Published in final edited form as:
Clin Oncol (R Coll Radiol). 2010 August ; 22(6): 486–497. doi:10.1016/j.clon.2010.03.013.

Anaplastic Thyroid Carcinoma: Pathogenesis and Emerging Therapies

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Abstract

Anaplastic thyroid carcinoma ranges from 1.3 to 9.8% of all thyroid cancers globally. Mutations, amplifications, activation of oncogenes and silencing of tumour suppressor genes contribute to its aggressive behaviour, and recent studies (e.g. microarrays, microRNAs) have provided further insights into its complex molecular dysregulation. Preclinical studies have identified numerous proteins over- or underexpressed that affect critical cellular processes, including transcription, signalling, mitosis, proliferation, cell cycle, apoptosis and adhesion, and a variety of agents that effectively inhibit these processes and tumour growth. In clinical studies of 1771 patients, 64% were women, the median survival was 5 months, and 1-year survival was 20%. The variables associated with survival in some series included age, tumour size, extent of surgery, higher dose radiotherapy, absence of distant metastases at presentation, co-existence of differentiated thyroid cancer and multimodality therapy. However, considerable bias exists in these non-randomised studies. Although more aggressive radiotherapy has reduced locoregional recurrences, the median overall survival has not improved in over 50 years. Newer systemic therapies are being tried, and more effective combinations are needed to improve patient outcomes.

Keywords

Anaplastic; chemotherapy; microarray; mutations; radiotherapy; surgery

Statement of Search Strategies Used and Sources of Information

This overview will summarise the current understanding of the molecular pathogenesis of anaplastic thyroid carcinoma, preclinical studies identifying promising new therapies, the impact of surgery and radiotherapy on outcomes, and new systemic therapies under investigation. It was prepared from articles obtained from PubMed using the search words ‘anaplastic thyroid carcinoma’. The search was limited to English and yielded 1882 articles.

Introduction

Thyroid cancers comprise 2.5% of all malignancies in the USA. The incidence continues to increase, and was estimated to be 37 200 in 2009, whereas death rates remain low at ~1630 [1]. The increased detection, mostly of small papillary thyroid cancers, in part reflects earlier identification from imaging the head/neck and upper chest for other reasons [2], although early detection may not fully explain the rising incidence [3,4]. Anaplastic thyroid carcinoma (ATC) is the least common type, occurring in only 1.7% of thyroid cancers in the

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USA [5]. Frequencies in other countries, based on either tumour registries or single centre experience, are: Australia (1.3%) [6], Luxembourg (1.9%) [7], Austria (2.0%) [8], Italy (2.9%) [9], Japan and Jordan (3.6%) [10,11], New Zealand (4.2%) [12], India (4.7%) [13], Israel (7.5%) [14] and the Netherlands (7.9%) [15]. In Germany, the incidence decreased dramatically by decades from 35% to 19% to 7% from 1965 to 1997. The change was attributed to iodised salt for goiter prevention and to more aggressive management of differentiated thyroid cancer [16]. Similar reductions by decade from 1970 to 1999 were also observed in Dublin, Ireland (24.3%; 18.3%; 9.8%, respectively), and attributed to an increase in dietary iodine [17].

Risk factors for ATC are not well understood, but patients may have a history of goiter, prior co-existing differentiated (or rarely, medullary) thyroid cancer or the patient may present with no known thyroid disease history and prior ATC on histological examination. Transformation from differentiated thyroid cancer is usually identified in the primary tumour, but may be found only in lymph nodes [18]. A case–control study of 126 patients, using benign goiter surgery patients as controls, found that ATC patients were more likely to have less education, other malignancies, late menarche, early first pregnancy, and blood group B [19]. These risk factors have also been associated with other thyroid malignancies [19].

Pathogenesis

Differentiated thyroid cancers (papillary, follicular, Hürthle cell) comprise most malignancies, and each tends to have a single mutation. As the tumours dedifferentiate, more mutations develop, with ATCs commonly having multiple genetic abnormalities.

Mutations in ATC have been reported in the following genes: p53 = 12/22 (55%); RAS = 37/166 (22%); BRAF = 61/231 (26%); β-catenin = 20/53 (38%); PIK3CA = 27/156 (17%); Axin = 18/22 (82%); APC = 2/22 (9%); PTEN = 10/84 (12%) [20]. In a recent study of 18 patients, 38% had BRAF, 17% NRAS, 6% HRAS, 6% BRAF/PIK3CA, and 33% had unknown mutations [21].

Abnormalities in chromosome numbers or integrity are gains, losses, amplifications and deletions affecting virtually every chromosome. Recent reports using array-comparative genomic hybridization (CGH) have found abnormalities in regions containing EGFR, MET, BRAF, K-RAS [22], CCND1, FOSL1, UBE2C, CDKN2A [23]. Liu and Xing [24] detected copy number gains in EGFR, VEGFR1/2, PDGFRA/B, PIK3Cα/β, KIT, PDK1, AKT1 and MET. This high level of genomic disarray illustrates the challenge in identifying targets for therapy.

MicroRNAs, recently identified small (~22 nucleotide) non-coding RNAs, seem to provide an additional posttranscriptional level of protein regulation, and can act as either tumour suppressors or oncogenes [25]. Although microRNAs are often underexpressed in cancers, they are frequently overexpressed in thyroid cancers. It is interesting, too, that each thyroid histological type has a different set of microRNAs that are preferentially altered, although overlap exists. Table 1 illustrates some of the microRNAs that have been examined.

In papillary thyroid cancers, the overexpression of microRNAs-221 and -222 can reduce $p27^{kip1}$ and affect the cell cycle [26]. The same investigators [27] found four microRNAs downregulated in ATC that may target proteins involved in the transformation of thyrocytes. Other micro- RNA targets include E2F (apoptosis and cell cycle), PTEN and hTERT [28]. Antisense inhibitors to several microRNAs have reduced cell growth, supporting their oncogenic role and providing evidence that microRNAs may be therapeutic targets [29].

Gene microarrays have dramatically altered the field of cancer cell biology, identifying many genes heretofore unsuspected to play a role in carcinogenesis, and providing fertile preliminary observations that have led to testable hypotheses. In thyroid cancer, Griffith *et al.* [30] carried out a meta-analysis of 21 studies, but only one included ATC patients. Onda *et al.* [31] studied 10 patient samples and 11 ATC cell lines. They identified 56 underexpressed and 31 overexpressed genes in their cell lines, including ones regulating cell structure and endocytosis (destrin), microtubules (stathmin), RaF inhibition (PBP), and Rab protein localisation (GD12). Recently, Montero-Conde *et al.* [32] identified several pathways altered in both poorly differentiated and anaplastic tissues, including cell cycle, focal adhesion, MAPK, cytoskeleton and TGFB1.

Although identifying which genes are altered in malignancies is important, understanding which proteins are affected, and how, may be more critical to developing therapeutic interventions. A large number of studies have examined proteins in ATC and cell lines [20], as summarised in Table 2.

These proteins participate in a broad spectrum of cellular events that, when dysregulated, initiate or promote carcinogenesis and its progression. Their identification provides the substrate for investigating their potential roles in ATC, and many have been the subject of such investigations, both *in vitro* and *in vivo*.

Therapeutics: Preclinical

In vitro studies have been conducted in a variety of ATC cell lines (Table 3), with some agents having more than one target. It should be noted that some long-established ATC cell lines may be derived from other tumours [33], and studies using only these lines are not included in this review.

We have determined that transcriptional activation of the transcription factor, PPAR-γ, inhibits cell growth in ATC cells, and the response is inhibited by PPAR-γ shRNA [34]. This effect is mediated via induction of mRNA and protein of the small GTPase, RhoB and was observed both in cell culture and in the nude mice xenograft model. Subsequent to RhoB activation, the cyclin kinase inhibitor, $p21^{waf1/cip1}$, mRNA and protein are induced. The essential role of RhoB in this signalling pathway was shown by using either RhoB siRNA or a dominant negative RhoB to inhibit PPAR-γ induced RhoB, p21 and cell growth. Furthermore, we found that the histone deacetylase inhibitor, depsipeptide, induces RhoB and p21 and inhibits cell growth, and that RhoB siRNA also silences the histone deacetylase inhibitor effects. Thus, we have identified a novel pathway in ATC cells in which RhoB is a critical signalling node that can be upregulated by multiple agents and that may offer additional therapeutic strategies.

There is a broad spectrum of potential druggable targets for which drugs are either in clinical trials or commercially available for other malignancies. These include EGF, VEGF, Akt/mTOR, Ras/Raf/Mek/Erk receptors and pathways. Other important targets include anti-apoptic genes and proteins, cell cycle and mitosis inhibitors, and epigenetic regulators (Table 3).

Further support for the continued development of therapeutics comes from preclinical *in vivo* studies. In ATC reports, these experiments are principally carried out using a xenograft model of human ATC cell lines injected ectopically into nude mice (Table 4).

These studies have been primarily monotherapy, although a few included two drug combinations. The results showed inhibitory effects on a variety of targets, including EGFR, VEGFR, MAPK, microvessel density, neovascularisation, apoptosis, MEK, ERK, tubulin,

farnesyl transferase and NF-κB. Furthermore, re-expression of the suppressor of cytokine signalling 3 can sensitise ATC cells and tumours to chemotherapy agents [35]. Many potential targets remain to be explored (Tables 2, 3), and multi-drug combinations will almost certainly be needed to provide long-term control of this highly aggressive and biologically genetically unstable tumour.

Clinical Management

The rarity of ATC means that no single institution sees a large number of patients. Published series often extend over one or more decades, during which the radiation and chemotherapy regimens change. Table 5 summarises the clinical features and outcomes of 1771 patients (36% men; 64% women) treated between 1949 and 2007. The median survival of all series was only 5 months, and the median 1-year survival was 20%. A reviewof 516 patients (33% men) in the Surveillance Epidemiology and End Results (SEER) database revealed a 19.3% 1-year survival [36].

All ATC patients are TNM stage IV, with IVA being surgically resectable, IVB being confined to the neck but unresectable, and IVC having distant metastases. Several variables have been associated with length of survival when examined by uni- or multivariate analyses, including patient age, tumour size, extent of surgery, radiotherapy, presence of distant metastases at presentation, co-existing differentiated thyroid carcinoma and chemotherapy. Several investigators concluded that younger patients fared better [37–40], whereas two did not [41,42]. A smaller tumour size, as would be expected, also carried a better prognosis [38,43,44].

Impact of Surgery

The extent of surgery is summarised in Table 6.McIver *et al.* [45] found that the median survivalwas3.5months inpatients undergoing surgery versus 3 weeks in those receiving palliative care. Of 13 patients surviving more than 1-year, eight had complete resections and one had only minimal residua. One patient had positive lymph nodes and lived 23 years with surgery as the only therapy. Passler *et al.* [16] reported that patients with an R0 versus R1/R2 resection had a median survival of 6.1months versus 2.2 months and a 3-year survival of 50% versus 4%,whereas Tan *et al.* [43] obtained a 60% 5-year survival in five patients with complete resection. Pierie *et al.* [38] noted a 1-year survival of 92% if resection was complete, 35% if incomplete and 4% if no resection.

Swaak-Kragten *et al.* [46] observed a 1-year survival of 32% in patients with locoregional complete resection versus 9% overall, whereas Haigh *et al.* [47] produced a median survival of 43 months versus 3 months and 2-year survival of 75% versus 6% in patients who had R0/R1 versus less surgery. Goutsouliak and Hay [48] showed that patients with more radical therapy (at least partial thyroidectomy) had a longer median survival (9.7 months versus 3 months), whereas Brignardello *et al.* [49] reported that maximum surgery extended 6-month survival (58% versus 10%). Kihara *et al.* [11] showed 1-year survival rates of 75, 17 or 0% in patients having complete, incomplete or no resection, respectively. Several other authors have supported the benefits of surgery [50–53], whereas one report found no correlation of the extent of surgery with progression-free rate [54]. An analysis of the SEER database also confirmed longer median- and long-term survivals in patients who had surgery and whose tumour was confined to the thyroid or invaded only locally (Table 7).

Although in general, patients with resectable neck disease fared better than those whose disease was unresectable, unfortunately the tumour size and local extension make R0 and R1 resections feasible in only a minority of patients (Table 6). These results have, therefore,

resulted in extensive use of external beam radiotherapy to improve locoregional control of the disease.

Impact of Radiotherapy

McIver *et al.* [45] found that patients receiving radiotherapy had a median survival of 2.3 months versus 3.5 months if surgery could be carried out, but only 3 weeks if palliative care was provided. However, their conclusionwas that radiotherapy had no effect on local recurrence. Junor *et al.* [50] found an initial response in 77 of 91 patients, but local relapses in 50. Tan *et al.* [43] found more partial and complete responses when patients received >40 Gy, Pierie *et al.* [38] noted a 1-year survival of 54% (versus 17%) if >45 Gy was delivered, and Swaak-Kragten *et al.* [46] noted improved survival from 1.7 to 5.4 months if total dose >40 Gy.

Because patients historically had local recurrences, Kim and Leeper [55] added doxorubicin to enhance radiosensitivity, and they administered hyperfractionated radiotherapy (Table 6) to reduce late injury to normal tissue and to shorten the therapy time in treating a rapidly dividing tumour. Nineteen patients (nine of whom had only a biopsy) had a median survival of 1-year and a long-term local control rate of 68%, with most patients succumbing to distant metastases [55]. Wang *et al.* [54] treated 23 patients with > 40 Gy radiotherapy, whereas 24 received palliative therapy (<40 Gy). The former group were healthier (Eastern Cooperative Oncology Group score ≤2 and no distant metastases) and had a longer median survival (11.1 months versus 3.2 months). They also found a trend towards longer survival in patients who received twice-daily fractionation [54].

Tennvall *et al.* [56] tried three radiotherapy delivery protocols in 55 patients to see if hyperfractionated accelerated radiotherapy would improve response. All protocols delivered a total dose of 46 Gy (dose/fraction and days of therapy varied) and all had surgery and radiotherapy (varying sequence). Hyperfractionated accelerated radiotherapy reduced treatment time and improved local control, but did not improve median survival (Table 8). Other reports have also supported the use of radiotherapy, at least for local tumour control [44,48,51,57].

In contrast, Dandekar *et al.* [41] used hyperfractionated accelerated radiotherapy in 31 patients, found no improvement in survival and discontinued the approach due to increased toxicity. Wong *et al.* [58] also tried hyper-fractionated accelerated radiotherapy, using only 1 Gy/fraction, treating every 6 h (Table 6), but two patients developed myelopathy.

Newer methods of delivering radiotherapy may also improve local tumour control by delivering higher doses to the planning tumour volume while sparing adjacent structures. Nutting *et al.* [59] compared conventional radiotherapy, three-dimensional conformal radiotherapy and intensity-modulated radiotherapy. Intensitymodulated radiotherapy successfully delivered a higher dose to the thyroid bed and locoregional lymph nodes, with lower spinal cord exposure. Bhatia *et al.* [42] used both three-dimensional radiotherapy and intensitymodulated radiotherapy, with no significant differences noted. All four patients surviving more than 2 years had no distant metastases and received aggressive radiotherapy with median and 1-year survivals of 7 months and 29% versus 1.5 months and 4.5% in those receiving palliative radiotherapy.

Systemic Therapies

Many studies over the past half century have used a variety of chemotherapeutic agents, mostly in an uncontrolled manner in individual series that span many years or decades. In general, most reports concluded that chemotherapy did not improve survival

[37,38,45,50,56,57,60], although some studies reported benefits as part of multimodal therapy [40,55,61]. One randomised Eastern Cooperative Oncology Group trial compared doxorubicin ± cisplatin and found one partial response in 21 patients receiving the single agent, but three complete responses and three partial responses ($P = 0.03$) in 18 patients with combination therapy [62]. There were two prolonged complete responses of 41.3 and 34.7 months, with one of the patients having concomitant thyroidectomy and radiotherapy, and the other having biopsy only.

Although surgery and radiotherapy have improved locoregional tumour control, and in a minority have prolonged survival, the overall survival has changed little in more than 50 years, due to distant metastases.

Newer Therapies

Newer strategies involving systemic treatment are desperately needed. Few recent prospective studies have been conducted in ATC patients. Ain *et al.* [63] carried out a phase II trial with Taxol and reported progressive disease in 42% of patients; stable disease in 5%; a partial response in 47%; and a complete response in 5%. The median survival was longer in responders ($n = 10$) at 32 weeks, versus non-responders ($n = 8$) at 7 weeks. A phase II trial of axitinib in thyroid cancer included two ATC patients; one had a partial response, the other, progressive disease [64].

A phase II trial of fosbretabulin in 26 patients demonstrated stable disease in 27%, but no partial responses [65]. As part of phase II trials enrolling patients with multiple thyroid histologies, axitinib produced a partial response in one of two ATC patients [64] and sorafenib produced stable disease in one of four ATC patients [66]. Two recent abstracts were presented at the American Society of Clinical Oncology: Nagaiah *et al.* (ASCO 6-09) reported that sorafenib produced a partial response in two and stable disease in four of 15 patients, whereas Ha *et al.* (ASCO 6-09) demonstrated a partial response in two and stable disease in four of eight patients with imatinib. In a phase I clinical trials programme, six ATC patients received one of a variety of newer agents; one patient had a partial response (17%) [67].

Several individual cases have also been published. Shinohara *et al.* [68] had a stage IVB patient who received multimodal therapy with extensive surgery, hyper-fractionated radiotherapy and combination chemotherapy (cisplatin, doxorubicin, peplomycin and granulocyte colony-stimulating factor (G-CSF)) and was alive for more than 2 years. Hogan *et al.* [69] observed neck and mediastinal tumour reduction from erlotinib (150 mg daily) in a patient whose tumour had focal strong membrane staining for EGFR, whereas Noguchi *et al.* [70] gave a stage IVB patient neoadjuvant valproic acid (a histone deacetylase inhibitor), doxorubicin, cisplatin and radiotherapy, producing 50% tumour reduction and permitting subsequent surgery. The patient was disease free 2 years later. Gefitinib and docetaxel in a phase I trial included one ATC patient, with a partial response of 4 months [71].

A number of thyroid trials are listed on www.clinicaltrials.gov. As of 8 November 2009, the following trials were recruiting ATC patients in the USA: com-bretastatin, sorafenib, pazopanib, and AG-013736 (phase II), and PPAR-γ agonist (CS-7017) + paclitaxel (phase I/II). Three trials were open in Europe (sunitinib, pemetrexed + paclitaxel, and bevacizumab + doxorubicin).

There are numerous genetic and epigenetic abnormalities detected by mutations and methylation analyses, array-CGH, microarray, microRNA, and protein expression, providing ample opportunities for drug discoveries. The success of treating ATC will probably require building upon knowledge recently obtained, and integrating evolving technologies with

systems biology. Approaches may involve a comprehensive molecular analysis combining genome-wide screening with high throughout screens for drug-gable targets. Individualised combination therapies that maximally inhibit major pathways and signalling nodes at multiple genetic and epigenetic levels, possibly incorporating developing delivery systems such as gene and virus therapies, and nanoparticles, will hopefully improve the outcome for patients with ATC.

Palliative Care

Given the overall bleak prognosis, and extremely short survival time, careful attention to the extent of treatment should be given as quickly as possible. For many patients, palliative care should be instituted to manage symptoms of pain, nausea, anxiety, fatigue, dyspnoea, depression, constipation and decreased appetite. In patients with oesophageal/ tracheal compression, bleeding or pain, selective embolisation of thyroid arteries was shown to improve swallowing, pain and breathing in one small series [72]. Throughout this arduous ordeal, both the patient and their family may benefit from emotional, psychological, spiritual and medical support. Ideally, a palliative care team, consisting of medical specialists, nurses, pharmacists, a social worker, physical and occupational therapists, a chaplain and an ethics consultant will be available.

Acknowledgments

The author thanks Kathleen Norton for typing the manuscript.

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Table 1

Thyroid carcinoma and microRNAs [20,73,74]

	MicroRNA			
Tumour	**Increase**	**Decrease**	**Effect**	**Gene(s) targeted**
PTC	221; 222	138; 219	↓ growth	KIT; $p27^{kip1}$
	146; 155; 181b	26a; 345		HOX B2;TRAF6; IRAK1
FTC	197; 34b	–	–	EFEMP2; ACVR; TSPAN3
	192; 328			
ATC	17–92; 106a,b	26a; 125b	↓ growth	HMGA1
	221; 222	138		hTERT
		30a,d		Rb; PTEN
	146b; 21	let7c		

ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma.

Table 2

Anaplastic thyroid carcinoma and protein expression [20,35,75–77]

Function	Overexpressed	Underexpressed
Transcription	PPAR-γ; HNF-1α; Id1; YBX1; HMG1(Y); Fra1; c–myc	NKX2-1; FOXE1; Pax8; CBX7
Signalling	EGFR; CXR4; pAKt1; pERK; JAK/STAT	SOCS 1,3,5
Mitosis	Aurora kinases; kα1 tubulin; topoisomerase-11	TACC3
Proliferation	MKI67; OEATC-1; RBBP4; SPAG9	
Cell cycle	Cyclins D1, D3, E	p21; p27
Apoptosis	IAPs; DJ-1; NF-κβ; LCN2	Bcl2; αB-crystallin
Adhesion	β-catenin; ILK1; FAK	E-cadherin
Tumour suppressor	p53	Rb; p16; PTEN

Table 3

In vitro studies in anaplastic thyroid carcinoma [20,35,77–83]

	Agonists	Antagonists
Transcription		
PPAR-γ	Thiazolidinediones	GW9662; siRNA
HMGI(Y)		Adenoviral antisense
Signalling pathways		
EGFR		Gefitinib; cetuximab
VEGF		Erlotanib; triptolide
EGFR/VEGFR		AEE788
BCR-ABL; c-KIT		Imatinib
BRAF		Sorafenib
MAPKK(MEK)		PD0325901; AZD6244
CXCR4		siRNA; AMD3100
PTEN/Akt	TZD (↑PTEN)	TZD (↓p-Akt); Akt1 inhibitor IV; SOCS
mTOR		RAD001
JNK		SP600125
Farnesyl transferase		Manumycin
JAK/STAT		SOCS siRNA
Mitosis		
Aurora kinases		Aurora kinase inhibitor; VX-680
Microtubules		Paclitaxel; combretastatin; valproic acid
Proliferation		
OEATC-1; RBBP4		siRNA
Oncolytic viruses		ONYX-015; ONYX-411; mutant vaccinia; adenovirus HSV-TK; p53-regulated; etoposide
SPAG9		siRNA
Cell cycle		
Cell cycle		Gemcitabine; opioid growth factor/OGF receptor
Cyclins		CCND1 siRNA; imatinib; plitidepsin; triptolide
CdK inhibitors	P53 adenovirus; BMP-7; TZDs; SOCS	siRNA; mithramycin
Apoptosis		
IAPs		siRNA; Smac
NF-κB		DHMEQ; triptolide
IGF-1		aIR3 antibody
DJ-1; LCN2		siRNA
PLK-1; DUSP26		siRNA
PPAR-γ	TZDs	
EGFR/VEGFR		AEE788
BCR-ABL1; c-KIT		Imatinib
Aurora kinase		VX-680
Integrin-linked kinase		QLT0267

	Agonists	Antagonists
STAT3	Mutant p53	Mutant p53 antisense
Hdm2		Nutlin-3
Migration		
Autotaxin	Autotaxin	IL1β;IL4;TGFB1
VEGFR2		VEGFR-2 inhibitor1
Protein degradation		
Proteosomes		Bortezomib; nutlin-3
Epigenetic		
Histone acetylation		Valproic acid; depsipeptide
Methylation		5-aza-dCR

Table 4

Anaplastic thyroid carcinoma *in vivo* xenograft studies [20,80]

Agent	Percentage inhibition	Agent	Percentage inhibition
Imatinib	44–67%	Manumycin	~100%
Gefitinib	53–>90%	Mutant vaccinia	~96%
AEE788	58%	Lovastatin	–
Paclitaxel	44– ~100%	dl1520 (ONYX-015)	23%
AZD6244	~75%	Lovastatin + ONYX-015	~55%
Combretastatin A4P	~60%	NGAL siRNA	~97%
AMD3100	92%	DHMEQ	>90%
		Triptolide	~60%

Table 5

Clinical characteristics and survival in anaplastic thyroid carcinoma

Reference	Years	Patients (male/female)	Age (range)	Survival (months)	Survival 1-year (%)
[45]	1949–1999	54/80	67 (mean)	3	9.7%
[40]	1950–1987	54/67	61 (mean) (24–91)	7.2	–
[84]	1954–1998	7/31	70 (mean) (15–93)	4.5	11.8%
[14]	~1957–1992	18/30	66 (mean) (35–85)	–	42%
[50]	1961–1986	27/64	70 (median) (38–92)	5	~20%
[16]	1965–1997	43/77	70.5 (median) (37–86)	3.1	12%
[85]	1966–1989	4/13	63 (mean) (43–83)	12	53%
[37]	1966–2006	16/34	72 (median) (36–104)	3	14%
[51]	1967–1994	7/26	66 (mean) (36–89)	2.5	9.7%
[43]	1968–1992	10/11	65 (mean) (38–83)	4.5	~23%
[38]	1969–1999	22/45	73 (median) (40–92)	~6	35%
[57]	1970–1986	17/34	67 (mean) (31–89)	2.7–3.4	6%
[86]	1970–1996	4/10	59 (median) (22–88)	5	21%
[44]	1971–1993	9/28	68 (median) (34–82)	3	0–20%
[46]	1972–2003	19/56	68 (mean)	2.9	9%

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Reference	Years	Patients (male/female)	Age (range)	Survival (months)	Survival 1-year (%)
			(40–89)		
[39]	1972–2003	58/130	68 (median)	3	13%
[47]	1973–1998	13/20	69 (median) (47–80)	3–43	0–75%
[58]	1975–1982	9/23	70 (median) (31–87)	<6	28%
[55]	1979–1987	13/6	60 (median) (33–71)	12	~22%
[87]	1979–2002	6/12	72 (median) (29–92)	6.2	30%
[52]	1981–1991	9/11	61 (median) (27–82)	–	15%
[54]	1983–2004	25/22	69 (median) (39–90)	5.6	–
[56]	1984–1999	17/38	76 (median) (46–94)	3.5	16%
[11]	1984–2002	7/12	73 (mean) (45–87)	9.4	21%
[48]	1985–1999	24/51	74 (median) (38–98)	5.1	~20%
[60]	1989–1999	–	–	–	41% (73% if incidental)
[53]	1990–2000	12/18	59 (mean) (40–79)	10	46%
[41]	1991–2002	14/17	69 (median) (51–85)	2.3	~8%
[88]	1992–1994	6/11	67 (median) (50–74)	–	–
[61]	1992–1999	11/28	69 (median) (39–88)	6	–
[19]	1993–2005	49/77	67 (mean) (37–88)	–	–

Reference	Years	Patients (male/female)	Age (range)	Survival (months)	Survival 1-year (%)
[42]	1995–2007	24/29	66 (mean) (27–88)	3	19%
[63]	1996–1999	13/6	58 (median) (47–86)	6	~30%
[89]	1997–2007	4/12	60 (median) (27–71)	11	~35%
[49]	2000–2005	9/18	70 (mean) (46–89)	3.9	~25%
Total		634/1137		5	20%

Table 6

Treatments for anaplastic thyroid carcinoma

Reference	No.	Surgery	Radiotherapy	Chemotherapy
[45]	134	Debulk =48; 'cure' = 35; biopsy=13 (residua: none = 29; minimal = 35; gross = 42)	41/42 with gross residua; 38/54 with near total resection	Alone in 4; postop adjuvant in 12; combination in 13
[40]	121	R0/R1=61; R2 = 45; R3 =25	58	64
[84]	38	23	12	3
[14]	48	R0/R2=34; R3 = 14	5000–6500 rads in 38; ≤ 4000 in 5	Adriamycin, cisplatin, vincristine, 5-FU or endoxan in 17
[50]	91	R0/R1=5; R2 =28; R3 = 58	Daily (30–60 Gy in most); CR = 34; PR = 36; SD =7; PD =9	18
[16]	120	R0 = 29; R1/R2 = 76; RX = 15	–	–
[85]	17	R0/R1=8	12	11
[37]	50	Total = 34 (curative intent in 16)	23 (46%)	18 (36%) – alone or with radiotherapy
[51]	33	R0 = 1; R1 = 2; R2 = 12; R3 = 18	NA	NA
[43]	21	R0/R1=5; R2 =5; R3 = 11	<40 Gy in 4 (PR = 1); 40–60 Gy in 5 (PR = 2, CR = 1); 60 + Gy in 9 (PR = 3, CR = 2)	6 (adriamycin ± other agent in all)
[38]	67	R0/R1=12; R2 = 32; R3 =23	>45 Gy in 27; ≤ 45 Gy in 29	21
[57]	51	R0/R1=15; biopsy = 8; R3 =28	<40 Gy in 25; 40–60 Gy in 21;> 60 Gy in 5	13 (adriamycin in 9)
[86]	14	TTX = 7; debulk = 6; biopsy =1	2	5
[44]	37	R0/R1=19; R2 = 5	>30 Gy in 21; < 30 Gy in 7; 1971–1983 = 200 cGy/d; 1984 HRT = (130 cGy BID)	Adriamycin (30 mg/m^2); mitomycin C; cyclophosphamide; cisplatin (70 mg/m^2) in 32
[46]	75	R0/R1=19 (12 local CR); R2/R3=56 (7 CR)	Radiotherapy in 72//Pre-1988: many schedules (30–60 Gy total; fractions = 2–3 Gy) 1988 protocol: TD = 50.6 Gy; 1.1 Gy BID 5 × /week	Pre-1988: some adjuvant (doxorubicin; endoxan; 5-FU; cisplatin) 1988: (a) doxorubicin (15 mg/m^2 week with radiotherapy); (b) prophylactic lung (1.5 Gy × 5 days + doxorubicin); (c) adjuvant doxorubicin – (50 mg/m^2 3 week) after radiotherapy
[39]	188	R0 = 16; R1 =15; R2 = 27; R3 =130	≤20 Gy in 15; 20–45 Gy in 69;> 45 Gy in 71 (daily in 104; BID in 51); TD =45–64 Gy	Adriamycin (20 mg/week) + vinblastine (2 mg), then HRT before surgery 124
[47]	33	R0/R1=8; R2 =16; R3=9	TD = 45–75 Gy	Doxorubicin; paclitaxel; cisplatin; carboplatin; VP-16; cyclophosphamide; melphalan; bleomycin
[58]	32	R2 = 10	HART (1 Gy, QID); TD=30–45 Gy	Adriamycin (40 mg q 3 weeks)
[55]	19	R0/R1=0; R2 =10; R3 = 9	HRT (TD =5760 rad; 160 rad BID, TIW) CR = 84%	Adriamycin (10 mg/m^2 week) with HRT
[87]	18	TTX = 3; TTX (3) + lobe (1) with radiotherapy	Single modality = 6 (6–40 Gy); multimodal = 7 (5–60 Gy)	4
[52]	20	12 total surgery; R0/R1 = 4	17.5 Gy in 7 fractions; days 10–20 of first 4 chemotherapy cycles; local CR in 5; PR in 7.	Doxorubicin (60 mg/m^2) + cisplatin (90 mg/m^2) q4wk in 12 ≤ 65 years; mitoxantrone (14 mg/m^2) q4wk in 8 ≥ 61 years
[54]	47	TTX/partial = 22; debulk = 4; biopsy =21	≤40 Gy in 24; > 40 Gy in 23 (daily in 14; 1.5 Gy BID in 9)	Adriamycin ± cisplatin, bleomycin in 4

Reference	No.	Surgery	Radiotherapy	Chemotherapy
[56]	16	A (1984–1988) R0/R1=7 R2 = 2	A Preop = 30 Gy; postop = 16 Gy (1 Gy BID, 5 days/week)	Doxorubicin (20 mg/week), start before radiotherapy
	17	B (1989–1992) R0/R1 = 12 R2 =2	B Preop = 30 Gy; postop = 16 Gy (1.3 Gy BID, 5 days/week)	
	22	C (1993–1999) R0/R1 = 15 R2 =2	C Preop = 46 Gy (1.6 Gy BID)	
[11]	19	R0/R1=4; R2 =6; R3=9	TD≥45 Gy in 9; <45 Gy in 4	Adriamycin, cisplatin, etoposide, paclitaxel alone or combination in 12
[48]	75	R0/R1=4; R2 =9; R3 = 49	Radiotherapy<40 Gy = 26 (+ surgery = 7); ≥40 Gy = 10 (+ surgery = 5);≥ 40 Gy + chemotherapy =7 (+ chemotherapy/ surgery = 2)	Platinum based = 9
[60]	40	R0 = 11; R1/R2 = 15; R3 =14	1.5–2 Gy qd; TD = 45–60 Gy in 14; 1.2 Gy BID, TD = 50–60 Gy in 5	Adriamycin ± cisplatin, etoposide
[53]	30	R0 = 3; R1 = 11; R2 =10; R3=6	TD = 40 Gy in 29 and 30 Gy in 1 (1.25 Gy BID 5 days/week) (boost to 50–55 Gy in 7)	Doxorubicin (60 mg/m^2) + cisplatin (120 mg/m^2): 2 cycles before radiotherapy, 4 cycles after radiotherapy
[41]	31	TTX = 2; lobe = 1; debulk = 7	HART (TD =60.8 Gy; 1.8 and 2.0 Gy BID; spinal cord <40 Gy)	None
[88]	15	R0/R1=7	2 Gy/day, 5 days/week (TD goal = 45–50 Gy)	Cisplatin (40 mg/m^2, day 1)+ adriamycin (60 mg/m^2, day 1) + etoposide (100 mg/m^2, days 1–3) + peplomycin (5 mg/day, days 1–5) q3 week; G–CSF
[61]	39	16 (+ radiotherapy/chemotherapy)	16 with surgery; 4 radiotherapy alone	16 with surgery; 9 chemotherapy alone Adriamycin; bleomycin; cisplatin
[42]	53	R0/R1=19; R2 = 12; R3 =22	IMRT = 13; 3DRT =40; 31 definitive, 22 palliative; fractions/ day = daily in 38, BID in 15	39 concurrent; 9 sequential; 5 none
[63]	19	TTX = 8; lobectomy = 3; biopsy = 8	5	Paclitaxel: 120 mg/m^2 (n = 7); 140 mg/m^2 (n = 12) over 96 h q3 week CR = 1; PR=9; SD =1; PD =8
[89]	16	Inoperable stage IV B	Neck: 2 Gy qd 5 days/week to 45 Gy (15 Gy boost); 45 Gy upper mediastinum; TD = 60 Gy	After radiotherapy: adriamycin =60 mg/m^2 + cisplatin 40 mg/m^2 q3 week CR = 1; PR=3; SD =4; PD =8
[49]	27	R0/R1 (+ minimal residua) = 14; R2 = 6; R3 =10	1.8–2 Gy qd · 5 days/week to 36–40 Gy; neoadjuvant in 5	Adriamycin 20 mg/m^2 + cisplatin 20 mg/m^2 q week with radiotherapy, then 60 mg/m^2 q3 week (n = 22) or paclitaxel 80–120 mg/m^2/week 6 week if no radiotherapy (n = 5)

Resectability: R0, intrathyroidal; R1, extrathyroid, macroscopically resectable; R2, partially resectable; R3, non-resectable.
NA, information not available; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TD, total dose; BID, twice daily; HRT, hyperfractionated radiotherapy; HART, hyperfractionated accelerated radiotherapy TTX = total thyroidectomy; IMRT, intensity-modulated radiotherapy.

Table 7

Disease extent and overall survival (%) in 261 patients with anaplastic thyroid carcinoma [90]

	No. (%)	Median (months)	1-year (%)	2 year (%)	5 year (%)
Confined within capsule	36 (13.8)	9	50.0	32.7	22.9
Invasion of adjacent structures	110 (42.1)	6	27.6	16.2	10.1
Further extension or distant metastases	95 (36.4)	3	7.4	2.1	–
Unknown	20 (7.7)	–	–	–	
Overall		4		12.9	7.5

Table 8

Hyperfractionated radiotherapy protocols and locoregional control [56]

	Gy/fraction (*n*)	Regimen	Days	Local control	Median survival (months)
A	1.0 (16)	30 Gy–surgery–16 Gy	70	31%	3.5
B	1.3 (17)	30 Gy–surgery–16 Gy	50	65%	4.5
C	1.6 (22)	46 Gy–surgery	21	77%	2.0