Multimodal Approach to Anaplastic Thyroid Cancer

By C. Michele Burnison, MD and Stephen Lim, MD

Introduction

Anaplastic thyroid cancer (ATC) remains an almost uniformly fatal disease; there are few long-term survivors (LTSs), with 2-year survival < 10% to 20%. Rapid cellular kinetics, with doubling times as short as 24 hours in vitro and 5 days in vivo, as well as multiple genomic derangements, account for ATC’s advanced clinical presentations and rapidly acquired resistance to all treatment modalities. Approximately half of patients have distant metastases (DMs) at diagnosis, while 50% to 70% of those with palpable disease likely have occult metastasis, developing DMs within 6 months; once DM develops, survival is reduced to 2 to 3 months. ATC does not concentrate iodine, nor does it express thyroglobulin; to date there is no chemotherapy (CTX) that has had an unequivocal impact on DMs.

Despite such dismal survival statistics, local control (LC) remains an important goal so as to prevent death by asphyxiation or hemorrhage, which are historically cited as the causes of death in 50% to 75% of patients. LC is ultimately determined by the relative, often interrelated, success of both surgery and radiation therapy (RT). Complete surgical extirpation is limited by the degree of extrathyroidal extension (ETE/ATC) and by the comorbidities typically seen in the affected population, which is largely elderly (< 10% under 50 years of age). Fewer than half of patients undergo resection, and fewer than half of those who do (< 25% to 30% overall) complete a gross total resection (GTR); far fewer (< 15%) achieve a microscopic complete (R0) surgical status. The success of RT is more difficult to quantitate. Eradication of disease is dependent on the volume of disease irradiated, the total dose applied, and the inherent radiosensitivity of the tumor. In ATC, these variables represent great challenges, since the volume of disease is typically large, the dose is constrained by the tolerance of the nearby anatomical structures (spinal cord, 50 Gy; esophagus, 60 Gy), and the biology is recognized to be one of the most explosive in oncology. Genomic instability leads to frequent mutations, accounting for both accelerated repopulation and acquired radioresistance. Resistance to RT is further enhanced by the hypoxia associated with larger bulk of tumors. Unless an effective dose can be applied such that the entirety of the tumor within the surgical bed is sterilized, mutated residual clonogens will likely require even higher doses per given volume of disease for eradication. Radiocurability is unlikely given the dose-limiting tolerance of the normal tissues; hence, surgery is retained in an aggressive multimodal approach.

A review of the literature regarding the role of RT in the management of ATC is especially tedious given the rarity of ATC (consisting of less than 2% of thyroid cancers) and the availability of only retrospective reviews, with no prospective randomized trials to guide patient care. A review of the literature may seem of questionable value given the apparent lack of change in long-term survival (LTS) over the past 50 years. Nevertheless, in the interest of securing LC, more recent literature attests to significant accomplishments, including changes in the pattern of the cause of death; improvement in the least short-term median survival (ms); and reports that some patients presenting with palpable tumors—and even a few with initially unresectable (R3) tumors—may become long-term, no-evidence-of-disease survivors (LTS/NED). However, these accomplishments have required the adoption of a multimodal strategy (MMS) incorporating surgery, RT, and sensitizing CTX (combined modality therapy [CM]); the efficacy of such a strategy must be individualized in accordance with the likelihood of accomplishing reasonable goals, and must be weighed against the risk of incurring significant acute and late toxicities.

In this article, we endeavor to clarify the role of RT and CTX in the treatment of ATC; we note important contributions of the historical literature, and we review more contemporary strategies.
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adopted by several renowned institutions, each of which in its own way has addressed the challenge of treating locally advanced tumors and of identifying treatment variables that may be predictive of LTS. Given that none of the available studies have stratified patients according to defined prognostic variables, the use of secondary metrics, described herein, may be useful to decipher the literature and extend interpretations so as to make them relative to individual patient care. Furthermore, while achieving “durable” LC (as opposed to only temporary LC) might be irrelevant for patients who may be currently doomed to succumb to initial or occult DMs, such a goal may become imperative should target therapies soon fulfill prospects of having an impact on metastatic disease. The evolving milestones in the development of these novel systemic therapies will also be reviewed.

Contributions From the Historical RT Literature

In order to support the hypothesis that more aggressive MMSs have a favorable impact on outcomes, we have arbitrarily divided this analysis into a review of the “historical literature,” which generally refers to treatment paradigms from before the 1980s but more specifically to those utilizing standard fractionated RT (SF/RT), and a consideration of the more “contemporary literature,” which includes discussion of the incorporation of novel RT strategies within the context of a MMS. However, this distinction is primarily descriptive, rather than a valid comparison, since the earlier literature is notably fraught with serious omissions and lacks standardization of important RT parameters, thereby limiting analysis of the specific merit of RT. On review of the historical literature, with few exceptions, RT parameters (total dose, fractionation, and field definition) were either ambiguous or omitted entirely. If reported, there also was often wide variation in the prescribed total doses, with ranges of 25 to 73 Gy.[7,12,14,15] If a study’s fractionation (FXN) schedule was cited, it was rarely standardized (or stratified); often it consisted of a “hybrid distribution,” with some patients having been treated with SF/RT, defined as 1.8–2.0 Gy per day (QD), while others were prescribed a “hypofractionated” (HYPOFXN/RT) schedule, typically > 3 Gy QD, to a lower total dose. The historical literature has generally reported on a “single modality” approach, either using surgery alone for the approximately 50% of resectable patients or using primary RT for the treatment of R3 disease. In only 10% of “typical ATC” (palpable tumors with ETE [ETE/ATC]) was an R0 resection achieved.[7] Furthermore, even when a near microscopic complete resection was achieved, almost 40% of tumors recurred within 2 months.[13] Other-wise, for the majority of patients there was no improvement in even short-term median survival (ms) with either surgery alone (including extensive resections) or RT (occasionally with CTX), vs patients who had biopsy alone (ms 3.5 vs 2.5 months).[13]

The RT literature evolved to validate the importance of securing a curative resection (GTR) coupled with postoperative (postop) RT as predictive of improved LC.[6,13] For patients without overt DMs, there was suggestion of improvement in at least short-term ms.[2,7] Pierie noted that inclusion of “incidental ATC” (iATC)—a small volume of ATC discovered at the time of thyroidectomy for another disease—skewed the survival statistics of relatively small study populations; he noted that more than half of patients in whom an R0 resection was able to be completed had iATC (with a 90% 3-year survival [3YS]), while < 7% (4/57) of the LTSs had more extensive tumor.[7] Haigh redefined a potentially curative surgery as a GTR, ie, resection of all visible disease, not necessarily R0 (microscopically complete), if followed by a minimum of 45 Gy of postop CM.[12] Nearly half of his study population had tumors of < 5 cm, although ETE was seen in over 80%. Of those who received organ-preservation surgery, GTR could be completed in 30% (8/26). This small subgroup, half of whom (4/8) had minimal R1 residuum, showed relatively improved survival, with ms of more than 3 years, and 1-year overall survival of 80%; most likely the population had predominantly intrathyroidal ATCs (IT/ATCs). Notably, four of five LTSs had completed GTRs as well as postop CM.[12] In summary, while a single-modality approach had failed,[6,13,16] a multimodal approach appeared to improve the LC for patients who had IT/ATC or small-volume ETE/ATC[6,17] and who were able to secure a GTR. In comparison, for those with R3 or incompletely excised (gR2) disease who were treated with postop CM, a palliative resection alone, or primary CM, the ms was invariably poor at 3 months—similar to the ms for patients with initial DM.[13] For the approximately 50% to 75% of patients (with or without DMs) who presented with locally advanced tumors, survival remained poor, even after doses “in the range of 45 to 75 Gy” plus CTX.[10,12,14] In a recent review of 188 patients treated from 1972 through 2003 using different treatment tactics, the relative distribution of patients left with R0, R1, R2, and R3 (unresectable) disease were 8%, 8%, 14%, and 69%, and their reported ms were 17, 8, 5, and 2 months, respectively.[18] Despite the omissions of RT parameters, the historical ATC literature eventually contributed to the
Radiosensitivity is a measure of the inherent susceptibility of cells to damage by RT. Radiosensitivity is known to be highly associated with occult DMs.[6,7] and of RT to secure LC, but it also has an impact on any prospects for LTS/NED, as extensive disease of disease, specifically the extent of ETE/palpable disease, not only influences the ability of surgery to that of the more well-differentiated elements.[25] Finally, it should be emphasized that the extent prognosis, which probably is related more to the volume and extent of the ATC component relative to recurrence.[7,18,24] It also remains controversial whether “mixed ATCs” have a more favorable prognosis, which probably is related more to the volume and extent of the ATC component relative to that of the more well-differentiated elements.[25] Finally, it should be emphasized that the extent of disease, specifically the extent of ETE/palpable disease, not only influences the ability of surgery and of RT to secure LC, but it also has an impact on any prospects for LTS/NED, as extensive disease is known to be highly associated with occult DMs.[6,7]

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varies throughout the cell cycle and with the availability of oxygen (required for cell kill). Increasing FXN may improve cell kill by allowing for reassortment and reoxygenation; however, if overall RT time is protracted, it will then facilitate accelerated repopulation as a result of cellular mutations and survival of resistant clones, phenomena typically observed after the first 3 to 4 weeks of RT.[26] Hyperfractionation (HPFXN/RT), giving smaller doses with multiple fractions per day but the same total dose over same amount of time, in concept decreases late toxicity, or conversely, allows for an increase in total dose with the same amount of late effects. However, only accelerated HPFXN/RT (HART) gives the same total dose over a shorter period of time and most efficiently compensates for cellular repopulation.[27] However, the efficacy of HART may be limited by the tolerance of the early-responding normal tissues, such as esophagus and skin. Although in concept late-responding tissues should be relatively spared, if the FXN dose is too high or the time between fractions is too short, then there may be insufficient time for repair of normal tissues or there may be depletion of stem populations, which will prove detrimental.[28] On the other hand, high-precision RT, using advanced technology, may allow higher doses to be delivered to tumor, and relatively less to critical structures if the latter are not in too close proximity to the target.[29-31] CM entails the concomitant use of RT and a chemotherapy agent that has been shown to be effective against a tumor—and ideally with different toxicities than those anticipated with RT. Different mechanisms of action include synergistic DNA damage or inhibition of repair of RT damage or of tumor repopulation.

Review of the contemporary RT literature

In the 1980s, several institutions investigated novel “dose-intensifying” approaches in an effort to address the challenges both of treating measurable volumes of ATCs and of the observed rapid proliferation of recurrent or persistent disease over time. Such strategies included using twice-a-day treatment (BID HPFXN/RT), typically along with condensed overall treatment times (HART), as well as employing CTX as a radiosensitizer (CM). Often, both tactics were used: preoperative (preop) or postop RT with either HPFXN/RT or HART, 1.2–2.0 Gy BID with CM—or a similar RT regimen interdigitated with CTX (sequential CM); notably, however, total doses were rarely escalated. Additionally, revolutionary improvements in technology, including 3-dimensional (3D) radiotherapy and, more recently, intensity-modulated radiation therapy (IMRT), have facilitated the delivery of higher total tumor doses, approximating 66 to 70 Gy,[19,29] while still remaining within the tolerance of nearby critical structures—a feat unattainable with earlier technologies. Moreover, several contemporary authors, recognizing the need for a GTR, pursued a preop RT approach. Such an approach is especially relevant for the 50% of initially R3 tumors. Some authors who have adopted a preop approach have reported some of the highest ms and lowest DcLF (death with a component of local failure) in the RT literature.[20,25,32]

The details of seven contemporary studies are included in Tables 1 and 2. These reports come from several, notably international, centers, including Memorial Sloan-Kettering Cancer Center,[33] Princess Margaret Hospital,[34] Royal Marsden Hospital,[22,35] MD Anderson Cancer Center,[19] Gustave-Roussy,[25] Lund University in Sweden,[32] and the Institute of Oncology in Slovenia.[20]

As can be seen, these treatment regimens are distinctively different with regard to total dose, FXN schedule, the use of CM, and the sequencing of treatments, as well as, importantly, the prognostic variables of different study groups. Many of these series are institutional reports of unique strategies, without controls[32,36]; none were randomized, and only two were prospective.[25,32]

Three institutions reported on the use of preop RT, generally split course, with an initial dose of 30–46 Gy prescribed for R3 tumors in the hope of changing the patient’s resectability status. Importantly, a change in resectability was recorded for 23%, 40%, and 70%, respectively.[20,25,32]

Several authors performed comparative analysis: patients were categorized by intent of treatment,[19] performance status,[34] resectability status,[20] or whether or not they had DMs.[20,25] Notably, Besic’s entire study population was entirely devoid of DMs.[20] With regard to treatment parameters, CTX was concomitant with RT in two series,[32,33] sequentially alternated with RT in another,[25] inconsistently used in three,[19,20,34] and avoided in two.[22,35] Similarly, FXN schedules included HPFXN/RT[33] or accelerated HPFXN,[20,22,25,35] while some authors reported outcomes on “hybrid distribution,” citing various percentages of HPFXN/RT and SF/RT courses (notably, less than half used HPFXN/RT).[19,20] Finally, with rare exception,[19,34] the extent of RT fields was similar (mastoid to carina). Other important RT treatment variables, including total dose and technique, varied significantly between studies and often within a study, although most noted a tendency for dose escalation over time.[19] Although 3D treatment planning was introduced in the 1980s, almost all of these contemporary studies relied on simple anteroposterior/posteroanterior (AP/PA) fields with electron boosts; only Bhatia and Posner...
comment on the use of 3D and IMRT treatment planning for ATC.[19,29] As noted, the lack of
stratification of study populations according to important prognostic variables is a serious omission,
specifically the lack of stratification according to tumor size or resection status. Such numerous
variations confound comparative analyses of these contemporary studies, other than on a
speculative basis.

Redefined metrics

TABLE 1

Anaplastic Thyroid Cancer (ATC): Definitive vs Postoperative External Beam Radiotherapy (EBRT)

Tables 1 and 2 include important metrics pertaining to the evaluation of the merits of RT in the
treatment of ATC. First, it should be emphasized that the LC statistics as reported in the literature
have typically defined LC as no evidence of progression, as opposed to disappearance, of disease for
the lifetime of the patient or the length of study. Thus, in any attempt to evaluate the ability of a
given regimen to optimally sterilize disease, LC rates need to be evaluated in the context of ms,
since otherwise they often appear over-inflated. The s/rCCR (no clinical evidence of disease at or
near the completion of all local therapies) metric seems advantageous as a more valid, though not
necessarily complete, assessment of “durable control.” At times this metric was calculated after
personal review of patient lists or by extracting information from the text. The s/rCCR metric takes
into account both the contribution of a successful initial surgery (%iGTR) and the observed r/CCR.
This metric also needs also be assessed in the context of the percentage of patients who show
progression of local disease during the course of RT (%r/POLD), as well as those who have local
recurrence after attempted resection, prior to commencing RT (%s/POLD); we have included both of
the latter values in Tables 1 and 2. Also, acknowledging the current, still realistic goal of using
multimodal therapy to prevent death by an uncontrolled primary, DcLF is cited. Of particular
importance is the identification not only of the number of LTSs, but also of the patient, tumor, and
treatment variables specific to these small cohorts of patients, since these give the prospects for
durable tumor control. Additionally, prognostic variables (ie, %DMs and %IT/ATC) and surgical
outcomes (GTR, gR2) have been tabulated, since these are relevant to survival statistics and to the
efficacy of treatment in relation to the observed toxicities. Other cited metrics/outcomes include
%pRTb, which defines the pre-RT bulk of disease (ie, combines the percentage of patients with
initially unresectable tumors [iR3] and gR2 irradiated tumors).

Seven representative international studies

TABLE 2

Anaplastic Thyroid Cancer (ATC): Preoperative or Definitive Approach

On overview, most of these series reported on study populations with very locally advanced tumors,
noteably with a high percentage of bulk tumor irradiated (pRTb ranging from 70% to 100%), while the
delivered total doses (with the exception of Bhatia) were only moderate (40 to 60 Gy). Similarly,
many included a high proportion of unresectable R3 tumors, typically 40% to 60%. Not
unexpectedly, those studies with a high percentage (> 25%) of initial DMs cite poor survival
outcomes even for short-term survival, with ms of 2 to 3 months, in accord with the historical
literature. Notably, for populations with a high percentage of either initial DMs or R3 tumors, it
remains challenging to decipher outcome statistics, given the competing causes of death (the DMs, an uncontrolled primary, or its associated occult DMs). Finally, given the small numbers of patients, seriously underpowered statistics, and varied risk factors, conclusions remain speculative and difficult to validate, although themes emerge.

Princess Margaret Hospital. Although principles of radiobiology support the use of HPFXN/RT in the hope of preventing rapid tumor repopulation, and despite the validation of HPFXN/RT in selected other head and neck cancers, there still is not a uniform consensus in the ATC literature regarding its superiority. Several authors have reviewed the subject, but the imbalance of other treatment variables confounds analysis.[32,37]

In a subgroup analysis, Wang specifically compared results between patients with a favorable prognosis (group A) who were treated with HPFXN/RT and patients in the same group who were treated with SF/RT; the patients all received the same total dose of 60 Gy, and none received CTX. Wang noted a trend for improvement in ms (10 vs 14 months) favoring the use of HPFXN/RT, although this was not significant, likely because the analysis was underpowered. There was no apparent improvement in LC. On more detailed review, the most significant advantage of HPFXN/RT was seen between the 6th and 9th months, when the survival of those treated with HPFXN/RT was nearly twice that of those treated with SF/RT; however, both regimens quickly failed after 1 year.

With the use of HPFXN/RT, there was an increase in skin toxicity but, importantly, not esophageal toxicity. Of note, none of the 60% of patients treated with aggressive 60 Gy SF/RT (nor any of the 40% treated with HPFXN/RT) showed r/POLD, despite the fact that most of those irradiated had a significant volume of disease. By current standards, it is unreasonable that even 60 Gy, one of the highest doses reported in these series, would effectively sterilize any measurable amount of tumor, which was present in more than half the patients (pRTb, 52%). Median survival was seemingly prolonged, especially for group A patients treated aggressively with a hybrid of high-dose SF/RT and HPFXN/RT, compared with historical controls (10 vs approximately 5 months).[10,15] Although more died with DMs (70%), there was still a disappointingly high 62% DcLF. These results suggest that the HFNX/RT treatment paradigm, despite the fact that fewer than half the patients were treated with HFNX/RT, may appear better than historical treatment with lower-dose, nonstandardized SF/RT; nevertheless, it is still seemingly inadequate (with regard to durable control) for a population with relatively few (13%) initial DMs as the competing mode of death, although many were still destined to develop occult DMs. A relatively high total dose may have postponed progression, as evidenced by the comparison of ms; however, it did not ultimately prevent it. Additionally, even in group B patients, who were treated for palliation with a short HYPO/FXN/RT regimen (> 3 Gy/2 weeks), there was no suggestion that this scheme had an impact on control; r/POLD was 23%, rRR was only 18%, and there was no r/CCR and high DcLF. Nevertheless, compared with historical controls, aggressive treatment worked better than a palliative approach, and ms nearly doubled in aggressively treated patients. A comparative analysis may be confounded by differences in patient populations; nevertheless, results for some remain encouraging, compared with the decree that no treatment has made any difference for any patient with ATC. In 2006, Wang commented that HPFXN/RT was well tolerated and that he and his colleagues at Princess Margaret Hospital are now exploring BID FXN with IMRT technology (although they are changing the treatment fields from hyoid to suprasternal notch) for patients with good performance status and without DMs.[34]

Memorial Sloan-Kettering. One of the most successful HPFXN/RT schedules was reported by Kim, notably for a population devoid of DMs, although only 19 patients were included. The reported high LC of 68% seems especially significant given the context of relatively improved 12-month ms, as does the impressive 67% r/CCR despite a high 90% pRTb. These results suggest a quite effective radiation regimen, although notably the four LTSs when treated had only minimal (likely resected) disease. Interestingly, this is one of the highest r/CCR percentages reported. CM (10 mg/m² doxorubicin once weekly) was used, but despite the HPFXN/RT regimen, RT was not accelerated.[36]

Lund University. Tennvall prospectively reviewed the impact of increasing preop therapy and increasing HPFXN/RT (over 10 then 7 then 3 weeks), in three consecutively treated cohorts of “generally R3” patients, all of whom were prescribed a total dose of 46 Gy. Local control, but not ms or %DcLF or resectability, improved with the sequential regimens. None of the patients who received entire preop HPFXN/RT and who went on to resection had a local recurrence. Notably, toxicity for the entire population, including those who received a preop dose of 46 Gy given at 1.25 Gy BID, was deemed acceptable, with 7% experiencing grade 3/4 toxicity and no reports of operative morbidity. It is noteworthy, however, that although overall LC (60%) was one of highest reported, and although DcLF was low at 24%, these outcomes are overshadowed by a poor ms of < 4 months; the latter finding is likely explained by the high percentage of marginally R3 tumors in an elderly population.
This very short ms limits the ability to evaluate the durability of LC with this specific regimen. Also, although after some component of preop RT, over 60% of these “marginally resectable” patients were able to achieve a GTR, nearly 40% of patients had gross disease remaining after all therapies, including 27% left with R3 disease. There were five patients who achieved NED/LTS status; four of the five patients had ETE/ATC and had been treated with CM and attempted resection. Although the ms was not different from that seen in historical controls—perhaps because 60% had received split-course RT and because treatment was of an elderly population—this regimen did result in significantly fewer patients succumbing to an uncontrolled primary, as well as in LTS/NED in several patients, all of whom had documented ETE/ATC.[32]

**Royal Marsden Hospital.** Two authors reported on the exclusive use of accelerated HPFXN/RT (HART), though with quite different FXNs and total doses, and with markedly different conclusions as to efficacy. Mitchell, with a subsequent update by Dandekar, reported on an elderly population having significant DMs (65%).[22,35] Treatment was one of the most aggressive regimens reported, both with regard to fraction size (1.8 + 2.0 Gy BID) and total dose (60.8 Gy [median, 57 Gy] over 3 weeks), although without CTX. The RT scheme was rigorous, conceivably to compensate for a low resectability rate of only 30% to 40% and a very high pRTb of 90% to 100%. Although the 60% rRR was reasonable, the 20% r/CCR was rather low, reflecting the considerable bulk of tumor. Despite such bulk, there was 75% LC and only 12% DcLF, suggesting improvement in sterilization. Again, however, this conclusion was undermined by a ms too low (2.5 months) for adequate assessment of durability. Surprisingly, 12% to 15% showed POLD during treatment. Furthermore, acute toxicity in this elderly population was high; while it likely was not warranted, this regimen was abandoned in favor of one that actually used lower doses, although it was still HART.[22] Importantly, as was well elucidated by Dandekar, there is a serious question regarding the efficacy of an aggressive regimen when patients who have multiple poor prognostic variables succumb from disease before they even recover from the acute effects of the aggressive regimen.[35]

**Gustave-Roussy.** De Crevoisier reported quite different results in a population with more favorable prognostic variables (younger, high resectability, fewer DMs; and 13% with IT/ATC, only 66% pRTb) using a less aggressive HART program, although treatment extended over 5 months. This prospective, generally postop strategy consisted of a sequential CTX/HART RT/CTX regimen; total dose was initially 40 Gy (for 73% of the study population) then later was escalated to 55 Gy. For the overall population of 30 patients, an exceptionally high 63% s/rCCR was reported; half of this was accounted for by successful GTR (s/CCR) and half by the degree of response of gR2 to RT (r/CCR). Nine of 20 patients (45%) who had an initial incomplete resection or no surgery (including four patients with initial R3 disease and five with gR2) demonstrated an r/CCR, and five of these sustained LC, suggesting durability of the response to RT. All seven who achieved LTS/NED had been taken to surgery, and notably more than half (four patients) had initial ETE/ATC. Remarkably, two had measurable disease irradiated (not GTR), including one who initially had R3 status. Validation of the data has been criticized, with note being made of a high percentage of “mixed tumors.” However, on personal review of the 13 patients with “pure ATC,” we found that there were two LTSs, all of whom had ETE. Furthermore, although not acknowledged, a ms of 7 months for those six patients with DMs is notably high, even though the numbers are very small. Compared with the regimens used in historical controls,[6,10,15] this regimen holds promise, with doubling of ms and half the DcLF seen in the historical literature. Although all LTSs had advanced ETE/ATC, they otherwise had relatively favorable prognostic variables, with few DMs and lesser amounts of bulky disease.[25]

**Institute of Oncology (Slovenia).** Besic reported on a study population entirely devoid of DMs, categorized according to initial resectability, and treated initially with either primary CM or primary resection followed by CM. Each population had comparable “hybrid distribution” of SF/RT and HPFXN/RT, and each was treated with a similar total median dose of 45 Gy (subsequently escalated to 64 Gy). Each also had a similar “hybrid distribution” of sensitizing CTX (cisplatin + doxorubicin). Reported ms was surprisingly the same—7 months—despite an inherently more favorable tumor status for the group A patients, who were treated initially with surgery (followed by postop CM), compared with the tumor status of the group B patients, who were initially R3 patients treated primarily with CM. Importantly, a subgroup of 12 of the group B patients (23%), upon reevaluation after receiving 20 to 50 Gy (typically 30 Gy), were able to go for resection (23% change in resectability), and a GTR was secured for 13% of the initially R3 patients (58% of those who went for resection). Notably, this subgroup of 12 patients who were able to be taken for resection after only rather low preop doses, and who then returned for the complete dose, showed an exceptionally high ms of 14 months and 50% 1YS. Additionally, they showed a low 18% DcLF, comparable to that
reported for initially resected group A patients, and this was despite a high 100% pRTb. They also demonstrated LC, which proved to be durable LC, given the protracted ms of 15 months.[20] Nevertheless, probably because of occult DMs associated with their R3 status, none were NED/LTS. De Crevoisier also reported on the re-evaluation of R3 patients after treatment with 30 to 40 Gy, citing a 40% change in resectability status for the 10 initially R3 patients, with all 4 of those whose status changed to resectable attaining a GTR and 1 becoming a LTS.[25] This change in resectability status after a moderate preop dose remains attractive for a population typically presenting with marginally resectable tumors. The evaluation of LTS/NED for these seven different treatment regimens is especially enlightening since it reflects the potential for achieving durable control with local therapies. On review of Tables 1 and 2, one may note that the range for LTS/NED (over 2 years) ranges from 7% to 30% for the different patient subgroups; surprisingly, LTS/NED was not predicted solely by those reporting outcomes for populations devoid of DMs. In contrast to the historical literature, four authors reported that some patients who initially had ETE/ATC became LTS/NED, especially those who were able to secure a GTR after a rigorous MMS—and invariably who did not have initial DMs.[19,25,32,36] Importantly, both De Crevoisier and Bhatia reported that a few patients (2 and 2, respectively) irradiated with gross postop disease (not GTR) were also LTS/NED. De Crevoisier cited LTS/NED status for a patient who initially had an R3 tumor that later became resectable (GTR) after preop RT and another patient who was left with gR2 disease. The most favorable results—37% LTS/NED, reported by De Crevoisier—likely reflected not only effective treatment but also more favorable patient and tumor parameters. Although Besic reported a fair 7-month ms (notably the same in resectable and unresectable patients), it remains a matter of speculation whether more favorable results, with respect to LTS, would have been obtained if patients had been treated exclusively with HPFXN/RT and CM, as opposed to fewer than half of patients having been so treated. Besic currently advocates an initial preop approach for most patients, with the exception of those with IT/ATC, noting the possibility of evaluating the effectiveness of CTX and reintroducing surgery when possible. In 2005, she recommended weekly doxorubicin and vinblastine, specifically with HPFXN/RT to a dose of 45–64 Gy, with subsequent re-evaluation for resection.[18]

**MD Anderson.** More recently, Bhatia reported results in series of patients treated at MD Anderson with a variety of RT schedules, 24% of whom were treated with IMRT. The overall population had a high (43%) rate of DMs and a correspondingly low ms of only 3 months. Three patients (16%) demonstrated s/POLD prior to RT. Although rRR was not reported specifically for group A patients who were treated aggressively, 16% (5/31), achieved LTS/NED status; none had DMs, all had ETE/ATC (not IT/ATC). and, importantly, this number included two patients irradiated with gR2. Furthermore, all had completed a median dose of 66 Gy and CM (cisplatin and paclitaxel). There was a suggestion of a dose response above 50 Gy. Toxicities included 23% of patients requiring hospitalization; IMRT and 3DRT toxicities were 31% and 20%, respectively (not significant); two patients demonstrated late esophageal stricture. Bhatia makes reference to the fact that use of IMRT allows for dose escalation while reducing toxicity. Interestingly, on multivariate analysis, the use of CTX was shown to impact survival. She, and others, have considered biologically targeted therapies as potential radiosensitizers, and also as holding promise for control of systemic disease.[19,38]

**Conclusions regarding the contemporary RT literature**

In 2005, Chen published an analysis of the most recent SEER database (1983-2002), categorizing 261 ATC patients into three groups (akin to Union for International Cancer Control [UICC] staging) on the basis of tumor extent: 1) those 36% of patients who presented with DMs, with an anticipated survival of < 3 months; 2) the < 15% who had IT/ATC, including the < 10% with iATC, with ms of 9 months; and 3) the majority, 42%, who presented with various degrees of ETE/ATC, with ms of 6 months and 16% 2-year overall survival. In particular, Chen noted that postop RT had an impact on the survival of those with group 3 disease (those who had ETE), but not on the survival of those with DMs, nor of those with IT/ATC (this last finding is controversial, however, because of the small numbers), while surgery benefited both those with IT/ATC and those with ETE/ATC.[11]

In summary, in contrast to the historical literature,[6,10,15] which reports on SF/RT and typically involves a single-modality approach to the treatment of ATC tumors, the more contemporary series have investigated novel MMS (including HPFXN/RT, sensitizing CTX, and dose escalation) to overcome the biological aggressiveness of ATC, yet still set within the confines of anatomical dose-limiting constraints. This review of several very specific treatment paradigms supports the hypothesis that although the overall survival reported for ATC has not changed in the last 20 years, significant advances have improved the quality of life for selected affected patients; less fortunate
patients, specifically those with initial DMs or tremendous tumor volume, never taken to surgery, may be better treated with a more gentle approach, including purely palliative measures. Although the effort of shifting through different outcome scenarios and searching for a logical thread may be fraught with misconceptions and statistical errors, the exercise reveals interacting, sometimes competing, dynamics variables that need to be examined and that may be instrumental in prospectively directing individual patient care: resectability, medical risks, bulk residuum, significance of DMs, duration of therapy, anticipated incurred toxicities, as well as cause of death. More concrete recent discoveries include: acknowledgement of the feasibility of HPFXN/RT prescribed to nearly 60 Gy and combined with CTX in the preop setting; recognition of the chance (23%[18], 40%[25], or 70%[32]) that an initially unresectable tumor may become resectable after CM, with a corresponding likelihood (13%, 40%, or 60%, respectively) of securing a GTR; and the shrinking, by approximately half, of the risk of death from local disease (with more than 70% succumbing to DMs, and less than 30% to uncontrolled local disease). This last development gives hope that at least a few, though perhaps as many as 10% to 30%, of patients who have no DMs at diagnosis and who have the vigor to endure aggressive multimodal therapies, may be able to achieve LTS/NED status.

Additionally, given that relatively archaic technology was used in most of these studies (there has been only one published report, and a preliminary report at that, of the incorporation of IMRT into the treatment paradigm), to some degree the risk-benefit ratio may be redefined and the efficacy of RT improved; nevertheless, dose escalation will likely still be limited by the tolerance of the esophagus, 60 to 66 Gy. In any case, an aggressive strategy, with its inherent toxicities, should be undertaken only in patients with at least 3 months estimated survival, specifically those without DMs. Other technical advances, such as PET/CT scanning, may further improve patient selection, helping not only to identify those with ATC who have documented metastatic disease, but also helping incorporate external beam RT earlier into the treatment paradigm of patients who present with mixed histologies that include a component of ATC. In conclusion, an aggressive sequential MMS needs to be thoughtfully considered in relatively high-performance patients who are without DMs and whose tumor shows an early therapeutic response to first-line therapy (whether resection or preoperative CM), with consideration especially given to incurred toxicities and realistic expectations for quality of life.

Current Specific Recommendations Regarding RT

National Comprehensive Cancer Network (NCCN) 2010 guidelines recommend consideration of an attempted organ-preserving resection and enrollment into ongoing clinical trials, with “consideration” of multimodal therapy. They go on to say: “although optimal results have been reported with HPFXN/RT combined with CTX, the panel acknowledged that considerable toxicity is associated with such multimodal treatment and that prolonged remission is uncommonly reported.” In consideration of the foregoing analysis, and in an effort to address more specific scenarios, we propose the following recommendations for consideration:

1) For patients with very large (> 7 to 10 cm [or > 200 cm^2]) primary tumors or DMs or significant comorbidities, and who have an anticipated survival of < 3 months, a palliative approach is advised: 4 Gy QD to 20 Gy total dose or 3 Gy QD to 30 Gy total dose (with AP/PA field) or referral to a hospice program for palliative care. Symptomatic or brain metastases are also treated with an HYPOFXN/RT schedule.

2) Should a patient be in relatively good health and have attempted resection of the primary tumor, after which he or she is ideally left with minimal gross residuum, consider prescribing 60–70 Gy with SF/RT or HPFXN/RT (1.2–1.5 Gy/day) or using a modified integrated boost HPFXN/RT technique with an initial regimen of 1.8–2.0 Gy QD for 30 FXNs (54 Gy) and then for the last 6 to 8 days, add to the fractions a second of 1.5 Gy in the afternoon to a limited boost field, resulting in a cumulative dose to high-risk volume of 63–66 Gy (depending on the suspected volume of the residuum); this is generally done with IMRT technology in the postop setting. This integrated boost, modified accelerated regimen has been reported by MD Anderson and the University of Florida for the treatment of selected thyroid cancer patients.[39]

3) For patients in relatively good health and who present with marginally resectable disease, there is a recommendation for enrollment in a clinical trial. However, if a suitable trial is unavailable, consider preop HPFXN/RT (1.2 Gy BID) to 46–54 Gy (ideally with IMRT initially or for boost field, depending on time constraints), with or without doxorubicin (20 mg/m^2/week) or cisplatin, followed by reevaluation as to resectability (and to confirm no DMs) at 2 to 4 weeks, with surgery performed...
approximately 4 to 6 weeks after RT; consider postop RT to a cumulative dose of 60–70 Gy if residuum consists of more than focal microscopic positive margins. If tumor remains unresectable, continue RT to a cumulative dose of 64–70 Gy, depending on the dose to critical structures, performance status, restaging studies, and time lag.

**Role of Chemotherapy and Novel Targeted Therapies in the Management of ATC**

ATC has very low response rates to systemic chemotherapy. In vitro chemosensitivity testing has shown that most ATC and poorly differentiated thyroid cancers (PDTCs) are very resistant to anticancer chemotherapy.[40] A study by Yamashita et al found no relationship between response to chemotherapy and the expression of multidrug resistance gene (MDR1) and its gene product, P-glycoprotein.[41] Clinically, combination chemotherapy with cisplatin, doxorubicin, etoposide, and peplomycin in 10 patients with ATC yielded only two partial responses, lasting 2 and 3 months, respectively. In patients with ATC, continuous infusion paclitaxel over 96 hours has been reported to give a 53% total response rate, with one complete response and nine partial responses out of 19 subjects.[42] In 13 patients with ATC who were treated with weekly intravenous paclitaxel, Higashiyama reported an overall response rate of 33%, with one complete response and three partial responses.[43] More recently, Kawada et al described an overall response rate of 14% and a median time to progression of only 6 weeks in 7 patients with ATC treated with IV docetaxel every 3 weeks.[44] A partial response has been described in a patient with an ATC treated with liposomal doxorubicin.[45] Despite modest response rates in patients with advanced, well-differentiated thyroid cancer and in patients with ATC, conventional cytotoxic chemotherapy has not shown any improvement in overall survival in these patients. Another type of systemic therapy is needed for these types of patients.

**Molecular abnormalities**

Because of the lack of efficacy of conventional chemotherapy, molecular abnormalities in all human malignancies are being sought in order to develop novel targeted agents. An attractive strategy is to target abnormalities within the cancer that are unique to the malignant cells. Many of these targets are related to cell signaling, cellular proliferation, and structural proteins. Mutations in *BRAF* have been described in ATC and PDTC.[46] *BRAF* mutations were found in three patients with ATC (10%) and two with PDTC (13%). Utilizing microdissection techniques, thyroid cancer specimens including both one sample of ATC with well-differentiated papillary areas and one sample of PDTC were analyzed for *BRAF* mutations. Both samples contained mutations in the well-differentiated areas and the poorly differentiated and anaplastic components. This suggests that the *BRAF* mutation was an early clonal event that arose from well-differentiated thyroid cancer before it dedifferentiated into a more aggressive subtype.

*PIK3CA* gene mutations have been described in 23% of ATC.[47] *PIK3CA* encodes the catalytic subunit phosphatidylinositol 3’-kinase (PI3K). When a well-differentiated component occurs in association with ATC that is found to have a mutation of *PIK3CA*, the well-differentiated tissues do not harbor the mutation. This suggests that this mutation is involved in the dedifferentiation and progression to a more clinically aggressive cancer. Hou et al described *PIK3CA* gene alterations, resulting in a gain of copy number, in 20% of differentiated thyroid cancers (DTC; 28% of follicular thyroid carcinoma and 12% of papillary thyroid carcinoma), 42% of ATC, and 17% of benign thyroid adenomas. *BRAF* mutations were found in 29% of ATC, and 43% of ATC that had a *BRAF* mutation also had a PI3K/AKT genetic alteration.[48] This suggests a pathogenic role of the PI3K/AKT pathway in the transformation of DTC to ATC.[49]

Mutations in the *p53* tumor suppressor gene result in loss of function and are implicated in a large number of human cancers. But mutations in *p53* have been described in only approximately 10% of thyroid cancers.[50,51] They are thought to be rare in well-differentiated thyroid carcinomas.[52,53] Mutations in *p53* may be more prevalent in a subset of ATCs that are derived from papillary carcinomas with a *BRAF* mutation.[54] Genetic alterations in receptor tyrosine kinases such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR) have been described in ATC.[55] RAS abnormalities are described in ATC.[55,56]

**Targeted therapy**

Clinical studies of targeted agents in patients with ATC are limited. Imatinib (Gleevec), an oral
tyrosine kinase inhibitor (TKI) of kit, bcr/abl, and PDGFR, was administered to 11 patients with locoregional or metastatic disease.[57] Of 8 evaluable patients, at 8 weeks there were 2 partial responses, 4 patients with stable disease, and no complete responses. The 6-month progression-free survival was 45% (95% confidence interval [CI], 9%–65%). The 6-month overall survival was 45% (95% CI, 16%–70%). Side effects included edema, fatigue, and hyponatremia.

REFERENCE GUIDE

Therapeutic Agents

- Axitinib (Inlyta)
- Cisplatin
- Combretastatin-A4 phosphate (fosbretabulin)
- Docetaxel
- Doxorubicin
- Etoposide
- Imatinib (Gleevec)
- Liposomal doxorubicin
- Paclitaxel
- Peplomycin
- Sorafenib (Nexavar)
- Valproic acid
- Vinblastine

*Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.*

Sorafenib (Nexavar), an oral TKI of BRAF, VEGFR1, and VEGFR2, was studied in a phase II trial.
involving 30 patients, 2 with PDTC/ATC.[58] The partial response and stable disease rates were 23% and 53%, respectively. The only two patients who had progressive disease as their best response were the two who had PDTC/ATC. A phase II trial of axitinib (Inlyta), an oral TKI of VEGFR 1, 2 and 3, involving 60 patients with advanced thyroid cancer, produced 1 partial response and 1 instance of progressive disease in the 2 patients with ATC.[59] Nagaiah et al reported a partial response rate of 13% and stable disease in 23% of 15 patients with ATC who had failed CTX and/or RT and who were treated with sorafenib.[60]

Valproic acid is a histone deacetylase (HDAC) inhibitor that has been shown to enhance the sensitivity to both doxorubicin and imatinib in thyroid cancer cell lines.[61-63] A case report describes one patient treated with a combination of neoadjuvant oral valproic acid daily and intravenous cisplatin and doxorubicin every 3 to 4 weeks.[64] The patient also received 40 Gy of external beam RT. Tumor size decreased noticeably. Following surgical resection, the patient then received 15 Gy intraoperatively and doxorubicin postoperatively. The postoperative specimen revealed a necrotic core and a ring of papillary carcinoma. Four of 26 lymph nodes showed only papillary carcinoma. The patient had no evidence of disease 2 years after surgery.

Combretastatin-A4 phosphate (fosbretabulin) is a novel antiangiogenic agent that preferentially inhibits blood flow through the blood vessels of malignant tumors. It has shown activity against anaplastic and medullary thyroid cancer when used in combination with chemotherapy in vitro[65] and in vivo in a mouse model.[66,67] A phase II trial of single-agent fosbretabulin in 26 patients with advanced ATC reported stable disease in 7 patients, with a median duration of response of 12.3 months.[68] No objective responses were seen. Toxicity included QTc prolongation, which resulted in delay and discontinuation of therapy. Other trials with fosbretabulin are ongoing.

Additional future considerations include the use of other TKIs, HDAC inhibitors, and mTOR inhibitors. ATC will continue to be a disease that requires combination therapy. The integration of targeted therapies into the treatment paradigm is still being investigated, and therein lies the promise for the control of systemic disease. These advances are especially relevant to the majority of patients who present with locally advanced disease, since they have a notably high likelihood of harboring occult metastases. Especially for this population with the most common, locally advanced disease, targeted therapies may significantly expand the proportion of patients offered multimodal therapy with curative intent. As has been the case with other oncologic models, it is then that the bulk of disease at the primary site of disease also needs to be optimally controlled. As we have noted in this review, such “durable control” is now potentially offered with an integrated multimodal approach to the treatment of ATC: organ-preserving surgery, innovative chemosensitization/HART radiation methodologies, and novel targeted therapies.

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