Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA* 2006; 295(18):2164-2167.	Review/Other-Tx	N/A	To examine trends in thyroid cancer incidence, histology, size distribution, and mortality in the United States.	The incidence of thyroid cancer increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002-a 2.4-fold increase (95% CI, 2.2-2.6; P<.001 for trend). There was no significant change in the incidence of the less common histological types: follicular, medullary, and anaplastic (P>.20 for trend). Virtually the entire increase is attributable to an increase in incidence of PTC, which increased from 2.7 to 7.7 per 100,000-a 2.9-fold increase (95% CI, 2.6-3.2; P<.001 for trend). Between 1988 (the first year SEER collected data on tumor size) and 2002, 49% (95% CI, 47%-51%) of the increase consisted of cancers measuring 1 cm or smaller; 87% (95% CI, 85%-89%) consisted of cancers measuring 2 cm or smaller. Mortality from thyroid cancer was stable between 1973 and 2002 (approximately 0.5 deaths per 100,000).	**4**
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59(4):225-249.	Review/Other-Tx	N/A	Summary of cancer statistics, 2009.	A total of 1,479,350 new cancer cases and 562,340 deaths from cancer are projected to occur in the United States in 2009. Overall cancer incidence rates decreased in the most recent time period in both men (1.8% per year from 2001 to 2005) and women (0.6% per year from 1998 to 2005), largely because of decreases in the three major cancer sites in men (lung, prostate, and colon and rectum [colorectum]) and in two major cancer sites in women (breast and colorectum). Overall cancer death rates decreased in men by 19.2% between 1990 and 2005, with decreases in lung (37%), prostate (24%), and colorectal (17%) cancer rates accounting for nearly 80% of the total decrease. Among women, overall cancer death rates between 1991 and 2005 decreased by 11.4%, with decreases in breast (37%) and colorectal (24%) cancer rates accounting for 60% of the total decrease.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
3. Schneider AB, Sarne DH. Long-term risks for thyroid cancer and other neoplasms after exposure to radiation. *Nat Clin Pract Endocrinol Metab* 2005; 1(2):82-91.	Review/Other-Tx	N/A (pooled analysis, review of unspecified number of previous cases)	Review of how to approach the clinical management of a patient with a history of radiation exposure in the thyroid area, and how to treat radiation-exposed patients who develop related neoplasms, especially thyroid cancer.	The steps to be taken in assessing and treating patients with a history of radiation exposure are as follows: 1) estimate the nature and magnitude of their risks; dose and age of exposure are most important; 2) carry out the appropriate diagnostic evaluation; 3) for high-dose exposure, evaluate thyroid function with thyroid stimulating hormone; 4) consider non-thyroid neoplasms; and 5) thyroid cancers in irradiated patients should be treated in the same way as thyroid cancers not related to radiation. Radiation-related thyroid cancers are often multifocal and as a group have a different spectrum of somatic molecular changes; however, these do not appear to affect their behavior.	4
4. Pal T, Vogl FD, Chappuis PO, et al. Increased risk for nonmedullary thyroid cancer in the first degree relatives of prevalent cases of nonmedullary thyroid cancer: a hospital-based study. *J Clin Endocrinol Metab* 2001; 86(11):5307-5312.	Review/Other-Dx	Pedigrees from 339 unselected patients diagnosed with nonmedullary forms of thyroid cancer and from 319 unaffected ethnically matched controls. Family histories of cancer were obtained from the cases and controls for 3,292 first degree relatives	Hospital-based case-control study at the Princess Margaret Hospital in Toronto, Ontario, Canada, and at 2 university hospitals in Montreal, Quebec, Canada to estimate the familial risk of nonmedullary forms of thyroid cancer.	17 cases (5.0%) and 2 controls (0.6%) reported at least one first degree relative with thyroid cancer. In relatives of patients with thyroid cancer, the incidence of any type of cancer (including nonmedullary forms of thyroid cancer) was 38% higher than in relatives of controls (incidence rate ratio, 1.4; 95% CI, 1.1-1.7). The relative risk for thyroid cancer was 10-fold higher in relatives of cancer patients than in controls (incidence rate ratio, 10.3; 95% CI, 2.2-47.6).	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
5. Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med* 2012; 366(18):1663-1673.	Experimental-Tx	752 patients	The comparison of two thyrotropin-stimulation methods (thyroid hormone withdrawal and use of recombinant human thyrotropin) and two radioiodine ((131)I) doses (i.e., administered activities) (1.1 GBq and 3.7 GBq) in a 2-by-2 design for patients with low-risk thyroid cancer after a complete surgical resection.	92% of patients had papillary cancer. There were no unexpected serious adverse events. In the 684 patients with data that could be evaluated, ultrasonography of the neck was normal in 652 (95%), and the stimulated thyroglobulin level was 1.0 ng per milliliter or less in 621 of the 652 patients (95%) without detectable thyroglobulin antibodies. Thyroid ablation was complete in 631 of the 684 patients (92%). The ablation rate was equivalent between the (131)I doses and between the thyrotropin-stimulation methods.	1
6. NCCN Clinical Practice Guidelines in Oncology. Thyroid Carcinoma. Version 3.2012. 2012.	Review/Other-Tx	N/A	NCCN Clinical Practice Guidelines in Oncology - thyroid carcinoma.	N/A	4
7. Machens A, Holzhausen HJ, Dralle H. Skip metastases in thyroid cancer leaping the central lymph node compartment. *Arch Surg* 2004; 139(1):43-45.	Review/Other-Tx	215 patients	To examine the hypothesis that discontinuous nodal metastasis, or skip metastasis, in thyroid cancer may display clinicopathologic features different from those seen in continuous nodal metastasis and thus may have a different prognosis (retrospective analysis).	Skip metastases (negative central and positive lateral or mediastinal compartments) were found in 13 (19.7%) of 66 papillary, 0 of 8 follicular, and 30 (21.3%) of 141 MTCs. After adjustment for multiple testing, skip metastasis was only associated with significantly fewer positive lymph nodes: 3.7 vs 12.9 nodes ($r = -0.43$, $P<.001$) in PTC and 6.0 vs 17.1 nodes ($r = -0.40$, $P<.001$) in MTC. No other significant correlation was identified with any other clinicopathologic variable.	4
8. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Res* 2003; 63(7):1454-1457.	Review/Other-Tx	N/A	To show (using signaling proteins) somatic mutation of BRAF, V599E, is the most common genetic change in PTCs (28/78; 35.8%).	BRAF (V599E) mutations were unique to PTCs, and not found in any of the other types of differentiated follicular neoplasms arising from the same cell type (0/46). Moreover, there was no overlap between PTC with RET/PTC, BRAF, or RAS mutations, which altogether were present in 66% of cases. The lack of concordance for these mutations was highly unlikely to be a chance occurrence.	4

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9. Elisei R, Cosci B, Romei C, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. *J Clin Endocrinol Metab* 2008; 93(3):682-687.	Observational-Tx	100 sporadic MTC patients	The aim of this study was to verify the prognostic value of somatic RET mutations in a large series of MTCs with a long follow-up. The correlation between the presence/absence of a somatic RET mutation, clinical/pathological features, and outcome of MTC patients was evaluated.	A somatic RET mutation was found in 43/100 (43%) sporadic MTCs. The most frequent mutation (34/43, 79%) was M918T. RET mutation occurrence was more frequent in larger tumors (P=0.03), and in MTC with node and distant metastases (P<0.0001 and P=0.02, respectively), thus, a significant correlation was found with a more advanced stage at diagnosis (P=0.004). A worse outcome was also significantly correlated with the presence of a somatic RET mutation (P=0.002). Among all prognostic factors found to be correlated with a worse outcome, at multivariate analysis only the advanced stage at diagnosis and the presence of a RET mutation showed an independent correlation (P<0.0001 and P=0.01, respectively). Finally, the survival curves of MTC patients showed a significantly lower percentage of surviving patients in the group with RET mutations (P=0.006).	2
10. Ito T, Seyama T, Mizuno T, et al. Unique association of p53 mutations with undifferentiated but not with differentiated carcinomas of the thyroid gland. *Cancer Res* 1992; 52(5):1369-1371.	Review/Other-Tx	"10 cases of differentiated papillary adenocarcinoma, 6 cases of undifferentiated carcinoma, and one cell line 8305C (JCRB 0824)"	Mutations in the p53 gene were investigated by direct sequencing analysis after polymerase chain reaction amplification of exons 5 to 8, using paraffin-embedded primary tumors and cultured cells.	No mutations in exons 5 to 8 were detected in 10 differentiated papillary adenocarcinomas, whereas 6 of 7 undifferentiated carcinomas were found to carry base substitution mutations. The results strongly suggest that, in human thyroid glands, p53 mutations play a crucial role in the progression of differentiated carcinomas to undifferentiated ones.	4
11. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg* 2007; 246(3):375-381; discussion 381-374.	Observational-Tx	52,173: 43,227 total thyroidectomies, 8,946 lobectomies	To examine whether the extent of surgery affects outcomes for PTC and to determine whether a size threshold could be identified above which total thyroidectomy is associated with improved outcomes.	For PTC <1 cm extent of surgery did not impact recurrence or survival (P=0.24, P=0.83). For tumors ≥1 cm, lobectomy resulted in higher risk of recurrence and death (P=0.04, P=0.009). To minimize the influence of larger tumors, 1 to 2 cm lesions were examined separately: lobectomy again resulted in a higher risk of recurrence and death (P=0.04, P=0.04).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
12. Hay ID, Grant CS, Bergstralh EJ, Thompson GB, van Heerden JA, Goellner JR. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? *Surgery* 1998; 124(6):958-964; discussion 964-956.	Observational-Tx	1,685 patients, followed for up to 54 post-op years	To compare cause-specific mortality and recurrence rates after either unilateral lobectomy or bilateral lobar resection in patients with PTC considered low risk by AMES criteria.	30-year rates for cause-specific mortality and distant metastasis were 2% and 3%, respectively. 20-year rates for local recurrence and nodal metastasis were 4% and 8%, respectively. There were no significant differences in cause-specific mortality or distant metastasis rates between unilateral lobectomy and bilateral lobar resection (P>.2). After unilateral lobectomy, 20-year rates for local recurrence and nodal metastasis were 14% and 19%, significantly higher (P=.0001) than the 2% and 6% rates seen after bilateral lobar resection.	2
13. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994; 97(5):418-428.	Observational-Tx	1355 patients	To determine the long-term impact of medical and surgical treatment of well differentiated papillary and FTC.	Median follow-up was 15.7 years; 42% (568) of the patients were followed for 20 years and 14% (185) for 30 years. After 30 years, the survival rate was 76%, the recurrence rate was 30%, and the cancer death rate was 8%. Recurrences were most frequent at the extremes of age (<20 and >59 years).	2
14. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1990; 71(2):414-424.	Review/Other-Tx	269 patients	Analysis of the course of PTC managed at the University of Chicago, with an average follow-up period of 12 years from the time of diagnosis.	In 15% of patients given thyroid hormone, the mass decreased in size. The peak incidence of cancer was when subjects were between 20-40 years of age. Tumors averaged 2.4 cm in size; 21.6% had tumor capsule invasion, and 46% of patients had multifocal tumors. 66% of the patients had near-total or total thyroidectomy. The overall incidence of postoperative hypoparathyroidism was 8.4%, but the incidence was zero in 83 near-total or total thyroidectomies carried out by 1 surgeon. 25% of the patients had continuing or recurrent disease, and 8.2% died from cancer. Deaths occurred largely in patients with class III or IV disease.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
15. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer* 1985; 56(3):531-538.	Review/Other-Tx	101 thyroids: subserially sectioned at 2-3 mm intervals	Systematic autopsy study of occult papillary carcinoma.	From 36 thyroids, 52 foci of occult papillary carcinoma were found, giving a prevalence rate of 35.6%, the highest reported rate in the world. The rate was higher, although not significantly, in males (43.3%) than in females (27.1%), but it did not correlate to the age of the patients. 26 glands contained one tumor focus and 10 glands contained two to five tumor foci. Only a minority of the smallest tumors can be detected with the method used.	4
16. Avram AM, Fig LM, Frey KA, Gross MD, Wong KK. Preablation 131-I Scans With SPECT/CT in Postoperative Thyroid Cancer Patients: What Is the Impact on Staging? *J Clin Endocrinol Metab* 2013; 98(3):1163-1171.	Review/Other-Dx	320 patients	To determine the contribution of preablation Iodine 131 planar with single-photon emission computed tomography/computed tomography to differentiate thyroid cancer staging.	In younger patients, diagnostic scans detected distant metastases in 5/138 patients (4%), and nodal metastases in 61/138 patients (44%), including unsuspected nodal metastases in 24/63 (38%) patients initially assigned pathologic N0 or pathologic Nx. In older patients distant metastases were detected in 18/182 patients (10%), and nodal metastases in 51/182 patients (28%), including unsuspected nodal metastases in 26/108 (24%) patients initially assigned pathologic N0 or pathologic Nx. Diagnostic scans detected distant metastases in 2/49 (4%) T1a, and 3/67 (4.5%) T1b patients.	4
17. Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery* 1987; 102(6):1088-1095.	Observational-Tx	860 patients	A novel prognostic scoring system was used to compare ipsilateral lobectomy with bilateral lobar resection in PTC.	Cancer mortality at 25 years in patients with an AGES score of 3.99 or less was 1% after ipsilateral lobectomy (n=131) and 2% after bilateral resection (n=603), whether subtotal or total (P=0.15). Of patients with an AGES score of 4 or more, those who underwent lobectomy alone (n=30) had a mortality rate from PTC at 25 years of 65%, while those undergoing bilateral resection (n=86) had a lower rate of 35% (P=0.06).	2
18. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. *Surgery* 1988; 104(6):947-953.	Review/Other-Tx	N/A	To examine a multifactorial system for the identification of low-risk patients who made up 89.4% of all patient seen between 1961 and 1980 and who have a death rate of only 1.8%.	The resultant high-risk group constitutes 11% of cases but carries a 46% mortality rate. The risk-group definition is completely clinical and is based on age, presence of distant metastases, and the size and extent of primary cancer. A mortality rate ratio of 26:1 now exists between high- and low-risk groups, respectively.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
19. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery* 1993; 114(6):1050-1057; discussion 1057-1058.	Review/Other-Tx	1,779 patients surgically treated at one institution during 1940 through 1989	An attempt to define a reliable prognostic scoring system for predicting PTC mortality rates with 15 candidate variables that included completeness of primary tumor resection but excluded histologic grade and DNA ploidy.	The final model included five variables abbreviated by metastasis, age, completeness of resection, invasion, and size (MACIS). The final prognostic score was defined as MACIS = 3.1 (if aged ≤39 years) or 0.08 x age (if aged ≥40 years), + 0.3 x tumor size (in centimeters), +1 (if incompletely resected), +1 (if locally invasive), +3 (if distant metastases present). 20-year cause-specific survival rates for patients with MACIS <6, 6 to 6.99, 7 to 7.99, and 8+ were 99%, 89%, 56%, and 24%, respectively (P<0.0001).	4
20. Pasieka JL, Zedenius J, Auer G, et al. Addition of nuclear DNA content to the AMES risk-group classification for papillary thyroid cancer. *Surgery* 1992; 112(6):1154-1159; discussion 1159-1160.	Observational-Tx	73 patients with primary or recurrent PTC: 48 DAMES low risk, 22 DAMES intermediate, 3 DAMES high risk	To prospectively assess whether nuclear DNA content added prognostic value to existing risk factors in patients with PTC.	Recurrences and/or distant metastases developed in only 4 (8%) of the DAMES low risk group. 12 (55%) of the intermediate-risk group had residual, recurrent, or distant metastatic disease, with one death from cancer at 120 months. Distant metastases developed in all three DAMES high risk patients, who died within 24 months from thyroid cancer. A statistically significant difference existed in the development of recurrence/metastases or death from cancer in the DAMES high-risk group compared with the other risk groups combined.	1
21. Alevizaki C, Molfetas M, Samartzis A, et al. Iodine 131 treatment for differentiated thyroid carcinoma in patients with end stage renal failure: dosimetric, radiation safety, and practical considerations. *Hormones (Athens)* 2006; 5(4):276-287.	Review/Other-Tx	5 patients	To present the authors' experience on (131)I treatment of 5 DTC patients with end stage renal disease.	None of the patients experienced any short-term side effects, while they all had undetectable thyroglobulin levels on the first post therapy evaluation off thyroxine. (131)I elimination in the first haemodialysis was about 60%. Staff incidental exposure and (131)I contamination were insignificant.	4
22. Grigsby PW, Siegel BA, Baker S, Eichling JO. Radiation exposure from outpatient radioactive iodine (131I) therapy for thyroid carcinoma. *JAMA* 2000; 283(17):2272-2274.	Review/Other-Tx	30 patients who received 131I therapy with their 65 household members and 17 household pets	To measure the radiation exposure to household members from patients receiving outpatient 131I therapy for thyroid carcinoma in accordance with the new regulations.	The patients received 131I doses ranging from 2.8 to 5.6 GBq (mean, 4.3 GBq). The radiation dose to 65 household members ranged from 0.01 mSv to 1.09 mSv (mean, 0.24 mSv). The dose to 17 household pets ranged from 0.02 mSv to 1.11 mSv (mean, 0.37 mSv). The mean dose to the 4 rooms ranged from 0.17 mSv (kitchen) to 0.58 mSv (bedroom).	4

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23. Wong JB, Kaplan MM, Meyer KB, Pauker SG. Ablative radioactive iodine therapy for apparently localized thyroid carcinoma. A decision analytic perspective. *Endocrinol Metab Clin North Am* 1990; 19(3):741-760.	Review/Other-Tx	N/A	Construction of a decision analytic model to examine whether patients with apparently localized thyroid carcinoma should receive radioiodine.	They study suggests that radioiodine modestly improves life expectancy by 2 to 15 months, depending on the patient's age and sex. This model predicts that the benefit of a reduction in the likelihood of recurrence outweighs the risk of leukemia from radioiodine.	4
24. Sawka AM, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein HC. Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *J Clin Endocrinol Metab* 2004; 89(8):3668-3676.	Review/Other-Tx	1,543 english references	A systematic review and meta-analysis of the effectiveness of RAI remnant ablation for well-DTC.	In 13 cohort studies in which the analysis of thyroid cancer-related outcomes was statistically adjusted to a variable degree for prognostic factors or cointerventions, rates of recurrences of thyroid cancer-related outcomes were significantly decreased in the following: one of seven studies examining thyroid cancer-related mortality, three of six studies examining any tumor recurrence, three of three studies examining locoregional recurrence, and two of three studies examining distant metastases. However, pooled analyses were suggestive of a statistically significant treatment effect of ablation for the following 10-year outcomes: locoregional recurrence (relative risk of 0.31, 95% CI, 0.2, 0.49) and distant metastases (absolute decrease in risk 3%, 95% CI, risk decreases 1-4%).	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
25. Hay ID, Thompson GB, Grant CS, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. *World J Surg* 2002; 26(8):879-885.	Review/Other-Tx	2444 patients	Analysis of PTC managed at the Mayo Clinic during six decades (1940-1999): temporal trends in initial therapy and long-term outcome in patients.	The 25-year rates for cause-specific mortality and TR were 5% and 14%, respectively. Temporal trends were analyzed for six decades. During the six decades, the proportion with initial MACIS (distant Metastasis, patient Age, Completeness of resection, local Invasion, and tumor Size) scores <6 were 77%, 82%, 84%, 86%, 85%, and 82%, respectively (P=0.06). Lobectomy accounted for 70% of initial procedures during 1940-1949 and 22% during 1950-1959; during 1960-1999 bilateral lobar resection accounted for 91% of surgeries (p <0.001). RRA after bilateral lobar resection was performed during 1950-1969 in 3% but increased to 18%, 57%, and 46% in successive decades (p <0.001). The 40-year rates for cause-specific mortality and TR during 1940-1949 were significantly higher (P=0.002) than during 1950-1999.	4
26. Sawka AM, Brierley JD, Tsang RW, et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. *Endocrinol Metab Clin North Am* 2008; 37(2):457-480, x.	Review/Other-Tx	N/A	Updated systematic review and commentary examining the effectiveness of RAI remnant ablation in well-DTC.	The incremental benefit of RRA in low risk patients with well-DTC after total or near-total thyroidectomy who are receiving thyroid hormone suppressive therapy remains unclear.	4
27. Sacks W, Fung CH, Chang JT, Waxman A, Braunstein GD. The effectiveness of radioactive iodine for treatment of low-risk thyroid cancer: a systematic analysis of the peer-reviewed literature from 1966 to April 2008. *Thyroid* 2010; 20(11):1235-1245.	Review/Other-Tx	N/A	A systematic analysis of the peer-reviewed literature from 1966 to April 2008 on the effectiveness of RAI for treatment of low-risk thyroid cancer.	The majority of studies did not find a statistically significant improvement in mortality or disease-specific survival in those low-risk patients treated with RAI, whereas improved survival was confirmed for high-risk (AJCC stages III and IV) patients. Evidence for RAI decreasing recurrence was mixed with half of the studies showing a significant relationship and half showing no relationship.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
28. Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid* 2006; 16(12):1229-1242.	Observational-Tx	2936 patients	To determine the effect of initial therapy on the outcomes of thyroid cancer patients.	Near-total thyroidectomy, RAI, and aggressive thyroid hormone suppression therapy were each independently associated with longer OS in high-risk patients. Near-total thyroidectomy followed by RAI therapy, and moderate thyroid hormone suppression therapy, both predicted improved OS in stage II patients. No treatment modality, including lack of RAI, was associated with altered survival in stage I patients.	1
29. Maxon HR, 3rd, Englaro EE, Thomas SR, et al. Radioiodine-131 therapy for well-differentiated thyroid cancer--a quantitative radiation dosimetric approach: outcome and validation in 85 patients. *J Nucl Med* 1992; 33(6):1132-1136.	Review/Other-Tx	85 patients	To determine the subsequent validation of radiation dose thresholds for 131I treatment of thyroid CA.	The successful ablation of thyroid remnants occurred after a single initial 131I administration in 84% of inpatients and in 79% of outpatients when treatment was standardized to a radiation dose of at least 30,000 cGy (rad). Administered activities low enough to permit outpatient therapy could be used in 47% of the patients. Lymph node metastases were treated successfully in 74% of patients with a single administration of 131I calculated to deliver at least 8,500 cGy (rad). For athyrotic patients with nodal metastases only, success was achieved in 86% of patients at tumor doses of at least 14,000 cGy (rad). These success rates are equal to or better than those reported with empiric methods of 131I administration.	4
30. Mallick U, Harmer C, Yap B, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med* 2012; 366(18):1674-1685.	Experimental-Tx	421 patients	To identify whether low-dose radioiodine (1.1 GBq [30 mCi]) is as effective as high-dose radioiodine (3.7 GBq [100 mCi]) for treating patients with DTC or whether the effects of radioiodine (especially at a low dose) are influenced by using either recombinant human thyrotropin (thyrotropin alfa) or thyroid hormone withdrawal.	Ablation success rates were 85.0% in the group receiving low-dose radioiodine vs 88.9% in the group receiving the high dose and 87.1% in the thyrotropin alfa group vs 86.7% in the group undergoing thyroid hormone withdrawal. All 95% CIs for the differences were within +/-10 percentage points, indicating noninferiority. The proportions of patients with adverse events were 21% in the low-dose group vs 33% in the high-dose group (P=0.007) and 23% in the thyrotropin alfa group vs 30% in the group undergoing thyroid hormone withdrawal (P=0.11).	1

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31. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009; 19(11):1167-1214.	Review/Other-Tx	N/A	Revised American Thyroid Association management guidelines for patients with thyroid nodules and DTC.	The revised guidelines for the management of thyroid nodules include recommendations regarding initial evaluation, clinical and ultrasound criteria for fine-needle aspiration biopsy, interpretation of fine-needle aspiration biopsy results, and management of benign thyroid nodules.	4
32. Hackshaw A, Harmer C, Mallick U, Haq M, Franklyn JA. 131I activity for remnant ablation in patients with differentiated thyroid cancer: A systematic review. *J Clin Endocrinol Metab* 2007; 92(1):28-38.	Review/Other-Tx	patient case notes (n = 41), prospective cohorts (n = 12), and randomized trials (n = 6)	A systematic review of the published literature was used to compare the success rates of remnant ablation using approximately 30 mCi with approximately 100 mCi (1.1 vs 3.7 GBq).	Observational studies confirmed the high ablation success rate (approximately 80%) using approximately 100 mCi, although 22% of studies reported a rate of 90% or greater. The pooled ablation success rate in these studies was 10% lower using 30 mCi compared with 100 mCi (95% CI, 3-17%; P=0.01).	4
33. Tuttle RM, Leboeuf R, Martorella AJ. Papillary thyroid cancer: monitoring and therapy. *Endocrinol Metab Clin North Am* 2007; 36(3):753-778, vii.	Review/Other-Tx	N/A	To compare and contrast the recommendations from the various guidelines in an attempt to define areas of consensus and explore possible reasons for differing recommendations for the management of thyroid cancer.	Staging systems that incorporate not only the usual tumor and patient risk factors available during initial therapy, but more importantly include variables that assess response to therapy, PFS, trend in serum Tg over time, and the negative predictive value of the various tests used in the follow-up of differentiated patients who have thyroid cancer, will greatly enhance our ability to tailor specific treatment and follow-up recommendations for individual patients.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Molinaro E, Leboeuf R, Shue B, et al. Mild decreases in white blood cell and platelet counts are present one year after radioactive iodine remnant ablation. *Thyroid* 2009; 19(10):1035-1041.	Observational-Tx	206 patients	To examine the rate of persistent anemia, leukopenia, and thrombocytopenia 1 year after a single RAI administration.	Comparison of the baseline complete blood count before RAI ablation (median administered activity of approximately 3700 MBq or 100 mCi) with the follow-up complete blood count done 1 year later demonstrated a statistically significant decline in total white blood cell (6.7 +/- 2.1 x 10(9) vs 6.0 +/- 1.8 x 10(9)/L, P<0.001; 9.7% below the reference range at 1-year follow-up) and platelet (272 +/- 67 vs 250 +/- 65 x 10(9)/L, P<0.001; 5.8% below the reference range at 1-year follow-up) with no significant change in hemoglobin (1.40 +/- 0.14 vs 1.40 +/- 0.14 g/L or 14.0 +/- 1.4 vs 14.0 +/- 1.4 g/dL; 1.5% below the reference range at 1-year follow-up). There were no significant clinical complications observed during the 1-year follow-up period. The changes in total white blood cell and platelets were not related to the method of preparation or the administered activity of RAI.	2
35. Sarkar SD, Beierwaltes WH, Gill SP, Cowley BJ. Subsequent fertility and birth histories of children and adolescents treated with 131I for thyroid cancer. *J Nucl Med* 1976; 17(6):460-464.	Review/Other-Tx	33 patients	Follow-up study was performed on 40 patients aged 20 years or less who had been treated with 131I after surgery for papillary-FTC.	The mean age at the time of the first 131I therapeutic dose was 14.6 years (range 6-20), and the average follow-up interval, from that first dose until follow-up, was 18.7 years (range 14-25). The mean total dose of 131I was 196 mCi (range 80-691). The incidences of infertility (12%), miscarriage (1.4%), prematurity (8%), and major congenital anomaly (1.4%) found in this series are not significantly different from those in the general population.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Fard-Esfahani A, Hadifar M, Fallahi B, et al. Radioiodine treatment complications to the mother and child in patients with differentiated thyroid carcinoma. *Hell J Nucl Med* 2009; 12(1):37-40.	Review/Other-Tx	100 patients, in their reproductive period, with at least one pregnancy after (131)I treatment	To study the outcome of pregnancy in females with DTC, treated with radioiodine (131)I and evaluate the genetic risks and health status of their offspring. A retrospective study of the medical records of these patients from 1999 to 2004.	The incidence of abortions before (131)I treatment was 16.83% (all were spontaneous abortions) and increased to 26.19% after (131)I treatment (15.87% induced and 10.3% spontaneous abortions). Spontaneous abortions were decreased. There was no significant difference between the mean last (131)I dose and the cumulative dose in patients with or without a history of abortions. Mean interval between the last dose of (131)I treatment and abortions vs the last dose and live child births showed a significant difference. All children had normal birth weight. Three congenital anomalies: Down's syndrome, cardiac abnormalities and macrocephaly were diagnosed. Three episodes of intrauterine death were also recorded.	4
37. Almeida JP, Kowalski LP. Pilocarpine used to treat xerostomia in patients submitted to radioactive iodine therapy: a pilot study. *Braz J Otorhinolaryngol* 2010; 76(5):659-662.	Review/Other-Tx	5 patients	To report on the experience with pilocarpine on the treatment of xerostomia in thyroid cancer patients submitted to adjuvant RAI therapy.	Sudoresis was the most frequent side effect of pilocarpine use, followed by fatigue and headache. Two patients reported relief of xerostomia using pilocarpine, but only one patient was able to tolerate the side effects. Pilocarpine seems to relieve xerostomia complaints in thyroid cancer patients because it is able to stimulate salivary flow, but the observed side effects made the patients refuse long-term therapy continuation.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Bohuslavizki KH, Klutmann S, Jenicke L, et al. Salivary gland protection by S-2-(3-aminopropylamino)-ethylphosphorothioic acid (amifostine) in high-dose radioiodine treatment: results obtained in a rabbit animal model and in a double-blind multi-arm trial. *Cancer Biother Radiopharm* 1999; 14(5):337-347.	Experimental-Tx	Rabbits: 15 total; Patients: 50 total	Radioprotective effects of amifostine were studied. Rabbits: 15 were studied prior to and up to 6 months after high-dose-RAI therapy applying 2 GBq 131I,10 animals received 200 mg/kg amifostine prior to HD-RIT and five served as controls. Patients: 50 total, 25 treated with 500 mg/m2 amifostine intravenously prior to high-dose-RAI therapy, and 25 patients receiving physiological saline solution served as controls.	Complete ablation of the thyroid was achieved in all rabbits 4 weeks after high-dose-RAI therapy. In control rabbits 6 months after high-dose-RAI therapy parenchymal function was reduced significantly (P<0.0001) by 75.3 +/- 5.3% and 53.6 +/- 17.4% in parotid and submandibular glands, respectively. In contrast, in amifostine-treated rabbits parenchymal function was not significantly reduced. Histopathologically, marked lipomatosis was observed in control animals but was negligible in amifostine-treated animals. In control patients, salivary gland function was significantly (P<0.001) reduced by 40.2 +/- 14.1% and 39.9 +/- 15.3% in parotid and submandibular glands, respectively, three months after high-dose-RAI therapy, and 11 patients developed xerostomia. In 25 amifostine-treated patients, salivary gland function was not significantly reduced (P=0.691), and xerostomia did not occur.	1
39. Iyer NG, Morris LG, Tuttle RM, Shaha AR, Ganly I. Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. *Cancer* 2011; 117(19):4439-4446.	Review/Other-Tx	14,589 patients received RAI	To evaluate patterns of RAI use and elevated risk of secondary primary malignancies in patients with low-risk (T1N0) well-DTC.	During the study period, the rate of RAI use in patients with low-risk (T1N0) well-DTC increased from 3.3% to 38.1%. For low-risk patients, the standardized incidence ratio of secondary primary malignancies was 1.21 (95% CI, 0.93-1.54), and the excess absolute risk was 4.6 excess cases per 10,000 person-years at risk. Secondary primary malignancies with significantly elevated risk because of RAI were salivary gland malignancies (standardized incidence ratio = 11.13; 95% CI, 1.35-40.2) and leukemia (standardized incidence ratio = 5.68; 95% CI, 2.09-12.37). The excess risk of leukemia was significantly greater in patients aged <45 years (standardized incidence ratio = 5.32; 95% CI, 2.75-9.30) compared with the excess risk in older patients (standardized incidence ratio = 2.26; 95% CI, 1.43-3.39).	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Park HS, Roman SA, Sosa JA. Treatment patterns of aging Americans with differentiated thyroid cancer. *Cancer* 2010; 116(1):20-30.	Observational-Tx	8,899: Adults aged ≥45 years with DTC ≥1 cm in the SEER database from 1988 to 2003	To evaluate treatment patterns of aging Americans with DTC.	Compared with younger patients, patients aged ≥65 years were more likely to have larger tumors, stage IV disease, extrathyroid extension, and nonpapillary histology. Elderly patients were less likely to undergo total thyroidectomy (74% vs 80%; P<.001) or to receive RAI (47% vs 54%; P<.001). These trends were most pronounced among those aged ≥80 years. Among the patients who did not undergo surgery, elderly patients did not report higher rates of contraindications to surgery.	2
41. Brierley JD, Tsang RW. External beam radiation therapy for thyroid cancer. *Endocrinol Metab Clin North Am* 2008; 37(2):497-509, xi.	Review/Other-Tx	N/A	To discuss the role of EBRT in the management of well-DTC, MTC, and ATC.	Evidence demonstrates that EBRT can control gross residual well-DTC. Also, in selected patients who have high risk features, EBRT improves local control after surgery and RAI. There is a more limited role for EBRT in MTC, but it remains the most effective single agent in the management of patients who have ATC.	4
42. Biermann M, Pixberg M, Riemann B, et al. Clinical outcomes of adjuvant external-beam radiotherapy for differentiated thyroid cancer - results after 874 patient-years of follow-up in the MSDS-trial. *Nuklearmedizin* 2009; 48(3):89-98; quiz N15.	Observational-Tx	351 patients	To evaluate the clinical benefit of EBRT for locally invasive thyroid carcinoma with DTC.	Mean follow-up was 930 days. In an actual treatment analysis, 96% (25/26) of the EBRT -patients reached complete remission vs 86% in the non-EBRT patients. Recurrences occurred in 0 vs 3% of patients: 6 reoperated for regional lymph node metastases, 1 tracheal invasion treated with tracheoplasty, 1 local invasion necessitating laryngectomy, 2 distant metastases (1 lung, 1 lung + bone). Serious chronic EBRT toxicity occurred in 1/26 patients.	1
43. Farahati J, Reiners C, Stuschke M, et al. Differentiated thyroid cancer. Impact of adjuvant external radiotherapy in patients with perithyroidal tumor infiltration (stage pT4). *Cancer* 1996; 77(1):172-180.	Observational-Tx	238 patients with differentiated PTC and FTC with stage pT4	To assess the impact of adjuvant EBRT with respect to the papillary and follicular types of thyroid cancer as separate entities.	In patients with DTC, EBRT was a predictive factor for improvement of both locoregional recurrence (P=0.004) and locoregional and distant failure (P=0.0003). When the time to first locoregional and distant failure was calculated separately for patients with PTC and FTC, there was a significant difference in the PTC group in favor of irradiated patients (P=0.0001), whereas there was no effect of EBRT in the FTC group (P=0.38).	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Chow SM, Law SC, Mendenhall WM, et al. Papillary thyroid carcinoma: prognostic factors and the role of radioiodine and external radiotherapy. *Int J Radiat Oncol Biol Phys* 2002; 52(3):784-795.	Observational-Tx	842 patients	To evaluate the role of radioiodine and EBRT treatment in PTC.	The 10-year cause-specific survival rates were as follows: Stage I, 99.8%; Stage II, 91.8%; Stage III, 77.4%; and Stage IV, 37.1%.	2
45. Samaan NA, Schultz PN, Hickey RC, et al. The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. *J Clin Endocrinol Metab* 1992; 75(3):714-720.	Observational-Tx	1,599 patients	Retrospective review to analyze the impact of prognostic variables of age, sex, histopathological diagnosis, extent of disease at diagnosis, and surgical intervention on well DTC and how surgical treatment, RAI, and RT influence the patients' outcomes.	The overall recurrence rate was 23%, and the death rate was 11%. This study showed that treatment with RAI was the single most powerful prognostic indicator for increased disease-free interval ($P<0.001$) and that its use significantly increased survival as well. No benefit was obtained from treatment with EBRT. Children had the best OS, but of the adult patients, females who had intrathyroidal papillary disease treated with total thyroidectomy, who had been given RAI, and whose disease had been diagnosed between 20-59 years of age had the best prognosis.	2
46. Lin JD, Tsang NM, Huang MJ, Weng HF. Results of external beam radiotherapy in patients with well differentiated thyroid carcinoma. *Jpn J Clin Oncol* 1997; 27(4):244-247.	Observational-Tx	699 patients	Retrospective review of the records of patients with papillary or FTC, of whom 72 received EBRT after surgery.	There were no significant differences in clinical parameters including surgical methods employed, histopathological types of cancer, follow-up stages, postoperative thyroglobulin levels, tumor size, accumulated 131I doses and survival rates between the two groups. To clarify the effect of EBRT in patients with local invasion, we compared the survival rates of the patients with clinical stage 3 in the two groups and again no significant difference was found. During the follow-up period, 21 (28.4%) of the 72 patients who received EBRT died of thyroid carcinoma. In our limited period of study, EBRT did not improve the survival rate of patients with well DTC, though it appeared to cause temporary tumor regression.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. Rosa Pelizzo M, Toniato A, Boschin IM, et al. Locally advanced differentiated thyroid carcinoma: a 35-year mono-institutional experience in 280 patients. *Nucl Med Commun* 2005; 26(11):965-968.	Review/Other-Tx	280 patients	To better define the most appropriate diagnostic and therapeutic protocol for locally advanced DTC.	With regard to OS, at univariate statistical analysis, the patient's age at diagnosis (threshold, 45 years), primary tumour size, local cancer extension at diagnosis (subtypes of T4), extent of thyroidectomy, performance of lymph node dissection and performance of post-surgical EBRT were found to be significant prognostic variables. With regard to the appearance of recurrent disease during follow-up, at univariate statistical analysis, the patient's age at initial diagnosis (threshold, 45 years), primary tumour size, local cancer extension at diagnosis (subtypes of T4), extent of thyroidectomy, performance of lymph node dissection, presence of metastatic lymph nodes, performance of post-surgical 131I therapy and performance of post-surgical EBRT were found to be significant prognostic variables.	4
48. Staunton MD. Thyroid cancer: a multivariate analysis on influence of treatment on long-term survival. *Eur J Surg Oncol* 1994; 20(6):613-621.	Observational-Tx	410 patients	Retrospective multivariate analysis studying the contemporary management of patients with follicular pattern thyroid cancer treated in a cancer hospital in the years 1932-72 and providing a follow-up of 20 years.	In papillary carcinoma thyroxine administration (P<0.005) and surgery (P<0.001) improved survival together with youth (P<0.001) and being female (P<0.05). In follicular carcinoma, thyroxine therapy (P<0.001) increased survival as did surgery but it failed to reach significance (P=0.19); increasing age (P<0.001), stage M1 (P<0.05) and 'complete' RT (P<0.05) decreased survival. In ATC survival was improved by thyroxine therapy (P<0.001), a new finding, but decreased by stages T3 (P<0.001) and M1 (P<0.05); however, RT, the mainstay in control of local disease, did not increase survival.	2
49. Lenio PT. External irradiation in treatment of papillary carcinoma of the thyroid. *Am J Surg* 1976; 131(3):281-283.	Review/Other-Tx	30 patients	Retrospective review of patients with papillary carcinoma of the thyroid with metastatic or direct extension of their disease was undertaken.	The primary treatment of papillary carcinoma of the thyroid remains surgical but with a consideration that irradiation may be of benefit in certain instances.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
50. Simpson WJ, Carruthers JS. The role of external radiation in the management of papillary and follicular thyroid cancer. *Am J Surg* 1978; 136(4):457-460.	Review/Other-Tx	137 patients with DTC (82 papillary and 55 follicular)	To demonstrate that external radiation in moderate dosage eradicates microscopic disease in DTC.	External radiation use could lead to a decrease in surgical complications by avoiding unnecessarily radical attempts at removing all potential microscopic disease. Gross tumor also responds favorably to external radiation, but its very slow regression rate has led to the misconception that external radiation is ineffective in the treatment of these cancers.	4
51. Kim TH, Chung KW, Lee YJ, et al. The effect of external beam radiotherapy volume on locoregional control in patients with locoregionally advanced or recurrent nonanaplastic thyroid cancer. *Radiat Oncol* 2010; 5:69.	Observational-Tx	23 patients	To evaluate outcomes of patients treated with EBRT for locoregionally advanced or recurrent nonanaplastic thyroid cancer and analyze the effect of EBRT volume on locoregional control.	There were no significant differences in the clinical parameter distributions between the limited field and elective field groups. In the limited field group, 6 (55%) patients developed locoregional recurrence and 3 (27%) developed distant metastasis. In the elective field group, one (8%) patient developed locoregional recurrence and one (8%) developed a distant metastasis. There was a significant difference in locoregional control rate at 5 years in the limited field and elective field groups (40% vs 89%, P=0.041). There were no significant differences in incidences of acute and late toxicities between two groups (P>0.05).	2
52. Rosenbluth BD, Serrano V, Happersett L, et al. Intensity-modulated radiation therapy for the treatment of nonanaplastic thyroid cancer. *Int J Radiat Oncol Biol Phys* 2005; 63(5):1419-1426.	Review/Other-Tx	20 patients	To review outcomes/toxicity in a series of thyroid cancer patients treated with IMRT.	With two local failures, 2-year local progression-free rate was 85%. There were 6 deaths, with a 2-year OS rate of 60%. For patients with M0 disease, the 2-year distant metastases-free rate was 46%. The worst acute mucositis and pharyngitis was Grade 3 (n=7 and 3, respectively). Two patients had Grade 3 acute skin toxicity and 2 had Grade 3 acute laryngeal toxicity. No significant radiation-related late effects were reported.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Urbano TG, Clark CH, Hansen VN, et al. Intensity Modulated Radiotherapy (IMRT) in locally advanced thyroid cancer: acute toxicity results of a phase I study. *Radiother Oncol* 2007; 85(1):58-63.	Review/Other-Tx	13 patients	To determine the toxicity of accelerated fractionation IMRT in locally advanced thyroid cancer.	G3 and G2 radiation dermatitis rates were 38.5% and 31%; G3 and G2 mucositis rates 8% and 53% and G3 and G2 pain 23% and 54%. 31% required enteral feeding. G3 and G2 xerostomia rates were 0% and 31%. Recovery was seen, with 62% patients having dysphagia G≤1 2-months after IMRT. 30% of patients developed L'Hermitte's syndrome. No grade 4 toxicity was observed. No dose limiting toxicity was found. Accelerated fractionation IMRT in this group of patients is feasible and safe.	4
54. Schwartz DL, Lobo MJ, Ang KK, et al. Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. *Int J Radiat Oncol Biol Phys* 2009; 74(4):1083-1091.	Observational-Tx	131 patients	To review institutional outcomes for patients treated for DTC with postoperative conformal EBRT.	Kaplan-Meier estimates of locoregional relapse-free survival, disease-specific survival, and OS at 4 years were 79%, 76%, and 73%, respectively. On multivariate analysis, high-risk histologic features and gross residual disease predicted for inferior locoregional relapse-free survival, whereas high-risk histologic features, M1 disease, and gross residual disease predicted for inferior disease-specific and OS. The IMRT did not impact on survival outcomes, but was associated with less frequent severe late morbidity (12% vs 2%).	2
55. Tubiana M, Haddad E, Schlumberger M, Hill C, Rougier P, Sarrazin D. External radiotherapy in thyroid cancers. *Cancer* 1985; 55(9 Suppl):2062-2071.	Observational-Tx	97 patients	To examine the role/effects of RT in the treatment of DTC.	15-years after RT, the survival rate was 57% and is approximately 40% at 25 years. The relapse-free survival is lower (39% at 15 years). In patients irradiated with an adequate dose (≥50 Gy) to residual neoplastic tissue after incomplete surgery, the incidence of local recurrence is low (actuarial probability of local recurrence 11% at 15 years vs 23% for patients treated by surgery alone, although the irradiated patients had larger and more extensive tumors).	2

Thyroid Carcinoma
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
56. Terezakis SA, Lee KS, Ghossein RA, et al. Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: Memorial Sloan-kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys* 2009; 73(3):795-801.	Observational-Tx	76 patients	To examine the role of EBRT in patients with advanced or recurrent nonanaplastic thyroid cancer.	The 2- and 4-year overall locoregional control rate for all histologic types was 86% and 72%, respectively, and the 2- and 4-year OS rate for all patients was 74% and 55%, respectively. No significant differences were found in locoregional control, OS, or distant metastases-free survival for patients with complete resection, microscopic residual disease, or gross residual disease. Grade 3 acute mucositis and dysphagia occurred in 14 (18%) and 24 (32%) patients, respectively. Late adverse toxicity was notable for percutaneous endoscopic gastrostomy tube use in 4 patients (5%).	2
57. O'Connell ME, A'Hern RP, Harmer CL. Results of external beam radiotherapy in differentiated thyroid carcinoma: a retrospective study from the Royal Marsden Hospital. *Eur J Cancer* 1994; 30A(6):733-739.	Observational-Tx	113 patients	To evaluate recurrence or regression patterns in patients with DTC (follicular and papillary) who received radical dose megavoltage EBRT.	Local recurrence, mostly within field, occurred in 19% of 53 patients with probable and definite residual microscopic disease (both follicular and papillary histologies). For gross residual disease (both follicular and papillary) in 49 patients, complete regression was obtained in 37.5%, partial regression in 25% and no regression in 37.5%. Median follow-up from diagnosis was 49 months (range 3-335). Overall 5-year survival rates were 85% for residual microscopic disease but only 27% for gross disease. 61 patients have died. 19 deaths were due to unrelated causes, 15 to distant metastases, 15 to uncontrolled local disease and 12 died with both local and distant tumors.	3

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. *Int J Radiat Oncol Biol Phys* 1988; 14(6):1063-1075.	Review/Other-Tx	1074 papillary and 504 follicular thyroid cancer patients	A report of the experience from 13 Canadian radiotherapy centres concerning the treatment and outcome for 1,074 papillary and 504 FTC patients followed for 4-24 years.	Surgical resection was carried out in almost all patients; there was no correlation between the type of operation and recurrence or survival. Treatment with external irradiation (201 patients) radioiodine (214 patients), or both (107 patients) was used more often in poor prognosis patients than in those with good prognostic factors, and was effective in reducing local recurrences and improving survival, especially in patients with microscopic residual disease postoperatively. Treatment complications were common but rarely fatal. Thyroid cancer was the cause of death in over half of the papillary cancer deaths and in two-thirds of the follicular cancer deaths.	4
59. Gottlieb JA, Hill CS, Jr. Chemotherapy of thyroid cancer with adriamycin. Experience with 30 patients. *N Engl J Med* 1974; 290(4):193-197.	Observational-Tx	30 total patients	To test the outcomes of patients with advanced refractory metastatic thyroid carcinoma who received chemotherapy with adriamycin at a starting dose of 45 to 75 mg per square meter intravenously every 3 weeks.	11 patients demonstrated a >50% decrease in the size of their metastases. Subjective improvement, particularly relief of pain from bony metastases, was also observed. Histologic cell types responding included medullary (solid) (3/5), papillary-follicular (3/10), Hürthle cell (2/5), spindle and giant cell (2/9) and unclassified thyroid carcinoma (1/1). Although the rate of disease progression in the responding and nonresponding patients was similar before the start of adriamycin, the median survival from this point on was significantly superior ($P<0.005$) in the responders (median 11 + and range of over 5 to 40 + months, 6/11 living) to that of the nonresponders (median 4 and range of 0.1 to 23 + months, 5/19 living). Before the need to limit the total cumulative dose of adriamycin delivered to 550 mg per square meter was recognized, adriamycin-induced cardiomyopathy developed in 3 patients, but this side effect has not been observed since that limitation.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
60. Mathur A, Moses W, Rahbari R, et al. Higher rate of BRAF mutation in papillary thyroid cancer over time: a single-institution study. *Cancer* 2011; 117(19):4390-4395.	Review/Other-Tx	628 patients with conventional PTC and 228 tumor samples	To investigate the clinical, pathologic, and molecular changes present in PTC over a 15-year period during which the incidence of PTC doubled.	The authors found no differences in age, sex, ethnicity, primary tumor size, rate of extrathyroidal invasion, or overall TNM cancer stage among the 3 time groups. The rate of BRAF V600E mutation was significantly higher in group III (88% BRAF V600E positive) as compared with groups I and II (51% and 43%, respectively) (P<.001). The rate of all the common somatic mutations was also significantly higher in group III (92% positive) as compared with groups I and II (68% and 64%, respectively) (P<.002).	4
61. Kloos RT, Ringel MD, Knopp MV, et al. Phase II trial of sorafenib in metastatic thyroid cancer. *J Clin Oncol* 2009; 27(10):1675-1684.	Observational-Tx	41 PTC Patients	Based on the pivotal role of Ras-Raf-MAP-ERK signaling and vascular endothelial growth factor in PTC, a phase II clinical trial of sorafenib targeting RAF and vascular endothelial growth factor receptor kinases in PTC was conducted.	6 patients had a PR (15%; 95% CI, 6 to 29) and 23 patients (56%; 95% CI, 40 to 72) had stable disease longer than 6 months. Median duration of PR was 7.5 months (range, 6-14). Median PFS was 15 months (95% CI, 10 to 27.5). In 14 (78%) of 18 Tg-assessable PTC patients, Tg declined more than 25%. Common grade 3 adverse events included hand-foot skin reaction, musculoskeletal pain, and fatigue.	2
62. Ahmed M, Barbachano Y, Riddell A, et al. Analysis of the efficacy and toxicity of sorafenib in thyroid cancer: a phase II study in a UK based population. *Eur J Endocrinol* 2011; 165(2):315-322.	Observational-Tx	34 patients	To evaluate the tolerability and efficacy of sorafenib in patients with thyroid carcinoma.	After 6 months, the RR rate was 15% and a further 74% of patients achieved stable disease in the first 6 months. After 12 months of treatment, the RR was 21%. In the MTC patients, the RR at 12 months was 25% and OS was 100%. In DTC patients corresponding rates were 18% and 79% respectively. Median overall and PFS points were not reached at 19 months. Commonest adverse events included hand-foot syndrome, other skin toxicities, diarrhoea and alopecia. Dose reduction was required in 79% patients. Median time on treatment was 16.5 months.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
63. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol* 2008; 26(29):4714-4719.	Observational-Tx	30 patients	Open-label phase II trial was performed to determine the efficacy of sorafenib in patients with advanced thyroid carcinoma.	7 patients (23%; 95% CI, 0.10 to 0.42) had a PR lasting 18+ to 84 weeks. 16 patients (53%; 95% CI, 0.34 to 0.72) had stable disease lasting 14 to 89+ weeks. 17 (95%) of 19 patients for whom serial thyroglobulin levels were available showed a marked and rapid response in thyroglobulin levels with a mean decrease of 70%. The median PFS was 79 weeks. Toxicity was consistent with other sorafenib trials, although a single patient died of liver failure that was likely treatment related.	2
64. Bible KC, Suman VJ, Molina JR, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol* 2010; 11(10):962-972.	Observational-Tx	37 patients	An investigation of the safety and efficacy of pazopanib in patients with metastatic, rapidly progressive, radioiodine-refractory DTCs.	Patients received a median of 12 cycles (range 1 to >23, total >383). Confirmed PRs were recorded in 18 patients (response rate 49%, 95% CI 35-68), with likelihood of response lasting longer than 1 year calculated to be 66%. Maximum concentration of pazopanib in plasma during cycle one was significantly correlated with radiographic response (r=-0.40, P=0.021).	2
65. Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *J Clin Oncol* 2008; 26(29):4708-4713.	Observational-Tx	60 patients	To assess the activity and safety of axitinib, an oral, potent, and selective inhibitor of vascular endothelial growth factor receptors 1, 2, and 3 in patients with advanced thyroid cancer.	PRs were observed in 18 patients, yielding an objective response rate of 30% (95% CI, 18.9 to 43.2). Stable disease lasting ≥16 weeks was reported in another 23 patients (38%). Axitinib was generally well tolerated, with the most common grade ≥3 treatment-related adverse event being hypertension (n=7; 12%).	2

Thyroid Carcinoma
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Schreinemakers JM, Vriens MR, Munoz-Perez N, et al. Fluorodeoxyglucose-positron emission tomography scan-positive recurrent papillary thyroid cancer and the prognosis and implications for surgical management. *World J Surg Oncol* 2012; 10:192.	Observational-Tx	141 patients	To compare outcomes for patients with recurrent or persistent PTC who had metastatic tumors that were FDG-PET positive or negative, and to determine whether the FDG-PET scan findings changed the outcome of medical and surgical management.	Between 1984 and 2008, 41/141 patients who had recurrent or persistent PTC underwent FDG-PET (n=11) or FDG-PET/CT scans (n=30); 22 patients (54%) had one or more PET-positive lesion(s), 17 (41%) had PET-negative lesions, and 2 had indeterminate lesions. Most PET-positive lesions were located in the neck (55%). Patients who had a PET-positive lesion had a significantly higher TNM stage (P=0.01), higher age (P=0.03), and higher thyroglobulin (P=0.024). Only patients who had PET-positive lesions died (5/22 vs 0/17 for PET-negative lesions; P=0.04). In 2/7 patients who underwent surgical resection of their PET-positive lesions, loco-regional control was obtained without evidence of residual disease.	2
67. Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med* 2013; 368(7):623-632.	Review/Other-Tx	20 patients	To determine whether the mitogen-activated protein kinase (MAPK) kinase (MEK) 1 and MEK2 inhibitor selumetinib (AZD6244, ARRY-142886) could reverse refractoriness to radioiodine in patients with metastatic thyroid cancer.	Of 24 patients screened for the study, 20 could be evaluated. The median age was 61 years (range, 44 to 77), and 11 patients were men. 9 patients had tumors with BRAF mutations, and 5 patients had tumors with mutations of NRAS. Selumetinib increased the uptake of iodine-124 in 12/20 patients (4/9 patients with BRAF mutations and 5/5 patients with NRAS mutations). 8/12 patients reached the dosimetry threshold for radioiodine therapy, including all 5 patients with NRAS mutations. Of the 8 patients treated with radioiodine, 5 had confirmed PRs and 3 had stable disease; all patients had decreases in serum thyroglobulin levels (mean reduction, 89%). No toxic effects of grade 3 or higher attributable by the investigators to selumetinib were observed. One patient received a diagnosis of myelodysplastic syndrome more than 51 weeks after radioiodine treatment, with progression to acute leukemia.	4

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Wohllk N, Cote GJ, Bugalho MM, et al. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. *J Clin Endocrinol Metab* 1996; 81(10):3740-3745.	Review/Other-Tx	101 patients	Analysis of peripheral blood or tumor DNA samples from 101 patients with apparent sporadic MTC was performed to assess the frequency of RET proto-oncogene mutations in this patient population.	6/101 patients with apparent sporadic MTC had peripheral blood DNA mutations more commonly associated with hereditary MTC. In 4 patients, these mutations led to the identification of previously unrecognized kindreds. The remaining 2 patients were examples of de novo mutations. A codon 918 mutation was found in 14/57 (approximately 25%) tumor DNA samples. Mutations were not identified in the remaining patients. In this large cancer center population, approximately 6% of patients with sporadic MTC carry peripheral blood DNA mutations, either inherited or de novo, more commonly associated with MEN 2A or familial MTC.	4
69. Eng C, Mulligan LM, Smith DP, et al. Low frequency of germline mutations in the RET proto-oncogene in patients with apparently sporadic medullary thyroid carcinoma. *Clin Endocrinol (Oxf)* 1995; 43(1):123-127.	Review/Other-Dx	67 patients	Systematic analysis for germline mutations of the RET proto-oncogene was performed in a series of patients with apparently sporadic MTC to determine whether they were true sporadic cases or unsuspected de novo MEN 2 cases.	In this series, there was one proven case of germline mutation in RET codon 620, which previously has been shown to be responsible for MEN 2, thus indicating heritable disease. No germline mutation in codon 918, typical of MEN 2B, was found.	4
70. Brierley J, Tsang R, Simpson WJ, Gospodarowicz M, Sutcliffe S, Panzarella T. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. *Thyroid* 1996; 6(4):305-310.	Observational-Tx	73 patients	Analyses of survival and prognostic factors and the role of RT in local control of MTC.	The overall cause specific survival was 70% and 57% at 5 and 10 years, respectively. In a univariate analysis, the following factors predicted for lower cause-specific survival: age as a continuous variable (P=0.003), male gender (P=0.008), presence of distant metastasis (P<0.0001), lymph node involvement (P=0.03), gross residual disease (P<0.0001), tumor size >4 cm (P=0.05), extraglandular invasion (P<0.004), vascular invasion (P=0.007), diarrhea (P<.0007), and abnormal postoperative calcitonin (P=0.02).	2

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. Fersht N, Vini L, A'Hern R, Harmer C. The role of radiotherapy in the management of elevated calcitonin after surgery for medullary thyroid cancer. *Thyroid* 2001; 11(12):1161-1168.	Observational-Tx	51 patients	To evaluate the role of RT in the management of elevated calcitonin after surgery for MTC.	Local relapse rate was significantly lower after RT (29% vs 59%) but there was no significant difference in 10-year survival between the two groups (72% vs 60%). In view of this favorable long-term survival of patients with elevated calcitonin on observation, we cannot recommend the routine use of RT. However, it does appear to have a role in those presenting with more advanced disease to reduce the incidence of loco-regional relapse.	2
72. Nguyen TD, Chassard JL, Lagarde P, et al. Results of postoperative radiation therapy in medullary carcinoma of the thyroid: a retrospective study by the French Federation of Cancer Institutes--the Radiotherapy Cooperative Group. *Radiother Oncol* 1992; 23(1):1-5.	Review/Other-Tx	59 patients	To review results of postoperative RT in medullary carcinoma of the thyroid.	Residual tumour was left in 11 cases, and 44 patients had positive cervical nodes. Using megavoltage RT, the whole neck and the upper mediastinum area were most often irradiated through a large anterior Y-shaped field without laryngeal shielding. The mean dose to the tumoral bed was 54 Gy. Dysphagia was observed in 32 patients (11, 17 and 5 scores were grade 1, 2 and 3, respectively). Dyspnea occurred in 5 cases and in 2 of these cases, it was considered to be severe. Local recurrences were noted in 18 (30%) patients, most of them occurring within the fields of irradiation. The average length of survival is 70.5 months and is shortened by the occurrence of distant failures except in patients with bone metastases.	4
73. Schwartz DL, Rana V, Shaw S, et al. Postoperative radiotherapy for advanced medullary thyroid cancer--local disease control in the modern era. *Head Neck* 2008; 30(7):883-888.	Observational-Tx	34: 10 patients had recurrent disease, 16 had mediastinal involvement, and 10 had distant metastasis	To catalog modern-era postoperative EBRT outcomes for advanced MTC.	Kaplan-Meier estimates of locoregional relapse-free survival, disease-specific survival, and OS at 5 years were 87%, 62%, and 56%, respectively. Disease in 3 patients with gross residual disease was controlled locoregionally. Distant disease at the time of EBRT did not predict survival. Two (9%) patients reported symptomatic chronic morbidity.	2

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
74. Wells SA, Jr., Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012; 30(2):134-141.	Experimental-Tx	331 total patients: vandetanib (231), placebo (100)	Patients with advanced MTC were randomly assigned in a 2:1 ratio to receive vandetanib 300 mg/d or placebo.	At data cutoff (July 2009; median follow-up, 24 months), 37% of patients had progressed and 15% had died. The study met its primary objective of PFS prolongation with vandetanib versus placebo (HR, 0.46; 95% CI, 0.31 to 0.69; P<.001). Statistically significant advantages for vandetanib were also seen for objective response rate (P<.001), disease control rate (P=.001), and biochemical response (P<.001). OS data were immature at data cutoff (HR, 0.89; 95% CI, 0.48 to 1.65).	1
75. Schoffski P, Elisei R, Muller S, et al. An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients (pts) with documented RECIST progression at baseline. *ASCO Meeting Abstracts* 2012; 30(15_suppl):5508.	Experimental-Tx	330 total patients	A phase III study of cabozantinib vs placebo in patients with progressive, unresectable, locally advanced or metastatic MTC.	The planned primary PFS analysis included events through the date of the 138th event. As of 15 June 2011, 44.7% of patients on cabozantinib and 13.5% on placebo were still receiving study treatment. Statistically significant PFS prolongation of 7.2 months was observed; median PFS for cabozantinib was 11.2 months vs 4.0 months for placebo (HR 0.28, 95% CI 0.19-0.40, P<0.0001). PFS results favored the cabozantinib group across subset analyses including RET status and prior TKI use. Objective response rate was 28% for cabozantinib vs 0% for placebo (P<0.0001). An interim analysis of OS (44% of the 217 required events) did not show a difference between cabozantinib and placebo.	1
76. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer* 2005; 103(7):1330-1335.	Review/Other-Tx	516 patients	Analysis of prognostic factors and treatment outcomes in patients with ATC reported in the SEER data base.	8% of patients had intrathyroidal tumors, 38% had extrathyroidal tumors and/or lymph node invasion, and 43% of patients had distant metastasis. The average tumor size was 6.4 cm (range, 1-15 cm). 64% of patients underwent surgical resection of their primary tumor, and 63% received EBRT. The overall cause-specific mortality rate was 68.4% at 6 months and 80.7% at 12 months.	4

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
77. Tan RK, Finley RK, 3rd, Driscoll D, Bakamjian V, Hicks WL, Jr., Shedd DP. Anaplastic carcinoma of the thyroid: a 24-year experience. *Head Neck* 1995; 17(1):41-47; discussion 47-48.	Review/Other-Tx	21 patients	The authors retrospectively reviewed their experience with patients with ATC gland at a cancer institute and identified a subgroup of patients with complete resection who have a 60% 5-year survival.	Estimated 5-year survival was 10% (median: 4.5 months). Tumor size >6.0 cm (P=.004) and female gender (P=.02) were significant prognostic factors. 5 patients who underwent complete resection had an estimated 5-year survival of 60% (median: 131 months). Four of these patients had postoperative RT with or without sequential chemotherapy. Two of these patients survived more than 10 years, and a third remains alive without disease at 26 months.	4
78. Tennvall J, Lundell G, Wahlberg P, et al. Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. *Br J Cancer* 2002; 86(12):1848-1853.	Observational-Tx	55 patients	Patients with ATC were prospectively treated according to a combined regimen consisting of hyperfractionated RT, doxorubicin, and when feasible surgery, then assessed for recurrence.	In only 13 cases (24%) was death attributed to local failure. 5 patients (9%) 'had a survival' exceeding 2 years. No signs of local recurrence were seen in 33 patients (60%); 5/16 patients in Protocol A, 11/17 patients in Protocol B, 17/22 patients in Protocol C (P=0.017). In the 40 patients undergoing additional surgery, no signs of local recurrence were seen in 5/9 patients, 11/14 patients and 17/17 patients, respectively (P=0.005).	1
79. Haigh PI, Ituarte PH, Wu HS, et al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. *Cancer* 2001; 91(12):2335-2342.	Observational-Tx	33 patients	To identify prognostic factors for ATC in patients who had prolonged survival.	Median survival was 3.8 months. Median age was 69 years. In patients treated with potentially curative resection, median survival was 43 months compared with 3 months with palliative resection (P=0.002); the median survival of 3.3 months with only chemotherapy and irradiation was no different than palliative resection (P=0.63). No association was found between survival and age, prior goiter, prior thyroid carcinoma, adjacent DTC, or tumor size.	2

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
80. Heron DE, Karimpour S, Grigsby PW. Anaplastic thyroid carcinoma: comparison of conventional radiotherapy and hyperfractionation chemoradiotherapy in two groups. *Am J Clin Oncol* 2002; 25(5):442-446.	Observational-Tx	Patients were divided into two groups: those treated between 1952 to 1980 (9 patients, group 1: received once-daily RT) and those treated between 1981 and 1999 (23 patients, group 2: received twice-daily RT with concurrent chemo-therapy)	To compare conventional RT and hyperfractionation chemoradiotherapy in two groups of patients with ATC.	Overall 2-year survival rates were 44% for group 1 and 52% for group 2. Two-year PFS was 53% for group 1 and 38% for group 2. 5 (16%) patients died within 60 days of diagnosis. Severe side effects included skin sequelae (one patient) and osteoradionecrosis of the mandible (one patient). There were 10 (52%) long-term survivors (>2 years).	2
81. De Crevoisier R, Baudin E, Bachelot A, et al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; 60(4):1137-1143.	Observational-Tx	30 patients	To analyze a prospective protocol combining surgery, chemotherapy, and hyperfractionated accelerated RT in ATC.	At the end of the treatment, a complete local response was observed in 19 patients. With a median follow-up of 45 months (range, 12-78 months), 7 patients were alive in complete remission, of whom 6 had initially received a complete tumor resection. OS rate at 3 years was 27% (95% CI, 10%-44%) and median survival 10 months. Main toxicity was hematologic. High long-term survival was obtained when RT-chemotherapy was given after complete surgery. This protocol avoided local tumor progression, and death was mainly caused by distant metastases.	1

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
82. Nel CJ, van Heerden JA, Goellner JR, et al. Anaplastic carcinoma of the thyroid: a clinicopathologic study of 82 cases. *Mayo Clin Proc* 1985; 60(1):51-58.	Review/Other-Tx	82 patients	Clinicopathologic study of patients with anaplastic carcinoma of the thyroid.	Relatively favorable prognostic features seem to be unilateral tumors, a tumor diameter of <5 cm, no invasion of adjacent tissue, and absence of nodal involvement. For resectable lesions, thyroid lobectomy with wide margins of adjacent soft tissue on the side of the tumor seems to constitute a safe, appropriately aggressive surgical approach. Total thyroidectomy and radical neck dissection results in an increased complication rate and has no advantage over a more conservative approach. RT, chemotherapy, immunotherapy, and combination RT and chemotherapy need further evaluation.	4
83. Chen J, Tward JD, Shrieve DC, Hitchcock YJ. Surgery and radiotherapy improves survival in patients with anaplastic thyroid carcinoma: analysis of the surveillance, epidemiology, and end results 1983-2002. *Am J Clin Oncol* 2008; 31(5):460-464.	Review/Other-Tx	261 patients	Analysis of the surveillance, epidemiology, and end results of surgery and RT in patients with ATC.	Median survival was 4 months. Distant or metastatic disease, tumor size >7 cm, and treatment with surgery plus or minus RT were statistically significant as prognostic for survival on multivariate analysis ($P<0.05$). When stratified by extent of disease, the addition of RT to surgery resulted in improved survival for patients with disease extending into adjacent tissue ($P=0.05$); however, patients who had disease confined to the capsule or had further extension or distant metastatic disease did not benefit from RT after surgery ($P>0.05$).	4
84. Pierie JP, Muzikansky A, Gaz RD, Faquin WC, Ott MJ. The effect of surgery and radiotherapy on outcome of anaplastic thyroid carcinoma. *Ann Surg Oncol* 2002; 9(1):57-64.	Observational-Tx	67 patients	Analysis of (authors') experience for prognosis and the effect of surgery and RT on patients with ATC (retrospective review).	Surgery was performed in 44/67 patients, with 12 complete resections. The 6-month and 1- and 3-year survival rates were 92%, 92%, and 83% after complete resection; 53%, 35%, and 0% after debulking; and 22%, 4%, and 0% after no resection, respectively ($P<.0001$). A radiation dose of >45 Gy improved survival as compared with a lower dose ($P=.02$). Multivariate analysis showed that age ≤70 years, absence of dyspnea or dysphagia at presentation, a tumor size ≤5 cm, and any surgical resection improved survival ($P<.05$).	2

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
85. McIver B, Hay ID, Giuffrida DF, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery* 2001; 130(6):1028-1034.	Review/Other-Tx	134 patients	A report the results of a 50-year experience of ATC.	Benign thyroid disease was present in 27 cases (20%) and well-differentiated thyroid carcinoma in 31 (23%). 62 patients (46%) had distant metastases at diagnosis, and 98% of the tumors were locally invasive. Primary treatment was surgical for 96 patients (72%). Complete resection was achieved in 29 cases (30%), with "minimal residual disease" in 25. Neither extent of operation nor completeness of resection affected survival (P>.4). Postoperative RT gave slightly longer median survival (5 vs 3 months), which was not significant (P<.08). Multimodal therapy, including operation, chemotherapy, and RT, did not improve survival.	4
86. Foote RL, Molina JR, Kasperbauer JL, et al. Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy. *Thyroid* 2011; 21(1):25-30.	Observational-Tx	25 total patients (subdivided into three different treatment groups)	Hypothesized that survival in newly diagnosed patients with stages IVA and IVB locoregionally confined ATC might be improved by utilizing an aggressive therapeutic approach, prioritizing both the eradication of disease in the neck and preemptive treatment of occult metastatic disease.	There were no deaths from therapy, but hospitalization was required in two patients (20%) because of treatment-related adverse events. 5 patients (50%) are alive and cancer-free, all having been followed >32 months (range: 32-89 months; median: 44 months) with a median overall Kaplan-Meier survival of 60 months. OS at 1 and 2 years was 70% and 60%, respectively, compared to <20% historical survival at 1 year in analogous patients previously treated with surgery and conventional postoperative radiation at our and other institutions.	2
87. Besic N, Auersperg M, Us-Krasovec M, Golouh R, Frkovic-Grazio S, Vodnik A. Effect of primary treatment on survival in anaplastic thyroid carcinoma. *Eur J Surg Oncol* 2001; 27(3):260-264.	Observational-Tx	79 patients (26 men, 53 women; age: 40-86 years, mean age 65 years)	A retrospective, non-randomized study to find out whether timing of the treatment modality had any influence on survival, and to find out if primary surgery prolongs survival in comparison to primary chemotherapy and/or RT.	In comparison to the primary surgery group, the patients from the primary chemotherapy and/or RT group were older and had faster growing, and larger tumours, which were not confined to the thyroid, and more frequently had regional metastases. There was no difference in the survival of the two groups (P=0.17). Survival for longer than one year was observed in 25% of patients with primary surgery and in 21% of patients with primary chemotherapy and/or RT. The best results (50% survival at one year) were obtained in patients in whom the tumour was surgically removed after primary chemotherapy and RT.	2

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
88. Busnardo B, Daniele O, Pelizzo MR, et al. A multimodality therapeutic approach in anaplastic thyroid carcinoma: study on 39 patients. *J Endocrinol Invest* 2000; 23(11):755-761.	Review/Other-Tx	39 patients	To investigate the role of multimodality treatment in patients with ATC.	9/16 patients, who underwent surgery and complementary treatment, had no local progression. In all but one, distant metastases developed, mainly in the lung, during or after post-surgical chemotherapy. The best results were obtained in younger patients with less advanced disease. Early diagnosis is mandatory. Only a few patients responded to chemotherapy, confirming that ATC is often resistant to anticancer drugs. Aggressive and appropriate combinations of RT, total thyroidectomy and chemotherapy may provide some benefit in patients with ATC. Preoperative chemotherapy and RT may enhance surgical resectability of the primary tumor.	4
89. Junor EJ, Paul J, Reed NS. Anaplastic thyroid carcinoma: 91 patients treated by surgery and radiotherapy. *Eur J Surg Oncol* 1992; 18(2):83-88.	Review/Other-Tx	91 patients	To evaluate outcomes of patients treated for ATC by surgery and RT.	Results show dyspnea to be the only symptom strongly influencing survival. Total or partial thyroidectomy is associated with increased survival. This association is most marked for patients presenting without dyspnea. 80% of patients responded to RT.	4
90. Troch M, Koperek O, Scheuba C, et al. High efficacy of concomitant treatment of undifferentiated (anaplastic) thyroid cancer with radiation and docetaxel. *J Clin Endocrinol Metab* 2010; 95(9):E54-57.	Review/Other-Tx	6 patients	Retrospective analysis to analyze activity using radiation plus docetaxel in the treatment of ATC.	5 patients completed radiochemotherapy. One patient has completed radiation but is still on treatment with docetaxel. 4 patients achieved complete remission and 2 PR. During RT, 4 patients developed severe mucositis/stomatitis and 2 dermatitis, necessitating hospitalization. 2 patients developed pneumonia and one urinary tract infection. All patients were hospitalized for a median of 17 days (range, 4-40 days) because of toxicites. After a median follow up of 21.5 months (range, 2-40 months), five patients are alive.	4
91. Wong CS, Van Dyk J, Simpson WJ. Myelopathy following hyperfractionated accelerated radiotherapy for anaplastic thyroid carcinoma. *Radiother Oncol* 1991; 20(1):3-9.	Review/Other-Tx	32 patients	A study of the effectiveness of myelopathy following hyperfractionated accelerated RT for ATC.	The median survival was <6 months. 2 patients developed radiation myelopathy at 8 and 13 months, total spinal cord dose being 39.9 and 48.3 Gy, respectively. The risk of spinal cord damage was much higher than expected.	4

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
92. Simpson WJ. Anaplastic thyroid carcinoma: a new approach. *Can J Surg* 1980; 23(1):25-27.	Review/Other-Tx	14 patients	An analysis of radiation fractions and their effectiveness on the treatment of ATC.	Less than 10% of patients with ATC survive 5 years when treated by operation and conventional irradiation, but survivors who are disease-free at 2 years appear to be cured. The administration of a small number of large radiation fractions (350 to 800 rads) failed to eradicate the local disease in 14 patients, all of whom died within 9 months. Hyperfractionation (100 rads qid at 3-hour intervals) caused complete tumor regression of 6/14 patients and partial regression in 7 others; the 1 patient whose tumour failed to respond was treated only once daily.	4
93. Mitchell G, Huddart R, Harmer C. Phase II evaluation of high dose accelerated radiotherapy for anaplastic thyroid carcinoma. *Radiother Oncol* 1999; 50(1):33-38.	Review/Other-Tx	17 patients	To describe the use of accelerated RT aiming to improve local response in patients with ATC. Toxicity was assessed prospectively.	3 patients with ATC demonstrated a complete clinical response and 7 patients achieved a PR. 5 patients had stable disease and 2 patients died before RT was completed. Toxicity from oesophagitis and dysphagia was high with 10 patients requiring intravenous fluids or nasogastric tube feeding.	4
94. Wang Y, Tsang R, Asa S, Dickson B, Arenovich T, Brierley J. Clinical outcome of anaplastic thyroid carcinoma treated with radiotherapy of once- and twice-daily fractionation regimens. *Cancer* 2006; 107(8):1786-1792.	Observational-Tx	47: 23 patients underwent radical RT with a radiation dose >40 Gy, and 24 patients underwent palliative RT with a dose ≤40 Gy	To assess local control, survival, and toxicity after RT in patients with ATC, and to compare clinical outcomes between once-daily and twice-daily fractionation regimens.	The 6-month local progression-free rate in patients who underwent radical RT was 94.1%, significantly higher compared with palliative RT (64.6%; P=.02). The median actuarial OS was greater in patients with radical RT (11.1 months) compared with palliative RT (3.2 months; P<.0001). The median OS in patients with twice-daily fractionation (13.6 months) was 3.3 months longer than patients treated with once-daily fractionation (10.3 months), but the difference was not statistically significant (P=.3). For patients treated with twice-daily fractionation, 3 patients had Grade 3 acute skin toxicity, and no patient had Grade 3 or higher esophageal toxicity.	2

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
95. Kim JH, Leeper RD. Treatment of locally advanced thyroid carcinoma with combination doxorubicin and radiation therapy. *Cancer* 1987; 60(10):2372-2375.	Observational-Tx	41 : 22 received combined regimen consisting of once weekly Adriamycin (10 mg/m2) before RT, 19 received the combined regimen, consisting of once weekly Adriamycin (10 mg/m2) before hyper-fractionated RT	A study of the treatment of locally advanced thyroid carcinoma with combination doxorubicin and RT.	Initial complete tumor response rates in the group 1 and 2 were 91% and 84%, respectively. Local tumor control rates at 2 years after combined therapy were 77% and 68%, respectively. The median survival time was 4 years for group 1 and 1 year for group 2. There was no disproportionately enhanced normal tissue morbidity seen with this combined approach. Patients in group 1 have a good quality of life, once the local disease is under control due to the indolent course of the disease. On the contrary, most patients in group 2 promptly developed distant metastases and died from the disease.	2
96. Bhatia A, Rao A, Ang KK, et al. Anaplastic thyroid cancer: Clinical outcomes with conformal radiotherapy. *Head Neck* 2010; 32(7):829-836.	Observational-Tx	53 patients	To review institutional outcomes for ATC treated with 3D-CRT or IMRT.	The Kaplan-Meier estimate of OS at 1 year for definitively irradiated patients was 29%. Patients without distant metastases receiving ≥50 Gy had superior survival outcomes; 5 such patients had no evidence of disease at last follow-up. Use of IMRT vs 3D-CRT did not influence toxicity.	2
97. Haugen BR, Kane MA. Approach to the thyroid cancer patient with extracervical metastases. *J Clin Endocrinol Metab* 2010; 95(3):987-993.	Review/Other-Tx	N/A	To compare standard fixed-dose radioiodine therapy vs the dosimetric approach in the treatment of patients with distant, or extracervical, metastases from DTC.	FDG-PET has a role in patient prognosis and guiding directed therapy for fluorodeoxyglucose-avid lesions. Patients with asymptomatic, stable, radioiodine-resistant metastases may be carefully monitored for disease progression. Patients with symptomatic disease should receive directed therapy with the goal of symptom relief. Patients with progressive metastatic disease should be considered for clinical trials or targeted systemic therapy (sorafenib or sunitinib), although these agents are not Food and Drug Administration (FDA) approved for patients with thyroid cancer.	4

Thyroid Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
98. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* 2006; 91(8):2892-2899.	Observational-Tx	444 patients: 223 had lung metastases only, 115 had bone metastases only, 82 had both lung and bone metastases, and 24 had metastases at other sites	To estimate the cumulative activity of (131)I to be administered to patients with distant metastases from thyroid carcinoma.	Negative imaging studies (negative total body (131)I scans and conventional radiographs) were attained in 43% of the 295 patients with (131)I uptake; more frequently in those who were younger, had well-differentiated tumors, and had a limited extent of disease. Most negative studies (96%) were obtained after the administration of 3.7-22 GBq (100-600 mCi). Almost half of negative studies were obtained more than 5 years after the initiation of the treatment of metastases. Among patients who achieved a negative study, only 7% experienced a subsequent tumor recurrence. OS at 10 years after initiation of (131)I treatment was 92% in patients who achieved a negative study and 19% in those who did not.	2
99. Wang W, Larson SM, Tuttle RM, et al. Resistance of [18f]-fluorodeoxyglucose-avid metastatic thyroid cancer lesions to treatment with high-dose radioactive iodine. *Thyroid* 2001; 11(12):1169-1175.	Observational-Tx	25 patients	To evaluate the ability of 131I to destroy FDG-avid metastatic lesions in thyroid cancer patients.	The average interval between the two PET scans was 12.9 months. The average interval between the 131I treatment and the follow-up FDG-PET was 10.1 months. The authors measured post-therapy changes in lesional volume, in standard uptake values of FDG, and in serum thyroglobulin levels. The total volume of FDG-avid metastases rose significantly (P=0.036) from a mean of 159 mL to 235 mL after 131I therapy, the maximum standard uptake values rose from 9.3 to 11.9, the median serum thyroglobulin levels at the time of the second PET scan was 132% of that at baseline.	2
100. Ain KB, Lee C, Williams KD. Phase II trial of thalidomide for therapy of radioiodine-unresponsive and rapidly progressive thyroid carcinomas. *Thyroid* 2007; 17(7):663-670.	Observational-Tx	28 patients	To assess thalidomide's tumoristatic effects and toxicity in a phase II trial in the treatment of distantly metastatic, rapidly progressive thyroid carcinomas unresponsive to radioiodine.	Median PR duration was 4 months (range: 2-6 months), and stable disease duration was 6 months (range: 2-14 months). Median survival was 23.5 months for responders (PR + stable disease) and 11 months for nonresponders. Most frequent toxicity was fatigue (69% grade 1-2, 8% grade 3-4). 4 patients had grade 3-4 infections (without neutropenia), one had pericardial effusion, and one had pulmonary embolus.	1

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

3D-CRT = 3D-confromal radiation therapy

ATC = Anaplastic thyroid cancer

CI = Confidence interval

DTC = Differentiated thyroid cancer

EBRT = External-beam radiation therapy

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

FTC = Follicular thyroid cancer

HR = Hazard ratio

IMRT = Intensity-modulated radiation therapy

MTC = Medullary thyroid cancers

OS = Overall survival

PFS = Progression-free survival

PR = Partial response

PTC = Papillary thyroid cancers

RAI = Radioactive iodine

RT = Radiotherapy