Anaplastic Cancer of the Thyroid: The Viper in the Pit

Rare but deadly anaplastic cancer of the thyroid (ATC) represents <2% of all thyroid cancers (TCs) but accounts for 14%–39% of deaths attributed to them.[1] ATC is usually advanced at presentation with local invasion and metastasis.[2] It is invariably fatal within 3–9 months of diagnosis; <15% of patients are alive at 2 years. Disease-specific mortality approaches 100%.[3] All ATCs are categorized as American Joint Committee Classification (AJCC) Class IV at diagnosis irrespective of tumor spread.[4]

These tumors may arise *de novo* but most often represent a terminal dedifferentiation of differentiated TC (DTC) and may represent progressive accumulation of hits in multiple oncogenic pathways. While DTC is associated with single mutations, ATC is characterized by multiple mutations. Approximately 50% of patients have prior or coexistent DTC.[3,5] In such situations, genetic changes of DTC as well as canonical changes that epitomize ATC are found together.[6]

While there appears to be a distinctive association between population iodine intake and benign thyroid disease, the relationship with malignant thyroid disease is less certain.[7] As early as in 1927, Wegelin demonstrated a difference in TC between endemic and nonendemic areas (Central Switzerland 1.04 V Berlin 0.09). He also predicted a drop in the incidence of cancer following iodization.[8] Animal studies indicate that iodine deficiency is a weak initiator but strong promoter of TC. Children in areas affected by the Chernobyl tragedy who were iodine deficient at the time of exposure had a 2–3-fold increase in the risk of TC.[9] In areas of iodine deficiency, the incidence of ATC is believed to have decreased following iodization. The incidence of DTC, however, has increased without an increase in mortality.

In the Tyrol region of Austria, an area in which goiter was endemic with population iodine mean of 36 mcg of iodine per gram of creatinine and iodization introduced at 10 ppm in 1963 and 20 ppm in 1992 resulted in iodine sufficiency (145 mcg per gram of creatinine). The overall incidence of TC did not change from 1952 to 1995, but there was a marked decrease in the percentage of ATC from 28.8% in 1952 to 76%–4.9% in 1986–1995.[10] Similar reports from other European countries and Latin American countries support a reduction in ATC with iodization. It must be noted, however, that in other countries such as Scotland and the Netherlands, there has been a decline in the reported incidence of ATC without a change in the iodination status.[11] In the SEER database from the US (a nonendemic goiter area), there appears to be an overall increase in the incidence rates of ATC from 1973 to 2014 (average annual percentage change: 3.0% [95% confidence interval (CI): 2.2%–3.7%]) despite overall low incidence rates.[12] A plausible explanation for increase in ATCs in areas where goiter is common is that people are less inclined to seek medical attention, thus allowing DTCs time to evolve into ATCs.[9] Following iodization and consequent overall reduction in goiters, earlier discovery occurs leading to a reduction in ATC (but not DTC) incidence.

The publication by Pradhan *et al.* in this issue of the journal is a large series from the gangetic plains of India. This is an area that was previously endemic for goiters, and the data must be therefore interpreted in this context.[13] Similarities and differences between the Indian data and a large multi-institutional database warrant comparison (observing caveats inherent because of differences in data collection and presentation) [Table 1].[12]

In the Indian cohort, patients were younger at presentation. The prevalence of ATC in men in both cohorts is significant dispelling earlier-held views that the vast majority of affected patients are women. Other than these, the data presented by Pradhan *et al*. are concordant with the larger American registry. Of note, half of the patients in the Indian cohort refused any form of therapy probably indicating advanced disease at diagnosis. Total thyroidectomy is recommended in patients who have disease that is deemed resectable;[3] we can assume that at least 20% of patients will have some form of resectable disease (disease-specific survival [DSS]: 10.00 [95% CI: 7.70–12.30] for Total Thyroidectomy (TT) patients [$P < 0.001$]).[12] Surgical reduction of the tumor is associated with increased DSS irrespective of the surgical procedure.

Table 1: Comparison of ATC in two populations - India and the US[12]

	Pradhan *et al*.	Janz *et al*.
Years	1991-2013	1973-2014
ATC, *n*	100	1527
Male, *n* (%)	45 (45)	568 (37.2)
Female, *n* (%)	55 (55)	959 (62.8)
Mean age at diagnosis	58 (36-86)	70.5 (15-102)
Any treatment given (%)	51	NR
Surgery (%)	46	52.5
Total thyroidectomy (%)	21	19.6
Subtotal/near-total thyroidectomy (%)	NR	6.2
Tumor reduction surgery (%)	7	NR
Lobectomy (%)	5.3	9.2
Nonsurgical therapy (%)	43	47.5
Median disease-specific survival (months)	3	4 (95% CI: 2.26-5.74)
Disease-specific deaths (%)	NR	100

CI: Confidence interval

Pradhan *et al*. have provided important information about the "viper in the thyroid cancer pit." It is clear that over the years, we have not made important strides in improving survival in patients unfortunate enough to develop ATC. It would be important to redouble our efforts to find markers and features that will allow us to predict the occurrence of or identify ATC early. Are there features or markers in patients with goiter that warrant closer follow-up? There is an evolving opinion to allow patients with "low-risk" DTC to be followed without surgery. A majority of ATCs evolve from preexisting DTC; are there markers that will allow us to decide which of the "low-risk DTC" will mutate to an ATC? Finding answers to these questions is important. There is much to be done!

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Conflicts of interest

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