Chapter 26
Thyroid Cancer

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Introduction

An estimated 56,460 persons in the USA will be diagnosed with various forms of thyroid cancer in 2012, the ninth most commonly diagnosed cancer overall [1]. With 76% of cases now identified in women, thyroid cancer has become the fifth most commonly diagnosed malignancy in that gender, up from the tenth most common only 10 years ago. Between 1998 and 2007, the most recent period for which Surveillance, Epidemiology, and End Results program (SEER) data are available, the average annual percent change in age-adjusted incidence of thyroid cancer in the USA—6.1%—was the highest among all cancers [2]. Worldwide, the incidence of thyroid cancer has been increasing as well [3]. The reasons underlying this marked increase are likely multiple, with one being the increasing number of diagnoses of incidental small cancers resulting from improved sensitivity of diagnostic imaging procedures such as ultrasound [4]. Mortality rates in patients with thyroid cancer have also been rising in the USA, albeit far more slowly. Although only 1,780 deaths from thyroid cancer are expected in 2012, the average age-adjusted mortality increased 0.6% per year between 1998 and 2007, most notably among men, who experienced a striking 1.6% increase per year [2]. In Texas, the mortality rates have been increasing faster than those in the rest of the USA.

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Thyroid cancer is subdivided into four major histologic subtypes: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC) (see Table 26.1 [5] for the American Joint Committee on Cancer (AJCC)-TNM staging system criteria and Table 26.2 [6] for SEER staging criteria). Of these, both PTC and FTC derive from the thyroid follicular epithelium, cells normally responsible for the uptake of iodine

Table 26.1 AJCC-TNM staging of thyroid carcinoma, 7th edition [5]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension limited to the thyroid
T1a	Tumor 1 cm or less, limited to the thyroid
T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid
T3	Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
T4a	Moderately advanced disease: Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Very advanced disease: Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
All anaplastic carcinomas are considered T4 tumors	
T4a	Intrathyroidal anaplastic carcinoma
T4b	Anaplastic carcinoma with gross extrathyroid extension
Regional lymph nodes (N)	
Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

(continued)

Table 26.1 (continued)

Anatomic stage/prognostic groups			
Differentiated			
		Under 45 years	
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
		45 years and older	
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
Medullary carcinoma (all age groups)			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
Anaplastic carcinoma			
All anaplastic carcinomas are considered Stage IV			
Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Note: All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest determines the classification)

for use in the production of thyroid hormone, under the influence of thyroid-stimulating hormone (TSH). PTC and FTC, collectively referred to as differentiated thyroid carcinomas (DTC), currently account for 96.5% of all incident thyroid cancers [2]. In addition to more extensive disease, the major risk factors for mortality

Table 26.2 SEER summary staging of thyroid carcinoma [6]

Stage	Description
Local	Confined to one lobe and/or isthmus; both lobes involved; thyroid gland capsule involved; multiple foci but confined to thyroid gland; through capsule of gland, but not beyond
Regional	Direct extension to pericapsular tissues, strap muscle(s), nerve(s), major blood vessels, soft tissue of neck, esophagus, larynx including thyroid and cricoid cartilages, sternocleidomastoid muscle, OR lymph nodes (anterior deep cervical, internal jugular, retropharyngeal, cervical NOS)
Distant	Direct extension to trachea, mediastinal tissues, skeletal muscle other than strap muscles and sternocleidomastoid, bone, OR other distant involvement, OR submandibular, submental, or other distant nodes

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from DTC include age greater than 45 years at diagnosis. MTC, on the other hand, arises from the calcitonin-secreting neuroendocrine-derived C cells within the upper portions of the thyroid lobes and represents 1.6% of incident thyroid malignancies. About 20% of patients with MTC have an inherited form of the disease, either multiple endocrine neoplasia type II or familial MTC; almost all inherited cases are due to autosomal dominant germline mutations of the *RET* proto-oncogene [7]. ATC likely develops as a consequence of multiple dedifferentiating mutations occurring in DTC and accounts for only about 1% of thyroid cancers. Although the 10-year relative survival rate for patients with DTC is greater than 90%, 10-year survival rates are worse for patients with MTC (80%) and ATC (13%) [8].

Historical Perspective

Unlike most other forms of cancer, no data exist from randomized controlled trials of any of the primary treatments commonly used for thyroid carcinoma (surgery, radioiodine, and thyroid hormone suppression for DTC; surgery for MTC; and chemotherapy and external beam radiation with or without surgery for ATC). Thus, current consensus guidelines for primary therapy are still based on a combination of large retrospective studies and expert opinion [7, 9, 10]. Investigators at The University of Texas MD Anderson Cancer Center have contributed extensively both to the body of retrospective studies and to the development of guidelines for therapy.

Since the early twentieth century, surgical resection of the thyroid gland has been the mainstay of treatment for thyroid malignancies, but debate has long focused on the optimal extent of primary surgery, i.e., partial versus total thyroidectomy. Early publications from MD Anderson Cancer Center emphasized the need for total thyroidectomy (removal of both lobes of the thyroid as well as the middle portion) in patients with DTC because of the high frequency of bilateral multifocal disease and provided some of the first evidence suggesting improved outcomes [11–13].

Radioactive iodine (131-I) was introduced for scanning and treatment of metastatic DTC in the mid-1940s. Use of radioactive iodine for adjuvant therapy after total thyroidectomy gained momentum after study findings were published in the early 1980s, including a seminal report from the MD Anderson multidisciplinary thyroid cancer treatment group describing a multivariate analysis that demonstrated improved disease-free survival in 706 patients with DTC [14]. Recently, analyses from a multicenter thyroid cancer registry led by MD Anderson investigators have provided the strongest evidence to date for improved survival among DTC patients presenting with National Thyroid Cancer Treatment Cooperative Study stages II, III, and IV treated with total thyroidectomy and adjuvant radioactive iodine [15]. TSH-suppressive thyroid hormone therapy was also found to improve survival, with greater degrees of suppression associated with optimal survival in patients with stages III and IV disease.

For patients with MTC, total thyroidectomy was established by the 1980s as the standard initial surgical procedure, with subsequent refinements focusing on the extent of nodal dissection [16, 17]. Early adoption of *RET* genotype-driven treatment strategies based on prospective testing in children and adults with inherited forms of MTC has resulted in personalized surgical management [18]. The role of external beam radiotherapy in both DTC and MTC has remained contentious, although recent retrospective studies have suggested durable disease control in patients at high risk of locoregional recurrence who receive adjuvant radiotherapy [19, 20]. One of the earliest publications describing a possible role for chemotherapy in patients with advanced or metastatic thyroid carcinoma contributed to the FDA approval of doxorubicin [21]. Traditionally, however, cytotoxic chemotherapies have been rarely used for DTC or MTC because of their limited efficacy and intolerable adverse effects. With the introduction of novel therapies targeting oncogenic mutant kinases and tumor angiogenesis, MD Anderson physicians have led a resurgence of clinical interest in systemic therapies for patients with disease refractory to standard approaches [22, 23].

The MD Anderson Cancer Center Experience

The MD Anderson Tumor Registry data set was derived from 6,460 men and women with a diagnosis of thyroid cancer who were seen between 1944 and 2004. Of this group, 1,677 patients who had received no previous treatment for their malignancy received definitive primary treatment at MD Anderson. After excluding patients with other primary malignancies except for superficial skin cancers, 1,232 patients remained and formed the basis of this report. Within this cohort, 1,028 (83.4%) had DTC, 111 (9.0%) had MTC, and 62 (5.0%) had ATC (Table 26.3). Thus, a disproportionate number of newly diagnosed patients with either MTC or ATC have been seen at our institution compared with the historical U.S. distribution of these histologies (9.0% vs. 1.6% for MTC, 5.0% vs. about 1% for ATC, respectively), suggesting that patients with more aggressive histologic variants may have been more likely to be referred.

Table 26.3 Histologic subtypes of thyroid cancer in 1,232 patients seen at MD Anderson between 1944 and 2004

	Histologic subtype				
	DTC[a]	MTC	ATC	Other	Total
Decade	[No. of patients]				
1944–1954	28	1	3	0	32
1955–1964	85	7	5	5	102
1965–1974	110	12	10	3	135
1975–1984	104	19	3	4	125
1985–1994	218	18	13	4	253
1995–2004	483	54	28	15	580
Total	*1,028*	*111*	*62*	*31*	*1,232*

ATC anaplastic thyroid carcinoma, *DTC* differentiated thyroid carcinoma, *MTC* medullary thyroid carcinoma

[a]Papillary thyroid carcinoma and follicular thyroid carcinoma are collectively known as differentiated thyroid carcinomas

Table 26.4 SEER stages for 1,028 patients with differentiated thyroid carcinoma who were treated at MD Anderson, 1944–2004

	SEER stage				
	Local	Regional	Distant	Unstaged	Total
Decade	[No. of patients]				
1944–1954	4	17	7	0	28
1955–1964	23	47	15	0	85
1965–1974	30	56	24	0	110
1975–1984	35	45	23	1	104
1985–1994	69	106	42	1	218
1995–2004	189	219	70	5	483
Total	*350*	*490*	*181*	*7*	*1,028*

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Among patients with DTC, 34% presented with local disease, 48% with regional extension, and 18% with distant metastases (Table 26.4). Between the first three and the last three decades, the proportion of patients who presented with regional and distant metastatic disease decreased from 74% to 63%, reaching a nadir in the last 10 years at 60%. Nonetheless, the frequency of patients with regional or distant metastatic disease at presentation was markedly higher than the 40% reported nationally between 1988 and 2005 [24].

Among MTC patients, 30% presented with localized disease, whereas 43% presented with regional disease and 25% with distant metastatic disease (Table 26.5). No major trend over time was identified, except for increased detection of localized disease in the last decade; the introduction of genetic testing for *RET* mutations to facilitate early diagnosis may have contributed to this recent stage migration [25]. Similar to our experience with DTC, the proportion of patients who presented with regional or distant metastatic MTC was considerably higher than the 52% reported from a national SEER dataset [26].

Table 26.5 SEER stages for 111 patients with medullary thyroid carcinoma who were treated at MD Anderson, 1944–2004

	SEER stage				
	Local	Regional	Distant	Unstaged	Total
Decade	[No. of patients]				
1944–1954	1	0	0	0	1
1955–1964	1	2	4	0	7
1965–1974	3	5	3	1	12
1975–1984	3	11	5	0	19
1985–1994	4	10	4	0	18
1995–2004	21	20	12	1	54
Total	*33*	*48*	*28*	*2*	*111*

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Table 26.6 SEER stages for 62 patients with anaplastic thyroid carcinoma who were treated at MD Anderson, 1944–2004

	SEER stage				
	Local	Regional	Distant	Unstaged	Total
Decade	[No. of patients]				
1944–1954	0	0	3	0	3
1955–1964	0	0	3	2	5
1965–1974	0	4	6	0	10
1975–1984	0	1	2	0	3
1985–1994	1	1	8	3	13
1995–2004	0	12	15	1	28
Total	*1*	*18*	*37*	*6*	*62*

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Among patients with ATC, 60% presented with distant metastatic disease, also higher than the 43% reported nationally (Table 26.6) [27].

Overall, the higher proportions of patients who presented with more advanced disease likely reflect referral patterns to the institution, although more extensive use of cross-sectional and functional imaging might also bias toward increased identification of regional and distant metastatic disease.

Kaplan–Meier survival analyses for the entire cohort of 1,232 patients demonstrate a significant trend toward improved outcomes over the 60-year period (Figs. 26.1, 26.2, 26.3, and 26.4), but visual inspection indicates that major survival advances began in the 1975–1984 decade (Fig. 26.1). Five-year survival estimates improved from 72–74% for the first three decades to 86–88% in the latter three decades, with corresponding 10-year survival estimates increasing from 59–62% to 76–80%. Significant trends in improved survival were observed in two subgroups: patients with localized disease (Fig. 26.2) and patients with distant metastases (Fig. 26.4), whereas the trend was similar but not significant for patients with regional disease (Fig. 26.3). These survival improvements may correspond to the broader adoption of adjuvant radioactive iodine for DTC and of total thyroidectomy as the standard primary treatment for all forms of thyroid cancer.

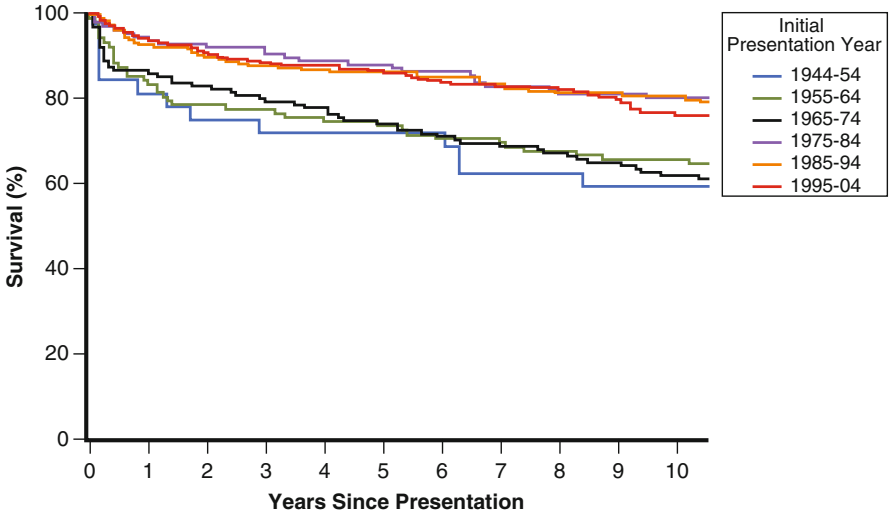

Fig. 26.1 Overall survival rates for 1,232 patients with thyroid cancer (all histologies and disease extent) (1944–2004) ($P < 0.0001$, log-rank test for trend).

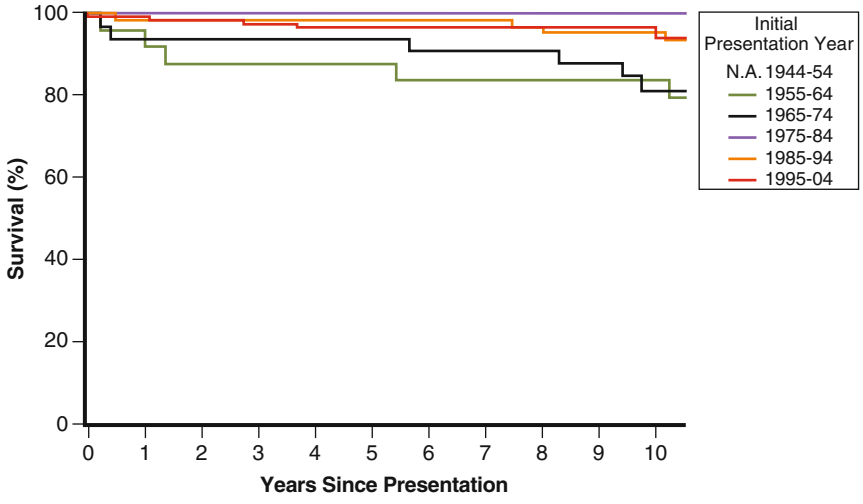

Fig. 26.2 Overall survival rates for 390 patients with local (SEER stage) thyroid cancer (all histologies) (1944–2004) ($P = 0.017$, log-rank test for trend). Because of the very small number of individuals with local thyroid cancer seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

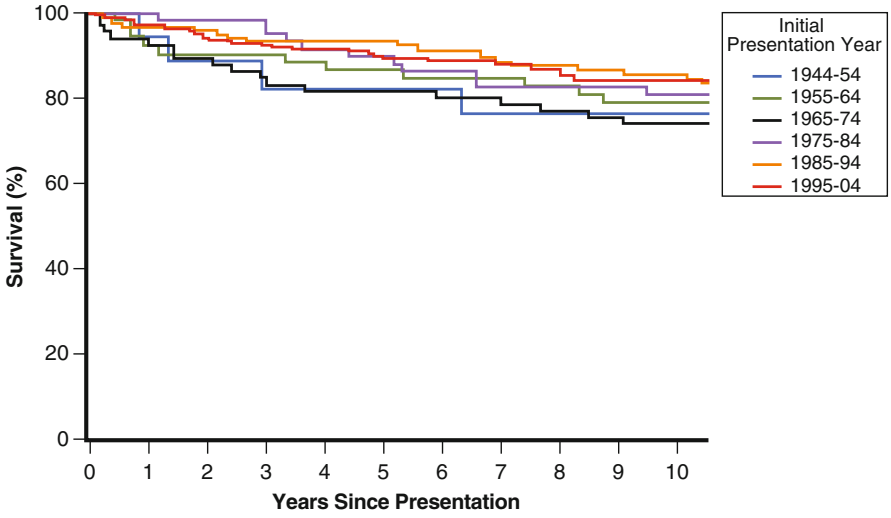

Fig. 26.3 Overall survival rates for 569 patients with regional (SEER stage) thyroid cancer (all histologies) (1944–2004) ($P = 0.225$, log-rank test for trend).

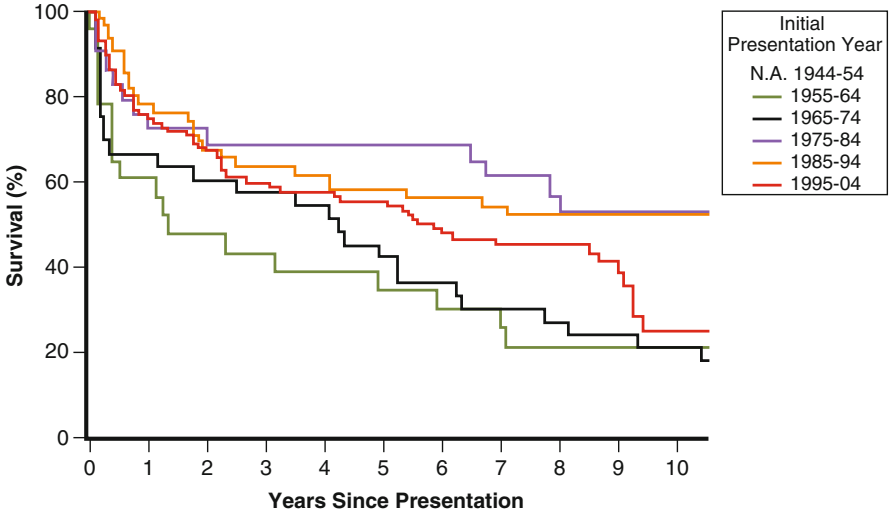

Fig. 26.4 Overall survival rates for 252 patients with distant (SEER stage) metastatic thyroid cancer (all histologies) (1944–2004) ($P = 0.003$, log-rank test for trend). Because of the very small number of individuals with distant thyroid cancer seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

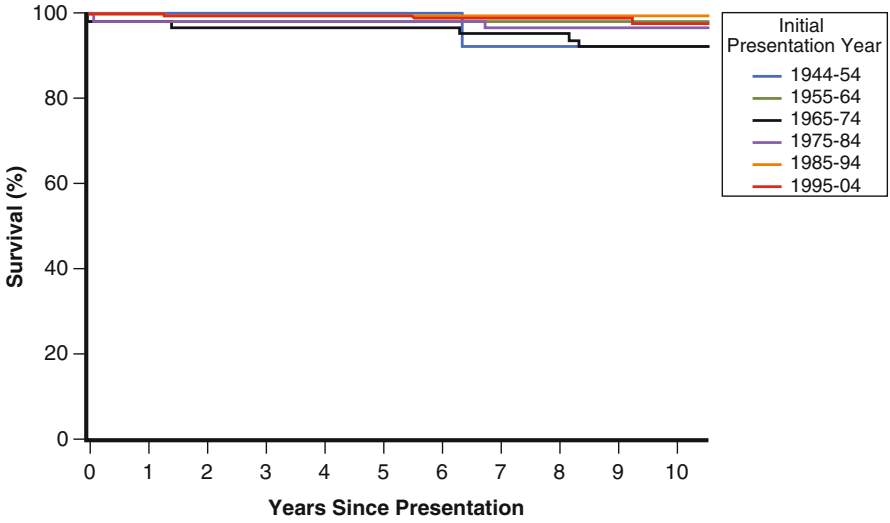

Fig. 26.5 Overall survival rates for 573 patients with differentiated thyroid carcinoma who were <45 years of age at diagnosis (1944–2004).

Analysis of the outcomes of DTC patient subgroups confirms and extends these overall survival findings. Because of the excellent relative survival rates associated with patient age of <45 years at diagnosis, only about 20% of patient deaths have occurred in this subgroup; however, no major trend can be observed due to the small number of events (Fig. 26.5). In contrast, improvement in survival rates in patients 45 years or older at diagnosis was seen beginning in the 1975–1984 decade (Fig. 26.6). When this older subgroup is evaluated on the basis of initial disease extent, a general trend toward improved outcomes in the later decades can be identified as well (Figs. 26.7, 26.8, and 26.9). The small number of cases and patient deaths limits the ability to evaluate time trends in outcomes in the MTC and ATC subgroups.

One important caveat must be considered in evaluating changes in patient outcomes over this 60-year period. If a secular trend existed in the use of imaging procedures for disease staging, leading to increased imaging in the latter decades, caution would have to be applied to interpreting any improvements in patient outcomes without considering a possible “Will Rogers phenomenon” associated with stage migration [28]. As with any other retrospective analysis spanning several decades, improvements in supportive care and management of comorbid diseases may also have contributed to increased survival.

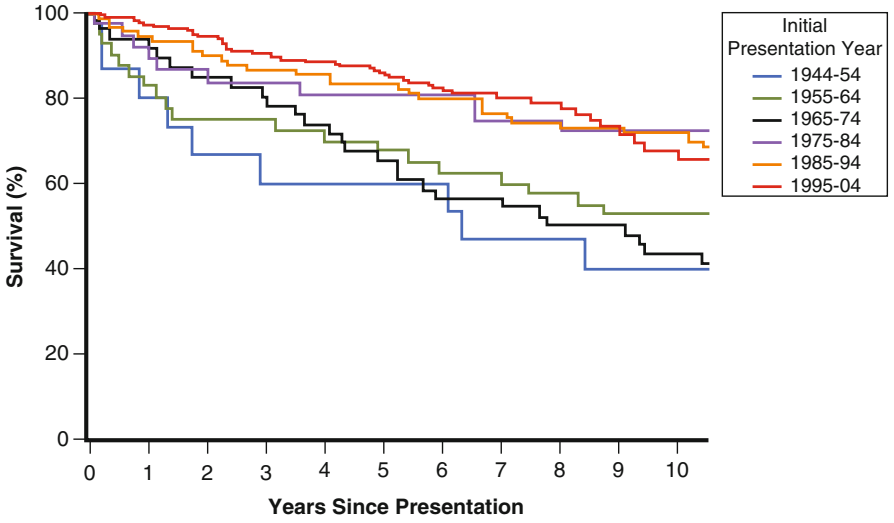

Fig. 26.6 Overall survival rates for 455 patients with differentiated thyroid carcinoma who were ≥45 years of age at diagnosis (1944–2004).

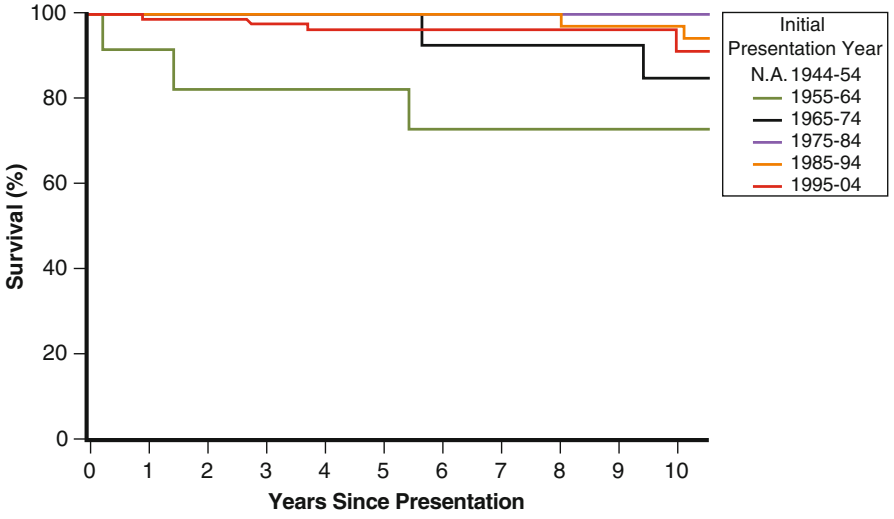

Fig. 26.7 Overall survival rates for 158 patients with local (SEER stage) differentiated thyroid carcinoma who were ≥45 years of age at diagnosis (1944–2004). Because of the very small number of individuals with local thyroid cancer seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

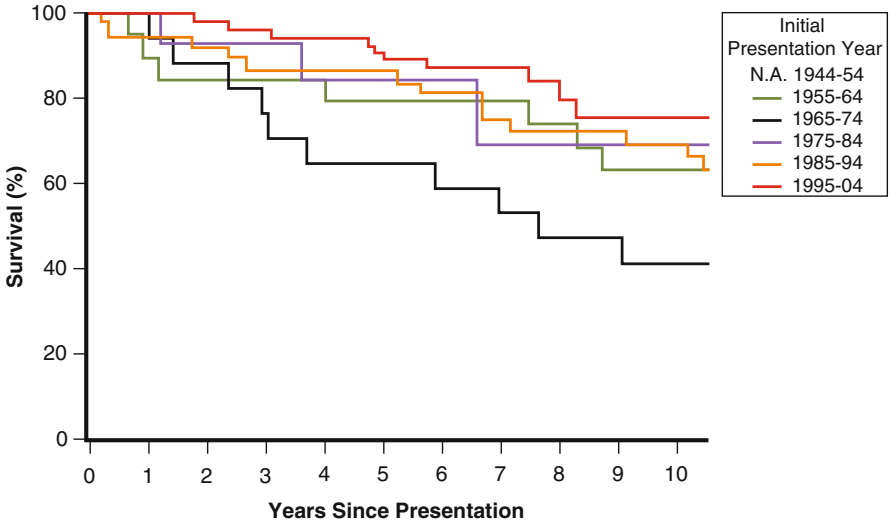

Fig. 26.8 Overall survival rates for 179 patients with regional (SEER stage) differentiated thyroid carcinoma who were ≥45 years of age at diagnosis (1944–2004). Because of the very small number of individuals with regional thyroid cancer seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

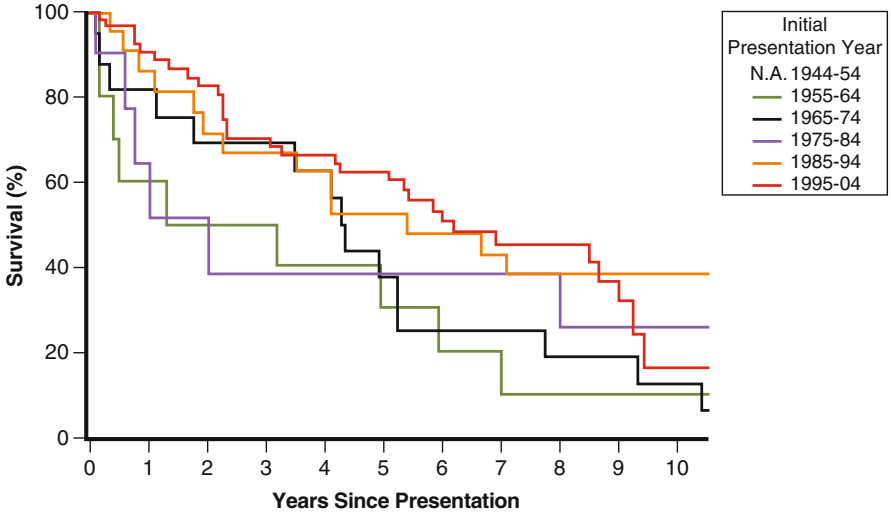

Fig. 26.9 Overall survival rates for 113 patients with distant (SEER stage) metastatic differentiated thyroid carcinoma who were ≥45 years of age at diagnosis (1944–2004). Because of the very small number of individuals with distant thyroid cancer seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

Current Management Approach

Our current multidisciplinary approach to treating patients with thyroid carcinoma is based on disease histology combined with disease extent and prognosis. Because death and morbidity can result from uncontrolled neck disease, even in patients with distant metastases, priority is also placed on interventions to prevent locoregional complications. Given the role of MD Anderson physicians in developing national consensus guidelines, there is extensive overlap between our disease-management approach and the approach recommended in the recently published national guidelines [7, 9, 10].

Patients with either DTC or MTC undergo comprehensive neck ultrasound as the primary staging procedure for locoregional disease [29]. Cross-sectional imaging with computed tomography or magnetic resonance imaging is indicated if grossly invasive disease is suspected or extensive regional metastases are appreciated on ultrasound. Although thyroid lobectomy with isthmusectomy is appropriate for patients with T1a N0 M0 DTC, we generally perform total thyroidectomy for most other patients with DTC and for all patients with MTC. A regional neck dissection should be performed if there is clinical, ultrasonographic, or intraoperative evidence of nodal involvement in the lateral neck compartments in patients with DTC, whereas a prophylactic central neck (level VI) dissection is generally performed along with the thyroidectomy in MTC patients and in those patients with DTC when central compartment nodal disease is noted intraoperatively. For patients with invasion of neck structures such as the esophagus, trachea, or strap muscles, more comprehensive resection of all gross disease should be performed whenever feasible while preserving and/or reconstructing structures to maintain functional voice and swallowing if possible.

The basis for selection of patients with DTC for adjuvant radioiodine continues to evolve. According to analyses from the National Thyroid Cancer Treatment Cooperative Study Group [15], improvements in overall survival are associated with adjuvant radioiodine treatment (also known as “remnant ablation”) in the following patient groups:

- PTC in patients younger than 45 years, with tumor greater than 4 cm, or in the presence of macroscopic extrathyroidal extension
- PTC at age 45 years or older, with tumor of at least 1 cm, or in the presence of multifocal tumors, extrathyroidal extension, or metastases to locoregional nodes
- FTC in patients younger than 45 years, with tumor greater than 4 cm, or in the presence of macroscopic multifocality, macroscopic invasion of either the tumor capsule or extrathyroidal tissues, poor differentiation
- FTC at age 45 years or older

Despite the absence of specific analyses demonstrating improved outcomes, radioiodine treatment is also recommended for those patients with more aggressive variants, such as tall cell, columnar cell, insular, or poorly differentiated histologies. In addition, we consider radioiodine therapy for younger PTC patients with tumors

less than 4 cm who demonstrate either microscopic extrathyroidal extension or cervical metastases, although no survival advantage was reported for this subgroup in this analysis. Patients with DTC and known residual or extracervical disease are also treated with higher therapeutic doses of radioiodine. Selection of the administered activity of 131-I is generally based on evaluation of tracer uptake on a diagnostic radioiodine scan performed several weeks after thyroidectomy, combined with the intraoperative and surgical pathology findings. Adjuvant external beam radiotherapy is considered only for those patients at very high risk of recurrent disease that would not be amenable to further organ-sparing surgical intervention.

Postoperative thyroid hormone therapy is necessary for both DTC and MTC patients to treat postsurgical hypothyroidism. In DTC patients, however, higher doses sufficient to suppress TSH levels are generally used initially to reduce the risk of disease recurrence or disease-related mortality. Concern for thyrotoxic complications provides a counterbalancing influence on the aggressiveness of therapy. For stage I and II disease, the serum TSH concentration should be at or slightly below the lower half of the reference range. However, for stage III and IV disease, the target concentration for serum TSH should be less than 0.1 mU/L. The presence of heart disease or low bone density may necessitate a lower level of TSH suppression with smaller doses of thyroid hormone. The dose also may be decreased in patients who remain disease-free for 5–10 years after primary therapy.

The treatment of metastatic DTC usually begins with high-dose radioiodine and is based on documentation of uptake on a pretherapy diagnostic scan. However, disease not visualized on a diagnostic scan is highly unlikely to receive a sufficiently effective radiation dose from therapy. In the setting of radioiodine-refractory disease, TSH-suppressive thyroid hormone therapy is sufficient to maintain asymptomatic stability or a minimal rate of progression in many patients. The development of symptomatic or bulky distant metastases, growing significantly over a 6- to 12-month interval, is an indication for consideration of systemic therapy, preferably within a clinical trial. Similar considerations for initiating systemic therapy are applied to patients with MTC, in whom radioiodine therapy has no beneficial role. Surgery, radiotherapy, cryotherapy, or other palliative localized interventions can be used to reduce symptoms secondary to bone or selected other distant metastases.

Management of ATC is rarely curative. Although surgery can occasionally completely resect small, localized ATC lesions, the high rate of recurrence justifies postoperative external beam radiotherapy. On the other hand, most patients do not benefit from cytoreductive surgery, and therefore the primary treatment is usually chemoradiation. Full course chemotherapy is generally initiated as soon as distant metastases are identified, but the prognosis remains quite bleak.

Further improvements in patient outcomes will require better approaches to the selection of appropriate patients and therapies. Improved prognostication should permit identification of patients who do not require initial treatments as aggressive as those currently used, thus reducing unnecessary risks and morbidity. At the other end of the disease spectrum, the development of more effective systemic therapies that target critical signaling pathways within these malignancies will lead to improved survival and reduced symptoms related to metastatic disease.

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