differentiated thyroid carcinoma. Necrosis (present in the upper left corner) is often more abundant in ATC, as are mitoses (including atypical forms, highlighted by the red circle).

ATC arising in the setting of a history of DTC. In comparison, patients with tumors with a minor ATC component had survival rates of 98%, 95%, 81% at these same time points, respectively. Choi and colleagues reported a 5-year cause- specific survival rates of 98%, 64%, and 11% for PTC, PTC with "microscopic anaplastic foci", and conventional ATC.[36] In a study of ATC diagnosed at MD Anderson Cancer Center between 1949 and 1977, Aldinger and colleagues evaluated the histology of long-term survivors (those living over a year) and found that 8 of the 11 cases had tumors with a small ATC component. However, when they evaluated the outcome of the 8 additional cases in their cohort with small foci of ATC, they found the survival ranged from 1-9 months. Although this is an older study and survival has improved with an increase in the number of patients receiving multimodal therapy, it still holds true that although the survival of patients with tumors with a minor ATC component is better overall compared to patients with conventional ATC, the clinical course of these patients is variable: many patients may have a comparatively prolonged survival; however, some do not. Moreover, additional tumor characteristics, such as stage and resectability, may be more important than the percentage of the ATC component. In a recent by Wong and colleagues, there was no difference in survival between patients with tumors with a major ATC component and those with tumors with a minor ATC component (defined as comprising $<10\%$ of the tumor).[54] Although this might have been due to the small cohort size (24 patients were included in the study), the finding is also likely a reflection of cohort characteristics: no tumors with a minor ATC component were limited to the thyroid (Stage IVA), resectability with negative margins was infrequent, and 38% of this group had distant metastases at diagnosis (Stage IVC). Additional data on this topic are needed to solidify a definition of ATC with a minor anaplastic component and to further elucidate other variables that impact survival in this subset of ATC patients. Finally, it is worth mentioning that Sugitani and colleagues reported a significantly better 1-year cause-specific survival for patients with anaplastic transformation in lymph nodes only compared to patients with conventional ATC (30% compared with 18%).

Molecular alterations of anaplastic thyroid carcinoma and treatment implications

There has been a rapid expansion in our knowledge of the molecular alterations associated with ATC (Fig. 7). The first two landmark studies on the topic were by Landa and colleagues and Kuntsman and colleagues, with several additional studies on the topic subsequently published.[29,37,39–45] Consistent with their aggressive behavior, ATC has a significantly higher mutation burden than is seen with PTC and poorly differentiated thyroid carcinoma.[29] Landa and colleagues found that the median number of mutations ± interquartile range for ATC and poorly differentiated thyroid carcinoma was 6+/-5 mutations and 2+/-3 mutations, respectively, both higher than that reported by The Cancer Genome Atlas (TCGA) study on PTC (1+/-1).[29,55]

ATC has been postulated to arise either from a well differentiated precursor or de novo. In line with the idea that most ATC arise from well differentiated thyroid carcinomas, at least half have a *BRAF* V600E mutation or a *RAS* mutation, i.e., known driver mutations in PTC and follicular thyroid carcinoma and activators of the MAPK pathway.[29] The *BRAF* V600E mutation rate in ATC is important given its treatment implications (discussed below). However, the reported *BRAF* V600E mutation rate varies widely from 11 to 91% between studies, with a mean rate of approximately 30%.[29,37–45] This wide range may be the result of different methods to detect molecular alterations which results in different sequencing coverage of genes and therefore different detection sensitivities. Additionally, there may be differences in cohort characteristics. For example, the highest *BRAF* V600E mutation rate was reported by a group in Korea, where the prevalence of the *BRAF* V600E mutation in PTC is higher than it is in other geographic regions.[38] The high *BRAF* V600E mutation rate could be due to

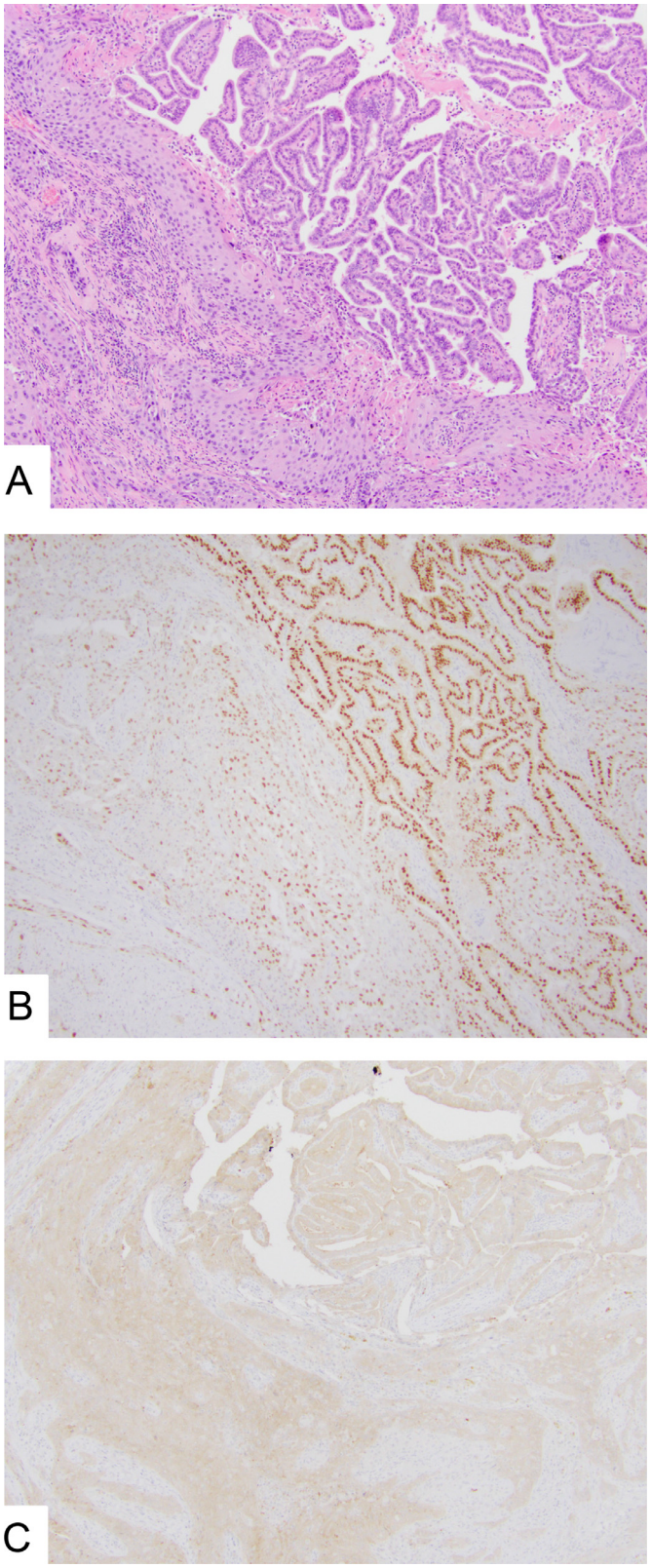

Fig. 5. This anaplastic thyroid carcinoma (ATC) demonstrates squamous differentiation and a papillary thyroid carcinoma (PTC) precursor (A). A precursor PTC would distinguish this ATC from a head and neck squamous cell carcinoma. If a precursor PTC is not present, PAX8 (B) has a high sensitivity for squamoid ATC, and there is a high rate of BRAF V600E positivity in squamoid ATC (C).

differences in genetic background or iodine intake. Also, the *BRAF* V600E mutation rate depends on whether the ATC has an associated PTC precursor. Duan and colleagues reported a *BRAF* V600E mutation rate of 56%, 85%, and 25% for their ATC cohort overall, ATC with a PTC component, and pure ATC. Chen and colleagues also found that ATC with a PTC component had a high *BRAF* V600E mutation rate.[50] The *BRAF* V600E mutation rate has also been found to be associated with older patient age in ATC, with a higher rate seen in older patients.[39,44] Lastly, it should be noted that rare ATC harbor other (non V600E) *BRAF* mutations.[29,41] Approximately 20-25% of ATC harbor *RAS* mutations, including *NRAS, HRAS*, and *KRAS* mutations.[29,39,40,45] *RAS* mutations and *BRAF* mutations are mutually exclusive in ATC. Interestingly, in the TCGA study it was shown that PTC with *BRAF* V600E and *RAS* mutations have different BRAF-RAS scores (a measure of MAPK transcriptional output which results in decreased expression of genes involved in iodine metabolism);[55] however, in ATC, all tumors score as BRAF-like regardless of whether the tumor has an underlying *BRAF* V600E mutation or a *RAS* mutation.[29] A few other frequently mutated genes include *NF1* and *NF2* (about 10% of tumors) and *PTEN* (about 12% of tumors).[29,39] Landa and colleagues found that all 3 tumors with *NF1* mutations also had a *PTEN* truncating alteration.[29] In contrast to poorly differentiated thyroid carcinoma, PTC, and follicular thyroid carcinoma, the vast majority of ATC lack gene rearrangements.[29,39] Rare ATC have been reported to have *ALK* rearrangements, a finding with treatment implications (see below).[56]

ATC have a high rate of secondary oncogenic mutations, including *TP53* mutations, *TERT* promoter mutations, *EIF1AX* mutations, and *PIK3A* mutations. *TP53* mutations are seen in 70% of ATC, which is in contrast to the low rate seen in poorly differentiated thyroid carcinoma (under 10%).[29,38–41,43,45] *TERT* promoter mutations are found in 55% of ATC, with the vast majority being the C228T mutation (and rarely the C250T mutation).[29,39,41,44,45] *TERT* mutations co-occur with *BRAF* V600E and *RAS* mutations. In contrast to the subclonal *TERT* mutations seen in PTC, *TERT* mutations in ATC are clonal and prevalent.[29] The rate of *TERT* mutations varies between studies likely in part due to cohort characteristics. For example, Oishi and colleagues evaluated 27 ATC with a precursor PTC and found the rate of *TERT* promoter mutation was over 90%.[57] Additionally, they highlighted the significance of *TERT* mutation in tumor dedifferentiation, reporting a *TERT* mutation frequency of over 90% in PTC with dedifferentiation to ATC compared to 13% for PTC without ATC.[57] Like *BRAF* V600E, *TERT* mutations are seen more frequently in older ATC patients.[44] Additionally, Shi and colleagues also found that the rate of distant metastases was higher in patients with ATC with the *TERT* C228T mutation (83% versus 31%, $p = 0.001$). Xu and colleagues reported a *TERT* mutation frequency of 75% and found that concomitant *BRAF/RAS* and *TERT* mutations were associated with a worse outcome than a mutation in only one of these genes.[9] Mutations in the eukaryotic translation initial factor *EIF1AX* are found in approximately 10% of ATC. Interestingly, in contrast to PTC in which *EIF1AX* was found to be mutually exclusive with *BRAF* and *RAS* mutations, in ATC *EIF1AX* demonstrates a strong association with *RAS*.[29] In fact, Landa and colleagues found that 93% of tumors with an *EIF1AX* mutation also had a *RAS* mutation. On the other hand, *PIK3CA* mutations, identified in 10-15% of ATC, tend to occur with *BRAF* mutations.[29]

When looking at pathways implicated in ATC tumorigenesis, clearly the MAPK pathway is important, but additionally, genes encoding members of the PIK3CA-PTEN-AKT-mTOR pathway are altered in approximately 40% of tumors, genes encoding components of the SWI/SNF chromatin remodeling complex are mutated in 35%, mutations in histone methyltransferases are seen in a quarter, and mutations in genes involved in the cell cycle (such as *CDKN2A* and *CDKN2B*) are present in 20% of ATC. Somatic mutations in members of the mismatch repair (MMR) pathway are found in a little over 10% of ATC (although there are 2 case reports of ATC associated with Lynch syndrome, it is thought to be an exceedingly rare association).[9,29,40,51] In the study by Wong

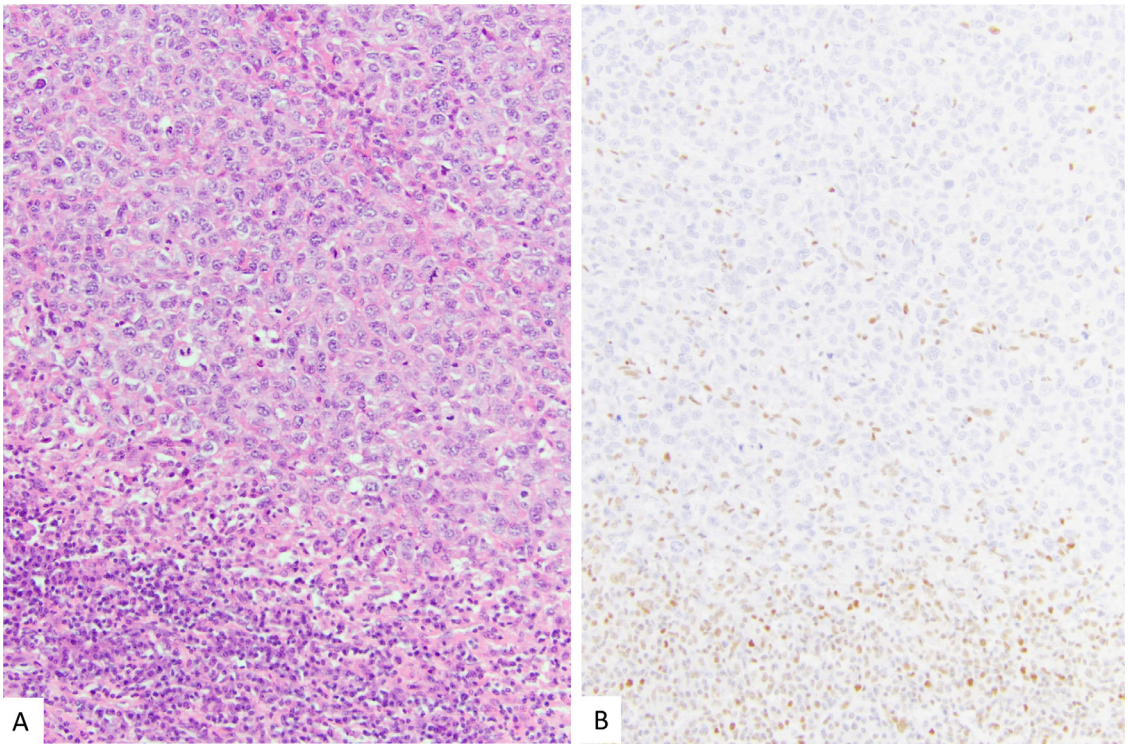

Fig. 6. This is a mismatch repair-deficient (MMR-d) anaplastic thyroid carcinoma (ATC) (A). There was loss of expression of MSH2 (shown) (B). There was also loss of MSH6 expression and intact MLH1 and PMS2 expression (not shown). The tumor had an *MSH2* mutation and demonstrated a hypermutated phenotype. Although this tumor has a marked peritumoral lymphoid infiltrate, MMR-d tumors were not histologically distinguishable from MMR-intact ATC, though all lacked a component of well differentiated thyroid carcinoma.

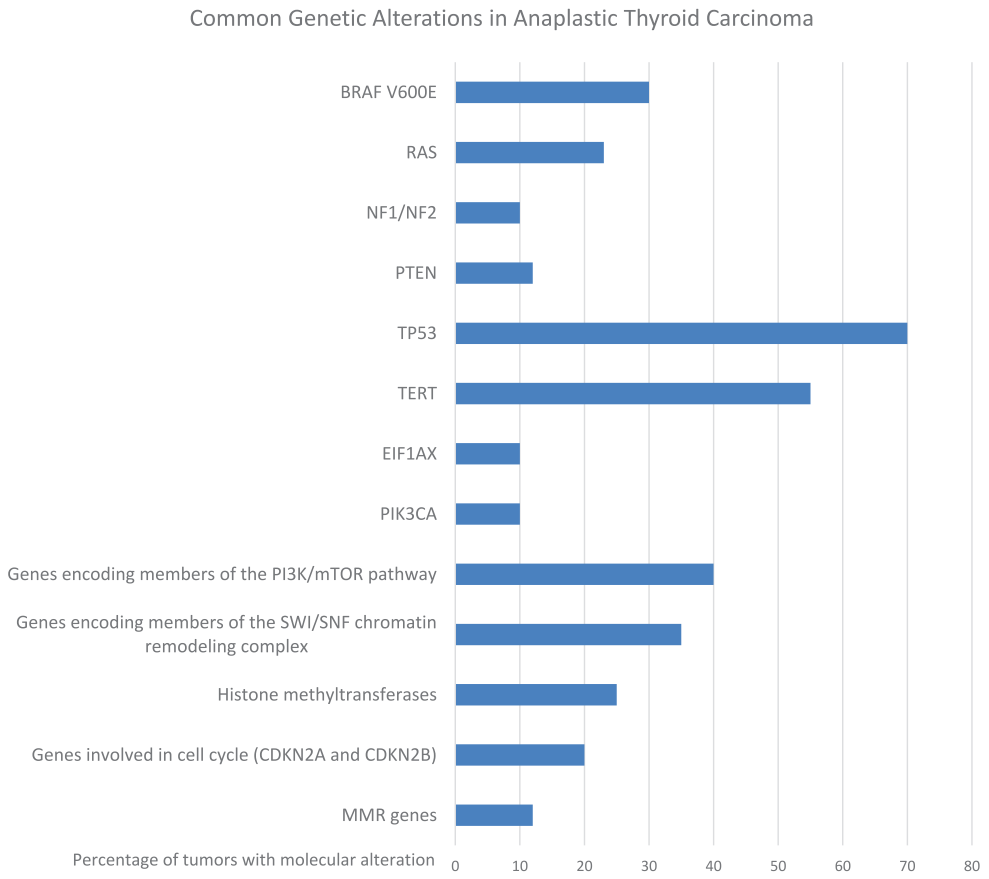

Fig. 7. Common genetic alterations in ATC. Data from references 29 and 37-45 were utilized to determine frequency of genetic alterations.

and colleagues,[51] MMR deficiency was associated with a better prognosis, although this finding was not confirmed in a recent large study by Xu and colleagues.[9] MMR-deficient tumors show a hypermutated phenotype[29,40,50] Although MMR deficiency is present in the majority of ATC with a hypermutated phenotype, some tumors with a high mutation burden show an APOBEC activity signature.[41] A subset of ATC has been shown to have amplification at the cytogenetic locus 9p24.1 containing genes for immune checkpoint proteins PD-L1 and PD-L2.

Although a detailed discussion of ATC treatment is beyond the scope of this review, a few updates on targeted therapy are highlighted. Because virtually all ATC patients either present with or develop distant metastases, ATC must be treated as a systemic disease. Conventional chemotherapy (taxanes, anthracyclines, and platins) have a low response rate in ATC.[58] As a result, novel treatments for ATC are needed. Because a significant subset of ATC harbors the *BRAF* V600E mutation, BRAF inhibitors (vemurafenib and dabrafenib) have been evaluated alone and in combination with MEK inhibitors (such as trametinib) in ATC, and in 2018 the FDA approved dabrafenib and trametinib for the treatment of *BRAF* V600E-mutant ATC. A phase 2 basket study by Hyman and colleagues evaluating the efficacy of vemurafenib in *BRAF*-mutated malignancies (which included 7 *BRAF* V600E-mutant ATC) showed promising results.[59] Subsequently a multicenter phase 2 trial of dabrafenib and trametinib in *BRAF* V600E-mutant ATC patients showed an overall response rate approaching 70%.[60] This finding was corroborated by a retrospective study published by Iyer and colleagues.[61] Although the duration of response is generally limited, sustained responses have been reported.[62] It is also possible that neoadjuvant treatment with these inhibitors may allow surgical resection in patients that were initially inoperable.[63] In addition to BRAF and MEK inhibitors, there is evidence that inhibiting the mTOR pathway with everolimus may be effective, especially in patients with tumors harboring mutations in genes encoding members of the PI3K/mTOR pathway.[64–66] In addition, it may be that more than one pathway needs to be targeted therapeutically. For example, Gibson and colleagues showed an exceptional response to dual pathway blockade in a patient with an ATC that was found to have both *BRAF* and *PIK3CA* mutations.[67] Finally, the data on efficacy of immunotherapy in ATC patients are currently limited. There are a few case reports with promising results.[68–71] Additionally, the results of a phase I/II study that enrolled 42 ATC patients treated with spartalizumab (a humanized monoclonal antibody against the PD-1 receptor) have just been reported.[72] Eight (19%) patients had a response, including 3 with complete responses and 5 with partial responses. The duration of response ranged from 16.7 weeks to 1.6 years (ongoing at data cutoff). Interestingly, one responder had a tumor with a tumor mutation burden (TMB) of 14 mutations/megabase (the highest TMB in the cohort) and an *MSH6* frameshift mutation.

Conclusion

In summary, although we have a solid understanding of histologic and immunophenotypic features, prognostic parameters, and molecular alterations of ATC, it is possible that combining extent of disease, histologic features, and molecular alterations will allow us to further risk stratify these tumors. Moreover, we anticipate the results of additional clinical trials that will elucidate the impact of targeted treatment and immunotherapy and look forward to additional treatment advances for patients with this aggressive thyroid malignancy.

Declaration of Competing Interests

None.

References

1. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974-2013. *JAMA.* 2017;317:1338–1348.
2. Mao Y, Xing M. Recent incidences and differential trends of thyroid cancer in the USA. *Endocr Relat Cancer.* 2016;23:313–322.
3. Chen J, Tward JD, Shrieve DC, Hitchcock YJ. Surgery and radiotherapy improves survival in patients with anaplastic thyroid carcinoma: analysis of the surveillance, epidemiology, and end results 1983-2002. *Am J Clin Oncol.* 2008;31:460–464.
4. Glaser SM, Mandish SF, Gill BS, Balasubramani GK, Clump DA, Beriwal S. Anaplastic thyroid cancer: prognostic factors, patterns of care, and overall survival. *Head Neck.* 2016;38(Suppl 1):E2083–E2090.
5. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer.* 2005;103:1330–1335.
6. McIver B, Hay ID, Giuffrida DF, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery.* 2001;130:1028–1034.
7. Akaishi J, Sugino K, Kitagawa W, et al. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. *Thyroid.* 2011;21:1183–1189.
8. Rao SN, Zafereo M, Dadu R, et al. Patterns of treatment failure in anaplastic thyroid carcinoma. *Thyroid.* 2017;27:672–681.
9. Xu B, Fuchs T, Dogan S, et al. Dissecting anaplastic thyroid carcinoma: a comprehensive clinical, histologic, immunophenotypic, and molecular study of 360 cases. *Thyroid.* 2020.
10. Deeken-Draisey A, Yang GY, Gao J, Alexiev BA. Anaplastic thyroid carcinoma: an epidemiologic, histologic, immunohistochemical, and molecular single-institution study. *Hum Pathol.* 2018;82:140–148.
11. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. Prognostic factors and therapeutic strategy for anaplastic carcinoma of the thyroid. *World J Surg.* 2001;25:617–622.
12. Spires JR, Schwartz MR, Miller RH. Anaplastic thyroid carcinoma. Association with differentiated thyroid cancer. *Arch Otolaryngol Head Neck Surg.* 1988;114:40–44.
13. Han JM, Bae Kim W, Kim TY, et al. Time trend in tumour size and characteristics of anaplastic thyroid carcinoma. *Clin Endocrinol (Oxf).* 2012;77:459–464.
14. Mohebati A, Dilorenzo M, Palmer F, et al. Anaplastic thyroid carcinoma: a 25-year single-institution experience. *Ann Surg Oncol.* 2014;21:1665–1670.
15. Besic N, Hocevar M, Zgajnar J, Pogacnik A, Grazio-Frkovic S, Auersperg M. Prognostic factors in anaplastic carcinoma of the thyroid-a multivariate survival analysis of 188 patients. *Langenbecks Arch Surg.* 2005;390:203–208.
16. Lee DY, Won JK, Lee SH, et al. Changes of clinicopathologic characteristics and survival outcomes of anaplastic and poorly differentiated thyroid carcinoma. *Thyroid.* 2016;26:404–413.
17. Canos JC, Serrano A, Matias-Guiu X. Paucicellular variant of anaplastic thyroid carcinoma: report of two cases. *Endocr Pathol.* 2001;12:157–161.
18. Chetty R, Govender D. Follicular thyroid carcinoma with rhabdoid phenotype. *Virchows Arch.* 1999;435:133–136.
19. Lai ML, Faa G, Serra S, et al. Rhabdoid tumor of the thyroid gland: a variant of anaplastic carcinoma. *Arch Pathol Lab Med.* 2005;129:e55–e57.
20. Sato K, Waseda R, Tatsuzawa Y, Soma R, Ueda Y, Katsuda S. Papillary thyroid carcinoma with anaplastic transformation showing a rhabdoid phenotype solely in the cervical lymph node metastasis. *Pathol Res Pract.* 2006;202:55–59.
21. Wan SK, Chan JK, Tang SK. Paucicellular variant of anaplastic thyroid carcinoma. A mimic of Reidel's thyroiditis. *Am J Clin Pathol.* 1996;105:388–393.
22. Dibelius G, Mehra S, Clain JB, Urken ML, Wenig BM. Noninvasive anaplastic thyroid carcinoma: report of a case and literature review. *Thyroid.* 2014;24:1319–1324.
23. Aldinger KA, Samaan NA, Ibanez M, Hill Jr CS. Anaplastic carcinoma of the thyroid: a review of 84 cases of spindle and giant cell carcinoma of the thyroid. *Cancer.* 1978;41:2267–2275.
24. Gaffey MJ, Lack EE, Christ ML, Weiss LM. Anaplastic thyroid carcinoma with osteoclast-like giant cells. A clinicopathologic, immunohistochemical, and ultrastructural study. *Am J Surg Pathol.* 1991;15:160–168.
25. Hashimoto H, Koga S, Watanabe H, Enjoji M. Unidifferentiated carcinoma of the thyroid gland with osteoclast-like giant cells. *Acta Pathol Jpn.* 1980;30:323–334.
26. Gopal PP, Montone KT, Baloch Z, Tuluc M, LiVolsi V. The variable presentations of anaplastic spindle cell squamous carcinoma associated with tall cell variant of papillary thyroid carcinoma. *Thyroid.* 2011;21:493–499.
27. French CA, Kutok JL, Faquin WC, et al. Midline carcinoma of children and young adults with NUT rearrangement. *J Clin Oncol.* 2004;22:4135–4139.
28. Bauer DE, Mitchell CM, Strait KM, et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. *Clin Cancer Res.* 2012;18:5773–5779.
29. Landa I, Ibrahimpasic T, Boucai L, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *J Clin Invest.* 2016;126:1052–1066.
30. Higgins SE, Barletta JA. Applications of Immunohistochemistry to endocrine pathology. *Adv Anat Pathol.* 2018;25:413–429.
31. Nonaka D, Tang Y, Chiriboga L, Rivera M, Ghossein R. Diagnostic utility of thyroid transcription factors Pax8 and TTF-2 (FoxE1) in thyroid epithelial neoplasms. *Mod Pathol.* 2008;21:192–200.
32. Weissferdt A, Moran CA. Anaplastic thymic carcinoma: a clinicopathologic and immunohistochemical study of 6 cases. *Hum Pathol.* 2012;43:874–877.
33. Bishop JA, Sharma R, Westra WH. PAX8 immunostaining of anaplastic thyroid carcinoma: a reliable means of discerning thyroid origin for undifferentiated tumors of the head and neck. *Hum Pathol.* 2011;42:1873–1877.
34. Venkatesh YS, Ordonez NG, Schultz PN, Hickey RC, Goepfert H, Samaan NA. Anaplastic carcinoma of the thyroid. A clinicopathologic study of 121 cases. *Cancer.* 1990;66:321–330.
35. Lloyd R.V., Osamura R.Y., Kloppel G., et al: WHO classification of tumours of

endocrine organs. Lyon (France): IARC Publications, 2017.
36. Choi JY, Hwang BH, Jung KC, et al. Clinical significance of microscopic anaplastic focus in papillary thyroid carcinoma. *Surgery.* 2013;154:106–110.
37. Duan H, Li Y, Hu P, et al. Mutational profiling of poorly differentiated and anaplastic thyroid carcinoma by the use of targeted next-generation sequencing. *Histopathology.* 2019;75:890–899.
38. Jeon MJ, Chun SM, Kim D, et al. Genomic alterations of anaplastic thyroid carcinoma detected by targeted massive parallel sequencing in a BRAF(V600E) mutation-prevalent area. *Thyroid.* 2016;26:683–690.
39. Khan SA, Ci B, Xie Y, et al. Unique mutation patterns in anaplastic thyroid cancer identified by comprehensive genomic profiling. *Head Neck.* 2019;41:1928–1934.
40. Kunstman JW, Juhlin CC, Goh G, et al. Characterization of the mutational landscape of anaplastic thyroid cancer via whole-exome sequencing. *Hum Mol Genet.* 2015;24:2318–2329.
41. Pozdeyev N, Gay LM, Sokol ES, et al. Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. *Clin Cancer Res.* 2018;24:3059–3068.
42. Rushton S, Burghel G, Wallace A, Nonaka D. Immunohistochemical detection of BRAF V600E mutation status in anaplastic thyroid carcinoma. *Histopathology.* 2016;69:524–526.
43. Sandulache VC, Williams MD, Lai SY, et al. Real-time genomic characterization utilizing circulating cell-free DNA in patients with anaplastic thyroid carcinoma. *Thyroid.* 2017;27:81–87.
44. Shi X, Liu R, Qu S, et al. Association of TERT promoter mutation 1,295,228 C>T with BRAF V600E mutation, older patient age, and distant metastasis in anaplastic thyroid cancer. *J Clin Endocrinol Metab.* 2015;100:E632–E637.
45. Tiedje V TS, Herold T, Synoracki S, Latteyer S, Moeller LC, Zwanziger D, Stuschke M, Fuehrer D, Schmid KW. NGS based identification of mutational hotspots for targeted therapy in anaplastic thyroid carcinoma. Oncotarget. 2017:42613-42620.
46. Ritterhouse LL, Barletta JA. BRAF V600E mutation-specific antibody: A review. *Semin Diagn Pathol.* 2015;32:400–408.
47. Ghossein RA, Katabi N, Fagin JA. Immunohistochemical detection of mutated BRAF V600E supports the clonal origin of BRAF-induced thyroid cancers along the spectrum of disease progression. *J Clin Endocrinol Metab.* 2013;98:E1414–E1421.
48. Asioli S, Erickson LA, Righi A, et al. Poorly differentiated carcinoma of the thyroid: validation of the Turin proposal and analysis of IMP3 expression. *Mod Pathol.* 2010;23:1269–1278.
49. Volante M, Collini P, Nikiforov YE, et al. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. *Am J Surg Pathol.* 2007;31:1256–1264.
50. Chen TY, Lorch JH, Wong KS, Barletta JA. Histologic features of BRAF V600E-mutant anaplastic thyroid carcinoma. *Histopathology.* 2020.
51. Wong KS, Lorch JH, Alexander EK, et al. Clinicopathologic features of mismatch repair-deficient anaplastic thyroid carcinomas. *Thyroid.* 2019;29:666–673.
52. Amin MB. *AJCC cancer staging manual.* 8th edition New York: Springer International Publishing; 2017.
53. Mete O, Seethala, R; Asa SL, et al. Protocol for the examination of specimens from patients with carcinomas of the thyroid gland. College of American Pathologists, 2019.
54. Wong KS, Lorch JH, Alexander EK, et al. Histopathologic features and clinical outcome of anaplastic thyroid carcinoma with a minor anaplastic component. *Endocr Pathol.* 2020.
55. Cancer Genome Atlas Research N. Integrated genomic characterization of papillary thyroid carcinoma. *Cell.* 2014;159:676–690.
56. Kelly LM, Barila G, Liu P, et al. Identification of the transforming STRN-ALK fusion as a potential therapeutic target in the aggressive forms of thyroid cancer. *Proc Natl Acad Sci U S A.* 2014;111:4233–4238.
57. Oishi N, Kondo T, Ebina A, et al. Molecular alterations of coexisting thyroid papillary carcinoma and anaplastic carcinoma: identification of TERT mutation as an independent risk factor for transformation. *Mod Pathol.* 2017;30:1527–1537.
58. Molinaro E, Romei C, Biagini A, et al. Anaplastic thyroid carcinoma: from clinicopathology to genetics and advanced therapies. *Nat Rev Endocrinol.* 2017;13:644–660.
59. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med.* 2015;373:726–736.
60. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. *J Clin Oncol.* 2018;36:7–13.
61. Iyer PC, Dadu R, Ferrarotto R, et al. Real-world experience with targeted therapy for the treatment of anaplastic thyroid carcinoma. *Thyroid.* 2018;28:79–87.
62. Prager GW, Koperek O, Mayerhoefer ME, et al. Sustained response to vemurafenib in a BRAF(V600E)-mutated anaplastic thyroid carcinoma patient. *Thyroid.* 2016;26:1515–1516.
63. Wang JR, Zafereo ME, Dadu R, et al. complete surgical resection following neoadjuvant dabrafenib plus trametinib in BRAF(V600E)-mutated anaplastic thyroid carcinoma. *Thyroid.* 2019;29:1036–1043.
64. Hanna GJ, Busaidy NL, Chau NG, et al. Genomic correlates of response to everolimus in aggressive radioiodine-refractory thyroid cancer: a Phase II study. *Clin Cancer Res.* 2018;24:1546–1553.
65. Harris EJ, Hanna GJ, Chau N, et al. Everolimus in anaplastic thyroid cancer: a case series. *Front Oncol.* 2019;9:106.
66. Wagle N, Grabiner BC, Van Allen EM, et al. Response and acquired resistance to everolimus in anaplastic thyroid cancer. *N Engl J Med.* 2014;371:1426–1433.
67. Gibson WJ, Ruan DT, Paulson VA, et al. Genomic heterogeneity and exceptional response to dual pathway inhibition in anaplastic thyroid cancer. *Clin Cancer Res.* 2017;23:2367–2373.
68. Cabanillas ME, Ferrarotto R, Garden AS, et al. Neoadjuvant BRAF- and immune-directed therapy for anaplastic thyroid carcinoma. *Thyroid.* 2018;28:945–951.
69. Iyer PC, Dadu R, Gule-Monroe M, et al. Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma. *J Immunother Cancer.* 2018;6:68.
70. Kollipara R, Schneider B, Radovich M, Babu S, Kiel PJ. Exceptional response with immunotherapy in a patient with anaplastic thyroid cancer. *Oncologist.* 2017;22:1149–1151.
71. Wirth LJ EE, Capdevila J, et al. Phase I/II study of spartalizumab (PDR001) an anti-PD1 mAB, in patients with anaplastic thyroid cancer. *J Clin Oncol.* 2018;35(15 Suppl):6024.
72. Capdevila J, Wirth LJ, Ernst T, et al. PD-1 blockade in anaplastic thyroid carcinoma. *J Clin Oncol.* 2020 JCO1902727.