Evidence Synthesis

Number 151

Screening for Thyroid Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA-290-2012-00015-I-EPC4, Task Order No. 4

Prepared by:
Kaiser Permanente Research Affiliates Evidence-based Practice Center
Kaiser Permanente Center for Health Research
Portland, OR

Investigators:
Jennifer S. Lin, MD, MCR
Erin J. Aiello Bowles, MPH
Selvi B. Williams, MD, MPH
Caitlin C. Morrison, MPH

AHRQ Publication No. 15-05221-EF-1
May 2017

This report is based on research conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2012-00015-I-EPC4, Task Order No. 4). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Jennifer Croswell, MD, MPH, formerly of AHRQ; current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations; Gunjan Tykodi, MD, for expert consultation; Todd Hannon, MLS, and Smyth Lai, MLS, for creating and conducting the literature searches; Elizabeth L. Hess, MS, ELS(D), for editorial assistance; Ning X. Smith, PhD, and Brittany Burda, MPH, for assistance with meta-analyses; and Louise Davies, MD, MS, Hyeong Sik Ahn, MD, PhD, Edward G. Grant, MD, and Mike Tuttle, MD, for their expert feedback on this report; and Barry Kramer, MD, MPH, Dawn Holman, MPH, and Monica C. Skarulis, MD, who provided expert review of this report.

Suggested Citation

Lin JS, Aiello Bowles EJ, Williams SB, Morrison CC. Screening for Thyroid Cancer: A Systematic Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 151. AHRQ Publication No. 15-05221-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2017.

Structured Abstract

Objective: We conducted this systematic review to support the U.S. Preventive Services Task Force in updating its recommendation on screening for thyroid cancer. Our review addresses the following Key Questions (KQs): 1) Compared with not screening, does screening adults for thyroid cancer lead to a reduced risk of thyroid-specific mortality or morbidity, reduced all-cause mortality, and/or improved quality of life? 2) What are the test performance characteristics of screening tests for detecting malignant thyroid nodules in adults? 3) What are the harms of screening for thyroid cancer in adults? 4) Does treatment of screen-detected thyroid cancer reduce thyroid-specific mortality or morbidity, reduce all-cause mortality, and/or improve quality of life? 5) What are the harms of treating screen-detected thyroid cancer?

Data sources: We searched MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials to locate relevant studies for all KQs. We searched for articles published from January 1966 to January 2016.

Study selection: We reviewed 10,424 abstracts and 707 articles against specified inclusion criteria. Eligible studies included those written in English and conducted in asymptomatic adult populations at general risk or with a prior personal history of radiation exposure.

Data analysis: We conducted dual independent critical appraisal of all included studies and extracted study details and outcomes from fair- or good-quality studies. We synthesized results by KQ and type of screening test (i.e., palpation or ultrasound). We used primarily qualitative synthesis. We used random-effects meta-analyses to pool surgical harms. We also summarized the overall strength of evidence for each KQ.

Results: We found no studies that met our inclusion criteria for KQ 1. Ten fair-quality studies were included for KQ 2. In two studies, neck palpation was not sensitive to detect thyroid nodules. Two methodologically limited studies that used selected sonographic features demonstrated that screening with ultrasound can be specific for detecting thyroid malignancy; one of these studies suggested that using a combination of high-risk sonographic features, such as microcalcification or irregular shape, can optimize both sensitivity and specificity. Three fair-quality studies met our inclusion criteria for KQ 3, none of which suggested any serious harms from screening or ultrasound-guided fine-needle aspiration. However, we found no screening studies that directly examined the risk of overdiagnosis. Two studies met our inclusion criteria for KQ 4, but neither was designed to determine if earlier or immediate treatment versus delayed or no surgical treatment improves the outcomes of patients with well-differentiated thyroid cancer. Fifty-two studies were included for KQ 5. Based on 36 studies, permanent surgical harms, hypoparathyroidism, and recurrent laryngeal nerve palsy are not uncommon. Best estimates of permanent hypoparathyroidism are from 2 to 6 events per 100 thyroidectomies and are more variable with lymph node dissection. The rate of recurrent laryngeal nerve palsy is estimated at 1 or 2 events per 100 surgeries. Based on 16 studies, treatment of differentiated thyroid cancer with radioactive iodine (RAI) treatment is associated with a small increase in second primary malignancies; RAI treatment is also associated with increased permanent adverse effects on the salivary gland, such as dry mouth.

Limitations: The vast majority of studies that evaluated the diagnostic accuracy of ultrasound to detect thyroid tumors are not in screening populations. High statistical heterogeneity for surgical harms of hypoparathyroidism could not be explained by known clinical heterogeneity across studies. Differences in study designs and variable reporting on radiation doses limits our understanding of the magnitude and precision around the excess risk for second primary malignancies due to RAI.

Conclusions: Although ultrasound of the neck using high-risk sonographic characteristics plus followup cytology from fine-needle aspiration can reasonably identify thyroid cancer, it is unclear if population-based or targeted screening can decrease mortality or improve important patient health outcomes. More importantly, screening results in the identification indolent thyroid cancer, and treatment of these cases of overdiagnosed cancer can pose real patient harms.

Table of Contents

Chapter 1. Introduction ... 1
Condition Definition ... 1
Prevalence and Burden of Disease ... 1
Risk Factors ... 2
Natural History ... 2
Screening ... 3
Treatment ... 4
Current Clinical Practice ... 5
Previous U.S. Preventive Services Task Force Recommendation ... 6
Chapter 2. Methods ... 7
Scope and Purpose ... 7
Analytic Framework and Key Questions ... 7
Data Sources and Searches ... 7
Study Selection ... 7
Quality Assessment and Data Abstraction ... 9
Data Synthesis ... 9
Expert Review and Public Comment ... 10
USPSTF Involvement ... 10
Chapter 3. Results ... 12
KQ 1. Compared With Not Screening, Does Screening Adults for Thyroid Cancer Lead to a Reduced Risk of Thyroid-Specific Mortality or Morbidity, Reduced All-Cause Mortality, and/or Improved Quality of Life? ... 12
KQ 2. What Are the Test Performance Characteristics of Screening Tests for Detecting Malignant Thyroid Nodules in Adults? ... 12
Diagnostic Accuracy of Palpation to Detect Thyroid Nodules ... 12
Diagnostic Accuracy of Screening Ultrasound to Detect Thyroid Cancer ... 13
Yield of Screening for Thyroid Cancer ... 14
KQ 3. What Are the Harms of Screening for Thyroid Cancer in Adults? ... 15
Limitations ... 16
KQ 4. Does Treatment of Screen-Detected Thyroid Cancer Reduce Thyroid-Specific Mortality or Morbidity, Reduce All-Cause Mortality, and/or Improve Quality of Life? ... 16
Limitations ... 17
KQ 5. What Are the Harms of Treating Screen-Detected Thyroid Cancer? ... 17
Surgical Harms ... 18
RAI Harms ... 20
Chapter 4. Discussion ... 23
Summary of Evidence ... 23
Key Contextual Issues ... 25
Diagnostic Accuracy of Ultrasound and FNA ... 25
Overdiagnosis ... 27
Limitations of the Review ... 29
Evidence Gaps and Future Research Needs ... 32
Conclusions ... 32

References **33**

Figures

Figure 1. Analytic Framework and Key Questions
Figure 2. Key Question 5 Results: Permanent Hypoparathyroidism From Surgery, Stratified by Type of Thyroidectomy
Figure 3. Key Question 5 Results: Permanent Hypoparathyroidism From Surgery, Stratified by Type of Lymph Node Dissection
Figure 4. Key Question 5 Results: Permanent Recurrent Laryngeal Nerve Palsy From Surgery, Stratified by Type of Thyroidectomy
Figure 5. Key Question 5 Results: Permanent Recurrent Laryngeal Nerve Palsy From Surgery, Stratified by Type of Lymph Node Dissection

Tables

Table 1. Included Studies for Key Question 2: Test Performance Characteristics of Screening Tests for Detecting Malignant Thyroid Nodules in Adults
Table 2. Key Question 2 Results: Diagnostic Accuracy of Screening Ultrasound
Table 3. Key Question 2 Results: Cancer Yield From Thyroid Cancer Screening
Table 4. Included Studies and Results for Key Question 3: Harms of Screening and Diagnostic Fine-Needle Aspiration
Table 5. Included Studies and Results for Key Question 4: Treatment Effectiveness of Screen-Detected Thyroid Cancer on Patient Health Outcomes
Table 6. Included Studies for Key Question 5: Harms of Surgical Treatment of Screen-Detected Thyroid Cancer
Table 7. Included Studies for Key Question 5: Harms of RAI Treatment of Screen-Detected Thyroid Cancer
Table 8. Results for Key Question 5: Harms of Surgical Treatment of Screen-Detected Thyroid Cancer
Table 9. Results for Key Question 5: Harms of RAI Treatment of Screen-Detected Thyroid Cancer
Table 10. Summary of Evidence, by Key Question

Appendixes

Appendix A. Search Strategy
  Table 1. Quality Assessment Criteria
  Table 2. Inclusion and Exclusion Criteria
  Figure 1. Literature Flow Diagram
Appendix B. Ongoing Studies
Appendix C. Excluded Studies

Chapter 1. Introduction

Condition Definition

Thyroid cancer starts in the thyroid gland, which is located in the front of the neck. The histologic types of thyroid cancer can be categorized into three groups based on their cellular origin and characteristics: cancer derived from the thyroid epithelium, which includes papillary and follicular carcinomas, most commonly differentiated; cancer from parafollicular (C) cells, called medullary carcinomas; and anaplastic carcinomas, the most undifferentiated type.[1, 2] Papillary microcarcinoma refer to papillary cancer smaller than 1 cm.

Prevalence and Burden of Disease

Palpable thyroid nodules are common, occurring in approximately 5 percent of U.S. adults age 50 years and older when screened by palpation. The prevalence of thyroid nodules increases to 16 to 68 percent of adults when screened by ultrasound.[3-5] In contrast, thyroid cancer is uncommon, and the lifetime risk of developing it is 1.1 percent.[6]

Since 1975, the incidence of detected thyroid cancer cases has been rising in the United States for both men and women.[7] Estimates published in 2014 showed the incidence of thyroid cancer increased from 4.9 cases per 100,000 persons in 1975 to 14.3 cases per 100,000 persons in 2009, representing an absolute increase of 9.4 cases per 100,000 persons (95% confidence interval [CI], 8.9 to 9.9).[2] However, over time mortality rates have remained stable at about 0.5 deaths per 100,000 persons per year.[6] According to the Surveillance, Epidemiology, and End Results Program (SEER), there are 13.5 new cases of thyroid cancer per 100,000 persons per year (age-adjusted and based on 2008–2012 cases).[6] Thyroid cancer is 2 to 3 times more common in women than in men,[1] and incidence is greater among whites and Asians than among blacks or American Indians/Alaska Natives.[6] Overall, a total of 601,789 adults were living with thyroid cancer in the United States in 2012.[1, 6] The American Cancer Society estimated 62,450 new cases of thyroid cancer would be identified in 2015.[8] One study estimated that if current trends continue, as many as 89,500 cases may be diagnosed in 2019, costing the United States $18.6 to $21.6 billion to treat cancer diagnosed from 2010 to 2019.[9]

Differentiated thyroid cancer accounts for 90 percent of all cases.[10] Within this category, papillary thyroid cancer accounts for about 70 to 80 percent of cases and follicular cancer accounts for 10 to 15 percent. Papillary microcarcinoma accounts for about 24 percent of thyroid cancer cases in the United States; it is typically found incidentally on imaging studies of the head or neck.[11] Most cases of differentiated cancer occur in adults ages 30 to 50 years.[12] Approximately 5 percent of cases of differentiated cancer occur in persons with a family history of thyroid cancer.[13] Papillary cancer is 3 times more common in women than in men. Hürthle cell is a rare subtype of follicular thyroid cancer, accounting for less than 3 percent of cases, and is no longer classified separately from follicular cancer by the World Health Organization.[14] Medullary and anaplastic thyroid cancer are much rarer forms, accounting for about 4 and 2 percent of cases of thyroid cancer, respectively. Medullary cancer most often occurs between the ages of 50 and 60 years. Approximately 25 percent of cases of medullary cancer are inherited and 75 percent are sporadic.[15, 16] Most anaplastic thyroid cancer cases are diagnosed after age 65 years, and the majority of cases occur in women.[17]

Risk Factors

Risk factors for thyroid cancer include exposure to radiation, family history of thyroid cancer, and inherited genetic syndromes. Other potential risk factors for the development of thyroid cancer include high iodine intake (either from the environment or diet), increased thyroid-stimulating hormone levels, obesity, and exposure to nitrate.[18]

Radiation exposure during childhood up to late adolescence is a well-known risk factor for thyroid cancer. Radiation exposure may come from environmental nuclear disasters (e.g., the Chernobyl accident); medical examinations (e.g., computed tomography [CT] scans, medical or dental x-rays); and medical treatment, including radiation therapy for head and neck cancer and radioactive iodine (RAI) (also called I-131 or 131I) treatment (e.g., for conditions such as hyperthyroidism).[18, 19, 20] A pooled analysis showed an excess relative risk of thyroid cancer of 7.7 (95% CI, 2.1 to 28.7) per Gy of radiation exposure.[21]

For a better understanding of radiation exposure dose in the United States, the average person is exposed to approximately 3 mSv per year from naturally occurring materials in the environment (note the radiation dose received in Sv is equivalent to the radiation exposure in Gy).[22] More than 80 million CT scans are performed per year in the United States alone, with an average dose of 2 to 20 mSv per examination.[22] For solid tumors, including thyroid cancer, observational and molecular studies have noted a linear dose-response relationship for radiation exposure.[21] There does not appear to be any critical threshold of radiation exposure as a risk factor for thyroid cancer.

Family history of thyroid cancer in a first-degree relative may increase one's risk of nonmedullary thyroid cancer by as much as 5-fold;[13, 23] inherited genetic syndromes may increase one's risk of thyroid cancer 10-fold.[24] The prevalence of persons with a family history of thyroid cancer is unknown. Most inherited genetic syndromes are rare. Familial adenomatous polyposis occurs in 1 per 10,000 to 15,000 persons, multiple endocrine neoplasia type 2 occurs in 1 per 30,000 to 50,000 persons, and Carney complex and Cowden syndrome are even rarer. Persons with familial adenomatous polyposis may be recommended for regular thyroid surveillance via palpation and/or ultrasound.[25] Persons with multiple endocrine neoplasia type 2 are recommended for prophylactic thyroidectomy because they have a 70 to 100 percent chance of developing medullary thyroid cancer during their lifetime.[26]

Natural History

The majority of cases of thyroid cancer have a very favorable natural history. However, if aggressive thyroid nodules are left untreated, they will grow over time, metastasize (most often to the lymph nodes and lungs), and can ultimately result in death.[27-29] The natural history varies by the three types of thyroid cancer: differentiated, medullary, and anaplastic.

The 10-year overall survival rates for papillary and follicular thyroid cancer are 93 and 85 percent, respectively, for all stages of the disease.[12] Approximately 12 percent of thyroid glands are found to be cancerous on autopsy, suggesting that a subset of differentiated cancer cases may be very slow growing and pose little to no risk to the patient.[30]

Historically, one of the most important prognostic factors for differentiated cancer is age older than 45 years.[10] Other important prognostic factors are larger tumor size and involvement of the lymph node.[28, 31, 32] Patients younger than age 45 years have a very low likelihood of dying of papillary or follicular cancer, which is classified as stage I or II depending only on whether there are distant metastases.[10] For patients older than age 45 years, staging for differentiated cancer also accounts for tumor size and lymph node metastases. Spread to lymph nodes in the neck is common for patients with papillary cancer, affecting approximately 50 to more than 75 percent of cases, but less common for patients with follicular cancer, affecting less than 10 percent of cases, as follicular cancer more commonly spreads to the lungs or bones.[33]

The 10-year survival rate for medullary thyroid cancer is 75 percent.[12] The primary feature of medullary cancer is the production of calcitonin, and levels of calcitonin production may be correlated with prognosis.[34, 35] The most important prognostic factors include age (patients age >40 or 45 years have poorer prognosis), disease stage (later-stage disease portends a worse outcome), and extent of surgery (patients with a lobectomy have a worse prognosis than those with a total thyroidectomy; the choice is often driven by whether metastatic disease exists).[16, 17, 36]

Anaplastic thyroid cancer is extremely rare but lethal. In 90 percent of incident cases, metastases to the lymph nodes or distant organs are present at the time of diagnosis.[37-39] Anaplastic thyroid cancer is highly aggressive and has a 1-year survival rate of only 20 percent.[12]

Screening

There are two primary methods to screen for thyroid cancer: 1) neck palpation during a physical examination, which can identify palpable nodules, and 2) ultrasound, which can identify both palpable and nonpalpable nodules, especially those smaller than 1 cm. Ultrasound can also identify characteristics of a thyroid nodule that help predict whether a nodule is benign or malignant.[40] Screening with both palpation and ultrasound can also identify abnormal cervical lymph nodes that may represent metastatic thyroid cancer. Screening for thyroid cancer could result in early detection of malignant thyroid nodules that are easily treatable, before the cancer spreads beyond the thyroid gland. Early detection could make treatment more effective, with potentially less harm than if administered later. Potential harms of screening include false-positive results, which may lead to unnecessary diagnostic tests. Screening may also result in overdiagnosis because it can detect very small and/or indolent tumors that might never affect a person's morbidity or mortality.[41, 42] Overdiagnosis might also lead to overtreatment.[43]

Diagnostic workup of a thyroid nodule typically includes measurement of serum thyroid-stimulating hormone and diagnostic ultrasound of the thyroid and neck (i.e., cervical lymph nodes).[5] Depending on the results of initial testing, additional laboratory testing and imaging may be conducted. Fine-needle aspiration (FNA), with or without ultrasound guidance, is the procedure of choice when evaluating thyroid nodules to obtain cytology. The American Thyroid Association (ATA) recommends FNA for nodules larger than 1 cm with intermediate or highly suspicious ultrasound features and for nodules larger than 1.5 cm with mildly suspicious ultrasound features. The ATA defines high, intermediate, and mild suspicion as follows:[5]

- High suspicion (malignancy risk of 70% to 90%): solid hypoechoic nodule(s) or solid hypoechoic component in partially cystic nodule(s), with at least one of the following features:
    - Irregular margins
    - Microcalcifications
    - Taller than wide shape
    - Disrupted rim calcifications, with a small extrusive hypoechoic soft-tissue component
    - Evidence of extrathyroidal extension
- Intermediate suspicion (malignancy risk of 10% to 20%): hypoechoic solid nodule(s) with smooth margins but without:
    - Microcalcifications
    - Extrathyroidal extension
    - Taller than wide shape
- Low suspicion (malignancy risk of 5% to 10%): isoechoic or hyperechoic solid nodule(s), or partially cystic nodule(s) with eccentric uniformly solid areas but without:
    - Microcalcifications
    - Irregular margin
    - Extrathyroidal extension
    - Taller than wide shape

FNA cytology, using the Bethesda System for Reporting Thyroid Cytopathology, can be classified as: 1) nondiagnostic/unsatisfactory, 2) benign, 3) atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), 4) follicular neoplasm or suspicious for follicular neoplasm, 5) suspicious for malignancy, or 6) malignant.[44] ATA guidelines recommend that persons with nondiagnostic cytology have repeat FNA with ultrasound guidance. Depending on the ultrasound characteristics, persons with indeterminate results (i.e., AUS/FLUS) may undergo additional testing (e.g., molecular testing, repeat FNA) before diagnostic surgery is pursued. Persons with nodules with malignant or suspicious cytology features generally proceed to surgery. Given the low-false negative rate of ultrasound-guided FNA, persons with nodules with a highly suspicious ultrasound pattern and benign FNA cytology are recommended to have repeat ultrasound with FNA in 12 months, whereas those with an intermediately suspicious ultrasound pattern are recommended to have repeat ultrasound in 12 to 24 months.[5]

Treatment

Surgery is the main form of treatment for thyroid cancer. The type of surgery depends largely on what proportion of the thyroid gland is involved. Surgical options include total thyroidectomy or partial thyroidectomy (the latter is also known as a lobectomy). A partial thyroidectomy may be sufficient as the initial treatment for low-risk differentiated thyroid cancer, and is recommended if surgery is chosen for low-risk papillary microcarcinoma restricted to one lobe of the thyroid.[5] Complete thyroidectomy (removal of the entire thyroid gland following initial lobectomy) may be performed for patients whose final pathology result comes back as malignant and for whom this diagnosis was not known or suspected preoperatively. Lymphadenectomy (lymph node dissection) may be done to remove lymph nodes that may have signs of thyroid cancer involvement (local lymph node metastasis). Preoperative neck ultrasound for cervical lymph nodes and FNA of sonographically suspicious lymph nodes are recommended to determine the need for therapeutic lymph node dissection.[5] The ATA recommends consideration of prophylactic lymph node dissection for clinically advanced papillary thyroid cancer without known nodal involvement, but this recommendation is based on low-quality evidence.[5] The most common permanent serious surgical harms from thyroidectomy, with or without lymph node dissection, include hypoparathyroidism (hypocalcemia) and recurrent laryngeal nerve palsy (vocal cord paralysis).

Additional treatment recommendations generally differ by postoperative disease status, tumor stage, and type of thyroid cancer. RAI is taken orally and absorbed by the thyroid. Postoperative RAI may be used for remnant ablation to destroy any normal remnant thyroid tissue or microscopic foci of cancer that may remain after surgery, which facilitates detection of recurrent disease during followup. RAI may also be used at higher therapeutic doses as adjuvant therapy to treat residual local cancer or metastatic spread outside the neck to improve the disease-free survival or disease recurrence rate in higher-risk patients.[5] The administered activity (dose) for ablation is lower than that for therapy. RAI is not routinely recommended for patients with low-risk differentiated thyroid cancer due to its adverse effects on, for example, salivary and gonadal function, as well as possible increased risk of second primary malignancies.[45, 46] However, RAI is routinely recommended for high-risk patients (the ATA defines “high risk” as macroscopic invasion of tumor into the perithyroidal soft tissues; incomplete tumor resection; distant metastases; postoperative serum thyroglobulin level suggestive of distant metastases; pathologic N1 disease with any metastatic lymph node ≥3 cm; or follicular thyroid cancer with extensive vascular invasion).[5, 45, 46]

External-beam radiation therapy and chemotherapy are not typically used in persons with differentiated thyroid cancer unless they have late-stage disease (stage III or IV) that did not respond to RAI therapy. Radiation therapy and chemotherapy are more commonly administered to patients with anaplastic thyroid cancer.

Current Clinical Practice

We are unaware of any professional medical society that recommends population-based screening for thyroid cancer. Although 2015 ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer do not address population-based screening, they do state that there is insufficient evidence to support screening in persons with a family history of follicular cell–derived, differentiated thyroid cancer.[5] To date, South Korea appears to be the only country in the world that regularly practices asymptomatic thyroid cancer screening using ultrasound; this practice happened opportunistically as an "add-on" option for persons undergoing sanctioned screening through an organized cancer screening program initiated in 1999.[47]

Previous U.S. Preventive Services Task Force Recommendation

In 1996, the U.S. Preventive Services Task Force (USPSTF) stated that screening asymptomatic adults or children for thyroid cancer by neck palpation or ultrasound is not recommended ("D" recommendation). It found a lack of evidence that early detection of thyroid cancer improves outcomes and noted that neck palpation had poor sensitivity for detecting lesions, which contributed to a large number of false-positive results and resulted in unnecessary invasive testing. However, for asymptomatic persons with a history of external upper body irradiation in infancy or childhood, the USPSTF had a separate recommendation ("C" recommendation): although it found that there is insufficient evidence to recommend for or against screening in these high-risk persons, recommendations for periodic palpation can be made on other grounds, including patient preference or anxiety regarding increased risk. Insufficient evidence would likely have resulted in an "I" statement using modern grading methods.

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this evidence review to update its 1996 recommendation regarding the effectiveness of thyroid cancer screening in average- and high-risk adults. This review addresses the benefit and harms associated with thyroid cancer screening and treatment of early-stage thyroid cancer.

Analytic Framework and Key Questions

We developed an analytic framework with five Key Questions (KQs) based on the previous review and a scan of research conducted since the previous review (**Figure 1**).

1. Compared with not screening, does screening adults for thyroid cancer lead to a reduced risk of thyroid-specific mortality or morbidity, reduced all-cause mortality, and/or improved quality of life?
2. What are the test performance characteristics of screening tests for detecting malignant thyroid nodules in adults?
3. What are the harms of screening for thyroid cancer in adults?
4. Does treatment of screen-detected thyroid cancer reduce thyroid-specific mortality or morbidity, reduce all-cause mortality, and/or improve quality of life?
5. What are the harms of treating screen-detected thyroid cancer?

Data Sources and Searches

We worked with a research librarian to develop our search strategy, which was peer reviewed by a second research librarian. We searched Ovid® MEDLINE, the Cochrane Central Register of Controlled Trials, and the publisher supplied segment of PubMed to locate relevant studies for all KQs. We searched for articles published from January 1966 to January 2016. The search strategy is included in **Appendix A Table 1**. We supplemented our database searches by reviewing reference lists from recent and relevant systematic reviews. We also searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform for relevant ongoing trials (**Appendix B**).

Study Selection

Two reviewers independently reviewed 10,424 titles and abstracts, using an online platform (Abstrackr[91]), and 707 articles (**Appendix A Figure 1**) against specified inclusion criteria (**Appendix A Table 1**). We resolved discrepancies through consensus and consultation with a third investigator. We excluded articles that did not meet inclusion criteria or those we rated as poor quality. **Appendix C** lists all excluded trials.

For the screening questions (KQs 1–3), we included any studies of asymptomatic adult populations, either at general risk (e.g., unselected) or with prior personal history of radiation exposure. We excluded populations that were selected based on very high radiation exposure due to environmental disasters, inherited genetic syndromes associated with a high risk for developing thyroid cancer, or a personal history of thyroid cancer. We included any screening studies evaluating palpation, ultrasound, or both. Diagnostic accuracy studies of palpation or ultrasound had to include a reference standard (i.e., ultrasound for detection of nodules on palpation, histopathology results from FNA or surgery for detection of cancer on ultrasound). We required diagnostic accuracy studies to apply the chosen reference standard to both screen-positive and screen-negative persons (e.g., all or a random subset of screen-negative persons). Given the limited number of diagnostic accuracy studies, we also included screening studies that described the yield of cases of thyroid cancer. We excluded diagnostic procedures that included enhanced ultrasound-based techniques (e.g., elastography) or FNA. For screening effectiveness (KQ 1), we included any patient health outcome of reduced morbidity or mortality associated with thyroid cancer. For test performance (KQ 2), we included cancer detection rates and measures of diagnostic accuracy (e.g., sensitivity, specificity, positive and negative predictive values). For harms of screening (KQ 3), we included direct harms of palpation and ultrasound, subsequent harms of diagnostic FNA, and measures of overdiagnosis. For overdiagnosis, we looked for studies that compared screened versus unscreened groups. Studies that examined the rising incidence of thyroid cancer over time, the incidence and natural history of thyroid nodules and cancer, and autopsy studies were not included but are summarized in the Discussion section.

For treatment questions (KQs 4, 5), we included any studies of surgery (i.e., complete thyroidectomy, near-total thyroidectomy, lobectomy), with or without lymph node dissection or RAI ablation. We excluded studies of chemotherapy, external-beam radiation therapy, and other nonsurgical ablative treatments other than RAI. To approximate the treatment of screen-detected cancer, we excluded treatment studies among persons with metastatic disease or anaplastic thyroid cancer. We excluded surgical studies for thyroid conditions other than cancer (e.g., multinodular goiter, thyroiditis). For treatment benefit (KQ 4), we required studies to have a control group (e.g., untreated, surveillance, delayed treatment). The most commonly excluded study designs were comparative effectiveness trials or observational studies comparing one active treatment versus another (e.g., thyroidectomy vs. thyroidectomy plus lymph node dissection, robotic vs. conventional surgery). To assess the benefit of treatment, we considered the patient health outcomes of recurrence, mortality, and quality of life. For treatment harms (KQ 5), we did not require a control group for direct procedural harms (e.g., hypoparathyroidism, recurrent laryngeal nerve palsy) but did for other types of harms (e.g., second primary malignancies from RAI). The evolution of standard of care for the diagnostic workup (e.g., use of ultrasound-guided FNA) and treatment of thyroid cancer over time has resulted in a change in the case mix of patients having surgery, lymph node dissection, and/or RAI, as well as improvements in surgical techniques and RAI administered activity (doses) over time. To identify the most applicable evidence, we excluded studies conducted prior to 1990 and single-surgeon case series. We also excluded transient harms and surrogate measures (e.g., luteinizing hormone/follicle-stimulating hormone, salivary markers).

For the greatest applicability to U.S. practice, we focused on studies conducted in developed countries ("very high" development according to the United Nations Human Development

Index).[48] Because of resource constraints, we included only studies that published their results in English.

Quality Assessment and Data Abstraction

At least two reviewers critically appraised all articles that met the inclusion criteria based on the USPSTF's design-specific quality criteria (**Appendix A Table 3**).[49] We supplemented these criteria with the Newcastle-Ottawa Scale for cohort and case-control studies[50] and Quality Assessment of Diagnostic Accuracy Studies I and II for studies of diagnostic accuracy[51, 52] (**Appendix A Table 3**). We rated articles as good, fair, or poor quality. In general, a good-quality study met all criteria. A fair-quality study did not meet, or it was unclear if it met, at least one criterion but had no known important limitations that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations. The most common fatal flaw for diagnostic studies included application of the reference standard to only those participants who screened positive (verification bias), because when missing data are not random or selective, analysis will generate biased estimates of diagnostic accuracy and generally lead to overestimation of both sensitivity and specificity. We also excluded diagnostic studies if they did not describe the followup of screen-negative persons. We excluded poor-quality studies from this review. Disagreements about critical appraisal were resolved by consensus and, if needed, in consultation with a third independent reviewer.

One reviewer extracted key elements of included studies into standardized evidence tables in Microsoft Excel® (Microsoft Corp., Redmond, WA). A second reviewer checked the data for accuracy. Evidence tables were tailored for each KQ and to specific study designs. Tables generally included details on study design and quality, setting and population (e.g., country, inclusion criteria, age, sex, race/ethnicity, risk factors for thyroid cancer), screening and treatment details, reference standard or comparator details (if applicable), length of followup, and outcomes (e.g., cancer yield, diagnostic accuracy, harms).

Data Synthesis

We synthesized results by KQ. We used a standardized summary of evidence table to summarize the overall strength of evidence for each KQ. This table included the number and design of included studies, summary of results, consistency or precision of results, reporting bias, summary of study quality, limitations of the body of evidence, and applicability of the findings.

Because of the limited number of studies and the clinical heterogeneity of the studies, we provided a narrative synthesis of results and used summary tables to allow for comparisons across different studies. For screening test performance (KQ 2) of palpation or ultrasound, we prioritized diagnostic accuracy (e.g., sensitivity, specificity) over yield (e.g., cancer incidence) outcomes. For harms of treatment (KQ 5), we stratified results by type of treatment (i.e., type of surgery, RAI). When possible, we conducted quantitative analyses for serious harms, including permanent hypoparathyroidism and permanent recurrent laryngeal nerve palsy. Quantitative analyses were not performed for other serious adverse events, as they were not commonly or consistently reported or defined.

For quantitative analyses, we used random-effects models to estimate rates of serious adverse events. We applied the restricted maximum likelihood estimation method to estimate 95 percent CIs. In subgroup analysis, when the number of studies was less than five, we used the fixed-effects model for the analysis. Analyses were performed using R version 3.2.2 (The R Project for Statistical Computing, Vienna, Austria). We visually inspected plots stratified or ordered by key study characteristics accounting for clinical heterogeneity among studies to see if these characteristics affected rates of surgical complications. Key study characteristics included the type of surgery (e.g., partial thyroidectomy, total thyroidectomy, with or without lymph node dissection, type of lymph node dissection), case mix of patients (e.g., histology of thyroid cancer, average tumor size, average age), setting (e.g., country, year), and type and definition of outcome (e.g., criteria for permanent adverse effect). We were not able to evaluate if study quality (all were fair quality) or surgical experience (experience and surgical volume were not reported in individual studies) affected rates of surgical complications. If mean tumor size was not reported in a study, we calculated the weighted mean tumor size by reported T stage category or tumor size category (if either was available). We assumed that T stage categories were equivalent to the following mean tumor sizes: T1=1.0 cm, T2=3.0 cm, and T3=5.0 cm. To calculate weighted means using tumor size categories that had been chosen by the study authors, we used the sum of the percentage of subjects in each category and multiplied it by the midpoint of each category. The proportion of subjects with advanced disease was based on the highest proportion of study subjects in one of the following categories: stage III–IV, T3–T4, lymph node involvement, or metastasis. We also examined whether pooled effects were biased due to small, imprecise studies having larger than expected effect sizes. We performed tests of publication bias that examined whether the distribution of the effect sizes was symmetric with respect to effect precision using funnel plots and Egger's linear regression method.

Expert Review and Public Comment

A draft research plan that included the analytic framework, KQs, and inclusion criteria was available for public comment in January 2015. We made no substantive changes to our review methods based on the comments received. A draft version of this report was reviewed by invited content experts and federal partners listed in the acknowledgements. Comments received during this process were presented to the USPSTF during its deliberation of the evidence and, subsequently, as appropriate, addressed in the final version of the report. Additionally, a draft of the full report was posed on the USPSTF Web site from November 22, 2016 through December 26, 2016. There were no changes made to the report based on these comments.

USPSTF Involvement

We worked with four USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and KQs and to resolve issues regarding the scope of the final evidence review. This research was funded by the Agency for Healthcare Research and Quality under a contract to support the work of the USPSTF. Agency staff provided oversight for the project, assisted in external review of the draft report, and reviewed the draft report.

Chapter 3. Results

KQ 1. Compared With Not Screening, Does Screening Adults for Thyroid Cancer Lead to a Reduced Risk of Thyroid-Specific Mortality or Morbidity, Reduced All-Cause Mortality, and/or Improved Quality of Life?

We found no studies that met our inclusion criteria for KQ 1. We found no randomized, controlled trials (RCTs) or controlled clinical trials that evaluated the effects of thyroid cancer screening on patient morbidity or mortality compared with no screening. Two cohort studies that compared screened individuals versus a comparator group did not meet our inclusion criteria for KQ 1. One study (n=4,296) of high-risk persons who were previously exposed to radiation was not included because screening was conducted with older technology (i.e., a thyroid scan using ^{99m}Tc-pertechnetate and a pinhole collimator), and it used a historical control as the comparator group.[53] One large Japanese cohort study (n=152,651) was excluded because the comparator group consisted of persons who presented with symptoms.[54]

KQ 2. What Are the Test Performance Characteristics of Screening Tests for Detecting Malignant Thyroid Nodules in Adults?

Ten fair-quality studies met our inclusion criteria for KQ 2 (**Table 1**). Two studies reported on diagnostic accuracy of palpation to detect nodules,[55, 56] two on diagnostic accuracy of ultrasound to detect cancer,[57, 58] four on cancer yield from screening using palpation plus followup ultrasound,[54-56, 59] four on cancer yield from screening using ultrasound only,[57, 58, 60, 61] and two older studies on cancer yield from screening adults with a history of childhood irradiation.[62, 63]

Evidence to inform the true diagnostic accuracy of screening using neck palpation or ultrasound to detect thyroid cancer is limited. In two studies in Finland (n=354) using a single examiner, neck palpation was not sensitive enough to detect thyroid nodules.[55, 56] On the basis of results of two methodologically limited studies conducted in South Korea (n=243), using selected sonographic features when screening with ultrasound can be specific for detecting thyroid malignancy;[57, 58] one of these studies suggested that a combination of high-risk sonographic features, such as presence of microcalcifications or irregular shape, can optimize both sensitivity and specificity. Among studies that provided the screening yield, ultrasound-based screening detected a greater proportion of cancer cases than did palpation. The clinical significance (i.e., morbidity and mortality) of cancer detected through either screening method is unknown.

Diagnostic Accuracy of Palpation to Detect Thyroid Nodules

Two fair-quality prospective studies, both included in the previous review, examined the accuracy of neck palpation to detect thyroid nodules.[55, 56] These two studies (n=354) were conducted by the same investigator in Finland in the late 1980s. Both studies used a single examiner to screen persons with neck palpation, which was immediately followed by ultrasound as the reference standard. However, only one study reported the diagnostic accuracy of palpation for all screened persons (regardless of the ultrasound results).[55] In that study, screening by neck palpation was conducted among 253 randomly selected persons ages 20 to 49 years from the community. An abnormal result from neck palpation (i.e., thyroid nodule or diffuse enlargement of the thyroid) was found in 5.1 percent of subjects, whereas an abnormal result from ultrasound was found in 27.3 percent. The sensitivity and specificity of palpation to detect thyroid nodules (size not reported) were 11.6 (95% CI, 5.1 to 21.6) and 97.3 percent (95% CI, 93.8 to 99.1), respectively.[55] In the other study, screening for thyroid nodules by neck palpation was conducted by a single examiner among 101 women ages 49 to 58 years who attended a mammogram screening program.[56] The palpation results were reported for the 36 patients with abnormal ultrasound results. The sensitivity of palpation to detect nodules in persons with an abnormal ultrasound result was 27.8 percent. In this study, a second examiner palpated a subset of persons and examination findings were concordant with those of the first examiner in 18 of the 25 cases.

Limitations

Both studies are fair-quality prospective studies. However, these older, single-examiner studies were conducted outside the United States, and only one reported results for all persons who underwent examination of the thyroid by palpation. In addition, the number of participants in both studies was relatively small, and no cancer was detected.

Diagnostic Accuracy of Screening Ultrasound to Detect Thyroid Cancer

The vast majority of studies that examined the diagnostic accuracy of ultrasound to detect thyroid cancer were not (or were not reported to be) conducted in screening populations. These studies were therefore not included for KQ 2 but are summarized in the Discussion section. We identified two fair-quality studies that examined the diagnostic accuracy of screening ultrasound to detect thyroid cancer, neither of which was included in the previous review.[57, 58] Both studies (n=243) were conducted by the same investigators in South Korea from 2004 to 2007 but had different study designs.

The better quality study prospectively examined the diagnostic accuracy of screening for thyroid cancer by ultrasound in 113 of 2,079 screened women ages 15 to 77 years who attended a breast ultrasound clinic.[57] Seventy-seven of the screened women (3.7%) revealed one or more malignant sonographic characteristics (e.g., presence of microcalcifications, irregular shape, ill-defined or microlobulated margin, marked hypoechogenecity, orientation of taller than wide). These 77 women and a small, nonrandomly selected subset of 36 screened women with probable benign ultrasound findings underwent ultrasound-guided FNA and either surgical confirmation or clinical followup at 2 years (depending on the FNA results). Among these 113 women who underwent FNA, 53 women were diagnosed with papillary thyroid cancer. The sensitivity and specificity of having one or more malignant features on screening ultrasound were 94.3 (95% CI, 84.3 to 98.8) and 55.0 percent (95% CI, 41.6 to 67.9), respectively (**Table 2**). Most screened women, however, did not undergo any further followup, including 756 women whose ultrasound results revealed a nonsuspicious nodule or other abnormalities and 1,209 women whose results showed normal-appearing glands.

The other study was a retrospective analysis of 130 individuals from a series of 16,352 asymptomatic persons who referred themselves to thyroid cancer screening.[58] A total of 1,009 screened persons had a sonographic lesion with one or more malignant features and were followed up with FNA. Malignant sonographic characteristics were defined as presence of microcalcifications, marked hypoechogenicity, well-defined spiculated margins, or solid rather than cystic nodule. The study sample included 58 of 150 lesions classified as malignant (all papillary thyroid cancer) and 82 of 823 lesions classified as benign by FNA results, for a total of 140 nodules in 130 persons. The 352 lesions with indeterminate or nondiagnostic FNA results were excluded from further analysis. The malignant lesions were diagnostically confirmed after surgical pathology, and the included benign lesions were all followed and confirmed to have no change in size by ultrasound or repeat FNA after at least 2 years. Among these 140 nodules, the sensitivity and specificity of having two or more malignant features on screening ultrasound were 94.8 and 86.6 percent, respectively (95% CI values could not be calculated) (**Table 2**). The authors found that the solid sonographic characteristic was sensitive (93.1%) but not specific (51.2%) for detecting malignancy, as opposed to other sonographic characteristics (i.e., microcalcifications, marked hypoechogenecity, and spiculated margins) that were specific, but less sensitive, for detecting malignancy. A total of 15,343 persons with no lesions or benign-appearing lesions had no followup after the initial screening with ultrasound.

Limitations

Both of these studies were fair-quality diagnostic accuracy studies conducted outside the United States. Both studies reported accuracy only among patients who had at least one study-defined malignant ultrasound characteristic and did not follow up on the vast majority (n=18,188) of screened individuals without these characteristics. Due to this study design, the potential amount of false-negative cases is generally unknown and estimates of sensitivity are likely overestimated. Despite the inherent limitations of the study design, we included these studies because they represent the only evidence of the accuracy of screening ultrasound in explicitly asymptomatic populations.

Yield of Screening for Thyroid Cancer

We found 10 studies that reported the yield of thyroid cancer cases from screening: four from palpation plus followup ultrasound,[54-56, 59] four from ultrasound only,[57, 58, 60, 61] and two older studies from palpation plus followup thyroid imaging using iodine or technetium in adults with a history of childhood irradiation[63, 64] (**Table 3**). Four fair-quality studies, two in Japan (n=199,084) and two in Finland (n=352), reported the yield of thyroid cancer cases from screening palpation followed by ultrasound (if applicable) from 1980 to 2005.[54-56, 59] Overall, from 0 to 4.3 thyroid cancer cases were detected per 1,000 persons, and 90 percent of cases (372/415) were revealed to be papillary thyroid cancer. Three fair-quality prospective studies and one fair-quality retrospective study (n=20,521) on ultrasound screening for thyroid cancer were conducted in South Korea from 1997 to 2007,[57, 58, 60, 61] three of which were exclusively among women who presented for breast cancer screening or followup.[57, 60, 61] In these four studies, 9.2 to

30.3 thyroid cancer cases were detected per 1,000 persons, and all but one case was diagnosed as papillary thyroid cancer. Studies were inconsistent in whether they reported the size and stage of screen-detected cancer. One study reported that 43 percent of ultrasound screen-detected patients had extrathyroidal extension.[61] All four studies reported that 33 to 63 percent of patients with screen-detected thyroid cancer had lymph node metastases, with the highest percent detected by palpation and the lowest percent detected by ultrasound.[54, 59-61]

Two fair-quality prospective studies, one conducted in the United States (n=1,500) and the other in Israel (n=443), reported the yield of thyroid cancer in persons who had been treated with irradiation in childhood.[63, 64] Most of the subjects had been exposed to irradiation to the head and neck for benign conditions (which is no longer practiced). Initial screening in these two cohorts was by palpation; patients with palpable nodules then received thyroid imaging using iodine or technetium radioactive tracer with blood testing, including thyroid function tests. No cancer cases were detected in the smaller study, and 11.3 thyroid cancer cases per 1,000 persons were detected in the larger U.S. study. The histology of the cancer cases was not reported.

Limitations

The majority of these studies allow for calculation of cancer yield but not test performance. Across the studies, there was some variation in how cancer was identified and defined using histology from FNA, surgery, or both. Cancer yield varied by screening modality; however, differences in population characteristics (e.g., age, sex, personal history of irradiation) may have contributed to this variation.

KQ 3. What Are the Harms of Screening for Thyroid Cancer in Adults?

We found three studies that met our inclusion criteria for KQ 3 (**Table 4**). We found no studies that examined the harms of thyroid cancer screening with palpation or ultrasound and no studies that directly examined the effects of overdiagnosis in a screened versus unscreened group. A number of other study designs may indirectly inform the clinical importance and magnitude of overdiagnosis in thyroid cancer screening; these studies are summarized in the Discussion section of this report. Overall, there is very limited evidence to evaluate the potential harms of screening for thyroid cancer, including harms of diagnostic followup with FNA. One small U.S. study found that about a quarter of persons who had undergone FNA of a thyroid nodule did not meet the Society of Radiologists in Ultrasound (SRU) recommendation for FNA.[65] Nonetheless, we found no evidence to suggest serious harms to patients from ultrasound-guided FNA.

Two fair-quality retrospective studies evaluated the harms of FNA of thyroid nodules.[66, 67] One large study at an institution in Japan reported the number of cases of needle tract implantation of papillary thyroid cancer from FNA.[66] This study found 7 cases of tumor on the line of needle insertion in a total of 4,912 persons who had undergone ultrasound-guided FNA from 1990 to 2002. Subjects with needle tract implantation were older (age ≥50 years) and had a high incidence of poorly differentiated cancer and extrathyroidal extension of the tumor. It is unclear what effect, if any, this complication had on patient morbidity or mortality. A second study at a single institution in the United States evaluated if bleeding complications due to FNA were related to antiplatelet or anticoagulant therapy in a cohort of 582 patients.[67] About a quarter of the patients were taking antiplatelet or anticoagulant medications; five of them developed a hematoma after ultrasound-guided FNA, as detected by "immediate" postprocedural ultrasound. There was no statistically significant difference in the incidence of hematoma between persons taking or not taking antiplatelet or anticoagulant medications, albeit the number of outcomes was small. This study found no major bleeding complications (e.g., bleeding requiring hospitalization) in the cohort who had undergone ultrasound-guided FNA for a thyroid mass.

Another fair-quality retrospective study was designed to determine the proportion of FNAs of thyroid nodules that did not meet clinical guideline recommendations and therefore would be considered "unnecessary" diagnostic workup.[65] This U.S. study included 400 consecutive subjects with thyroid nodules who subsequently received ultrasound-guided FNA at a single institution. Ninety-six (24%) subjects had FNA of a nodule that did not meet the SRU recommendation published in 2005.[68] The SRU recommends FNA for nodules that have a maximum diameter of 1.0 cm or larger and have microcalcifications, nodules 1.5 cm or larger and are solid or have coarse calcifications, nodules 2.0 cm or larger and are mixed solid and cystic, and nodules with substantial growth since a prior assessment using ultrasound.

Limitations

Although they met our review's inclusion criteria, these fair-quality retrospective studies did not report serious harms to patients (e.g., health outcomes resulting from needle tract implantation, hematoma, or "overuse" of FNA). The SRU recommendation varies slightly from the most recent guidelines set by the ATA. It is unclear what proportion of FNAs would be considered "unnecessary" using the ATA's current recommendations.

KQ 4. Does Treatment of Screen-Detected Thyroid Cancer Reduce Thyroid-Specific Mortality or Morbidity, Reduce All-Cause Mortality, and/or Improve Quality of Life?

We found two unique studies (reported in five articles)[69-73] that met our inclusion criteria for KQ 4 (**Table 5**). We found no trials designed to evaluate if earlier treatment or treatment of screen-detected, well-differentiated thyroid cancer results in better patient outcomes compared with observation (i.e., delayed treatment) or treatment of symptomatic, well-differentiated thyroid cancer. Due to major limitations in the study designs (e.g., lack of adjustment for confounders), it is uncertain if earlier or immediate treatment versus delayed or no surgical treatment improves patient outcomes for papillary carcinoma or papillary microcarcinoma.

One fair-quality retrospective observational study using SEER data from 1973 to 2005 compared survival rates of persons treated versus not treated for papillary thyroid cancer.[69] Treatment included partial or total thyroidectomy, with or without postoperative RAI ablation. In total, 35,663 persons were analyzed; only 440 (1.2%) had not been treated. Compared with treated patients, untreated patients were older (mean age, 51 vs. 46 years), had a shorter length of followup (mean, 5.9 vs. 7.6 years), had more missing data on tumor size (46% vs. 16% undocumented size), and had a smaller proportion of small tumors (≤1 cm) (13% vs. 40%). Overall, untreated persons had a slightly worse 20-year survival rate compared with treated persons (97% vs. 99%; p<0.001). These results were not adjusted for age, sex, tumor size, or any other potential confounders between treated and untreated persons, which limited our ability to compare the effect of treatment (vs. a case mix of patients) on patient outcomes. In a subgroup analysis limited to the 381 untreated patients from 1983 to 2005, patients who were recommended for treatment had a slightly lower 10-year survival rate than those who were not recommended for treatment (98.1% vs. 99.3%; p<0.001). In comparison, treated patients had a 10-year survival rate of 99.5 percent. Survival rates were not adjusted for other important confounders.

One fair-quality prospective study (reported in four separate articles) in Japan conducted from 1993 to 2013 examined the recurrence of disease in and the survival rate of persons with papillary microcarcinoma who opted for immediate surgery versus observation or active surveillance.[70-73] From 1993 to 2004, 1,395 persons were analyzed, 340 of whom opted for observation with ultrasound once or twice per year.[70] Thirty-two percent (n=109) of those who opted for observation ultimately had surgery. After approximately 6 years of followup, two persons in the immediate surgery group and no persons in the observation group had died. Three percent (32/1,055) of subjects in the immediate surgery group experienced disease recurrence, and no subjects in the observation group developed distant metastases. An additional 2,153 persons were diagnosed with papillary microcarcinoma from 2005 to 2013, 1,179 of whom opted for active surveillance and 974 of whom opted for immediate surgery.[73] Only 8 percent (n=94) of those who opted for observation ultimately had surgery. After approximately 4 years of followup, no patients in either group developed distant metastases or died from thyroid cancer. Again, patients self-selected into one of two groups; therefore, the observation group had several statistically significant differences compared with the immediate surgery group at baseline, and outcomes were not adjusted for any confounders.

Limitations

Although these fair-quality observational studies met our review's inclusion criteria, neither was adequately designed to evaluate the benefit of early surgical treatment versus observation (i.e., delayed or no surgery). Both studies had minimal or no adjustment for potential confounders that could have affected the decision for treatment versus observation of thyroid cancer.

KQ 5. What Are the Harms of Treating Screen-Detected Thyroid Cancer?

Fifty-two studies met our inclusion criteria for KQ 5. Thirty-six studies reported on surgical harms (i.e., total or partial thyroidectomy [including lobectomy], with or without lymph node dissection) (**Table 6**) and 16 studies reported on RAI harms (**Table 7**). Due to changes in the dose of RAI and the case mix of persons receiving RAI over time, we excluded older studies that addressed the long-term sequelae of RAI but summarize these studies in the Discussion section of this report. Overall, permanent surgical harms, hypoparathyroidism, and recurrent laryngeal nerve palsy are not uncommon. The rate of permanent hypoparathyroidism varies widely; best estimates are from 2 to 6 events per 100 thyroidectomies and are more variable with lymph node dissection. The rate of permanent recurrent laryngeal nerve palsy is less variable and estimated at 1 or 2 events per 100 surgeries (including with lymph node dissection). Other serious surgical harms include death, adverse cardiopulmonary events, airway injury, wound complications, and infection. Having thyroid cancer is associated with an increased risk of second primary malignancies; however, best evidence suggests that treatment of differentiated thyroid cancer with RAI is independently associated with a small increase in second primary malignancies, although differences in study designs and variable reporting on radiation doses limit our understanding of the magnitude and precision of this small excess risk. Nonetheless, studies demonstrate that common clinically used doses of RAI are associated with an increased risk of both second solid and hematologic malignancies. RAI treatment is also associated with increased permanent adverse effects to the salivary gland, such as dry mouth.

Surgical Harms

We found 36 studies that reported surgical harms, 32 studies of permanent hypoparathyroidism (hypocalcemia),[73-104] 28 studies of permanent recurrent laryngeal nerve palsy (vocal cord paralysis),[73, 74, 76, 78-84, 86-103, 105, 106] two studies of surgical mortality,[107, 108] and 15 studies of other major surgical harms[73, 78, 79, 82, 85, 86, 88, 98-100, 102, 103, 107-109] (**Table 8**).

Studies reporting permanent or serious surgical harms were quite varied. The majority of studies were retrospective observational studies, although we also included three trials.[77, 88, 94] Cohort size ranged from 76 to 13,854 persons. Only seven studies were conducted in the United States.[92, 96, 99, 101, 105, 107, 108] Most of the studies included persons who had undergone surgery for thyroid cancer in the 1990s and 2000s. The average age of subjects was in the mid-40s to early 50s, with a predominance of women. The main surgeries evaluated were total or partial thyroidectomy, with or without lymph node dissection. Two studies reported surgical harms from partial thyroidectomy alone.[75, 81] Lymph node dissection could be unilateral, bilateral, or not specified, as well as prophylactic, therapeutic, or not specified. Overall, there were 64 study arms in 36 studies. There was some variation in how permanent harm was defined, but it was generally defined as the adverse outcome persisting beyond 6 months.

Overall, there was large variation in the rate of permanent hypoparathyroidism due to total or partial thyroidectomy without lymph node dissection (15 study arms); the 95% CI of the pooled estimate ranged from 2 to 6 events per 100 surgeries (I^2=73%) (**Figure 2**). The rate of permanent hypoparathyroidism from thyroidectomy with lymph node dissection was even more varied (I^2=73%); the 95% CI for unilateral neck dissection (10 study arms) ranged from 1 to 4 events per 100 surgeries and, for bilateral neck dissection (9 study arms), from 1 to 10 events per 100 surgeries (I^2=91%) (**Figure 3**). Given the very high statistical heterogeneity, it may be misleading to quantitatively pool rates of hypoparathyroidism across studies. A study by Viola et al,[77] an outlier for hypoparathyroidism from total thyroidectomy with bilateral lymph node dissection, was an RCT that used the "most sensitive methods available" to determine hypocalcemia. However, other studies with comparatively high estimates of permanent hypoparathyroidism from lymph node dissection did not differ notably from the other included studies in study design, population, setting, tumor, intervention, or outcome characteristics.[83, 86,

[89] The rate of hypoparathyroidism did not seem to vary by year, setting, country, study-level proxy for more advanced tumors (average age, tumor size, histology), indication for lymph node dissection (prophylactic vs. therapeutic), or definition of "permanent" outcomes. In these pooled analyses, we excluded studies that did not distinguish between permanent and temporary harms. Both the funnel plots and Egger's test suggested biased estimates due to smaller studies. Smaller studies in general appeared to report fewer events.

In contrast, there was little variation in the rates of permanent recurrent laryngeal nerve palsy due to thyroidectomy, with or without lymph node dissection. The 95% CI for recurrent laryngeal nerve palsy from thyroidectomy without lymph node dissection (14 study arms) was 1 to 2 events per 100 surgeries (I^2=13%) (**Figure 4**). Estimates were similar for thyroidectomy with lymph node dissection (33 study arms) (**Figure 5**).

One fair-quality prospective study (n=2,153) by Oda et al[73] evaluated the differential surgical harms between persons who received immediate surgery (n=974) versus active surveillance (n=1,179) for papillary microcarcinoma. Persons who received active surveillance self-selected to be followed by serial neck ultrasound and laboratory testing. Ultimately, 94 of the 1,179 persons in the active surveillance group had surgery. Median followup was 47 months (range, 12 to 116 months). Permanent hypoparathyroidism was more common in the immediate surgery group (16/974) than in the active surveillance group (1/1,179) ($p<0.0001$). Recurrent laryngeal nerve palsy was uncommon and therefore not different between the two groups (2 vs. 0 events in the immediate surgery vs. active surveillance groups). The difference in surgical harms resulted from the lower number of persons in the active surveillance group going on to surgery.

Two fair-quality studies reported on surgical mortality.[107, 108] A large prospective observational cohort study in the United States of 5,584 persons with thyroid cancer who had undergone surgical treatment in 1996 found 15 deaths (0.3%) within 30 days, five of which were persons with undifferentiated or anaplastic cancer.[108] Surgical mortality did not differ by type of surgical procedure, albeit the number of deaths was too low to make any meaningful conclusions. In a large retrospective study in the United States of 13,854 persons with thyroid cancer who had undergone surgery in 1999 to 2003, the same-stay mortality rate was 0.2 percent among those who had undergone lobectomy (9/4,238 patients) and 0.1 percent among those who had undergone total thyroidectomy (12/9,616 patients) ($p=0.22$).[107] The study did not report mortality by type or stage of cancer. However, it did report other serious perioperative harms, including myocardial infarction, cerebrovascular accident, pulmonary embolus, pneumonia, airway injury (including tracheal injury), chyle leak, bleeding or hematoma requiring reoperation, and wound complications or infections. Because these harms were not consistently reported or defined, we do not discuss them further here.

Limitations

No studies reported serious adverse events not necessarily related to surgery (e.g., death, cardiopulmonary events) in an untreated control group. Clinical and statistical heterogeneity limited confidence in pooled estimates of permanent hypoparathyroidism. The studies did not allow us to evaluate if surgical experience or surgical volume influenced the rate of permanent surgical complications. Statistical tests for publication bias for pooled analyses of hypoparathyroidism suggested biased estimates due to small studies. Pooled estimates may underestimate complications of hypoparathyroidism.

RAI Harms

We found 16 studies that reported harms of RAI. Eight studies addressed the risk of second primary malignancies,[45, 110-116] six addressed permanent adverse effects on salivary glands,[117-122] one focused on hyperparathyroidism,[123] and one on reproductive harms[124] (**Table 9**).

Eight fair-quality retrospective studies (n=320,912) examined the incidence of second primary malignancies in persons with differentiated thyroid cancer being treated or not treated with RAI.[45, 110, 116] Three of the studies were conducted using SEER data, none of which reported the indication for, nor the dose of, radiation from RAI. The largest of these three studies (n=37,176) included persons with papillary thyroid cancer and used SEER data from 13 registries with data from 1973 to 2006.[45] Second primary malignancy was defined as a solid or hematologic cancer diagnosed more than 6 months after the index thyroid cancer was diagnosed. With an average of 11 years of followup (408,750 person-years), patients who received RAI experienced an excess absolute risk of 11.9 cancer cases per 10,000 person-years compared with a reference cohort. The standardized incidence ratio (SIR), the ratio of observed to expected second primary malignancies, was 1.18 (95% CI, 1.10 to 1.25) among persons who received RAI compared with a reference population of identical age, sex, race/ethnicity, and time. For persons who did not receive RAI, the SIR was 1.02 (95% CI, 0.98 to 1.06) compared with the same reference population. The second study (n=28,286) included persons with papillary or follicular thyroid cancer using SEER data from 1973 to 2002.[110] Second primary malignancy was defined as cancer diagnosed more than 2 months after the index thyroid cancer. With an average of 10 years of followup (292,490 person-years), patients who received RAI had an excess absolute risk of 13.3 cancer cases per 10,000 person-years compared with a reference cohort (the general U.S. population). The SIR for second primary malignancies at any site in persons who received RAI was 1.21 (95% CI, 1.12 to 1.31) compared with the general U.S. population. Among persons who did not receive RAI, the SIR was 1.05 (95% CI, 1.00 to 1.10) compared with the general U.S. population. The third SEER study (n=29,456) included persons with thyroid cancer of any histology diagnosed from 1973 to 2000.[116] Second primary malignancy was defined as any cancer diagnosed at least 2 months after the index thyroid cancer, which included newly diagnosed thyroid cancer. On average, there was about 8 years of followup (280,580 person-years). This study did not report the number of excess cancer cases by RAI exposure status. In a subgroup of persons from 1988 to 2000, the SIR for second primary malignancies at any site in those who received RAI was 1.14 (95% CI not reported) compared with a reference population of identical age, sex, race/ethnicity, and time. The SIR for second primary malignancies appeared to be similar in persons who did not receive RAI (1.19 [95% CI not reported]), although the statistical significance between groups was not reported. It is unclear what accounts for the difference in findings in this study compared with the previous two SEER studies. However, the primary aim of the study was not to determine the excess risk of second primary malignancy from RAI, and it differs from the other two SEER studies in three main ways: 1) it was not limited to papillary cancer, 2) it included thyroid cancer as a second primary malignancy, and 3) it had shorter followup for assessment of second primary malignancy.

Three smaller studies (n=4,273), from South Korea,[113] Finland,[112] and Hong Kong[111, 125] also examined the incidence of second primary malignancies in persons with differentiated thyroid cancer being treated or not treated with RAI. These studies generally reported the cumulative radiation doses in gigabecquerel (GBq) units (1 GBq=27.03 mCi). Radiation doses in clinical practice vary and generally correspond to the indication for RAI, such that lower doses (1.11 GBq) are used for ablation and higher doses (≤5.5 GBq) are used for adjuvant therapy for known or suspected residual disease.[5] The largest study (n=2,468) included persons with differentiated thyroid cancer with at least 1 year of followup after thyroidectomy at a national university hospital in South Korea from 1976 to 2010. Second primary malignancy was defined as a nonsynchronous, nonthyroidal malignancy diagnosed at least 12 months after the index thyroid cancer diagnosis or RAI treatment. With an average of 7 years of followup (total person-years not reported), patients who received the highest cumulative dose of RAI (≥37 GBq) had an excess risk of 101.4 cancer cases per 10,000 person-years compared with the general Korean population. The excess risk decreased with lower cumulative doses (22.3 to 36.9 GBq; 24.6 cancer cases per 10,000 person-years), and no excess risk was observed at cumulative doses below 22.2 GBq. The study from Finland (n=910) included persons treated for differentiated thyroid cancer at one of two university hospitals from 1981 to 2002. Cases were matched to five controls with no prior thyroid cancer (selected from a national population register) on age, sex, and place of residence. Second primary malignancy was defined as an invasive cancer diagnosed at least 12 months after the index thyroid cancer was diagnosed. With an average of 16 years of followup (14,104 person-years) for all cases, patients who received more than the median cumulative dose of RAI (>3.7 GBq) had an excess risk of 25.3 cancer cases per 10,000 person-years compared with the controls. However, persons who did not receive any RAI also had an excess risk of 29.2 cancer cases per 10,000 person-years compared with controls. The third study from Hong Kong (n=895) included persons with papillary or follicular thyroid cancer using data from a single hospital in Hong Kong from 1971 to 2009.[111] This study used the "standard" ablative dose (3 GBq), but higher doses were considered in the presence of more extensive disease. Second primary malignancy was defined as cancer diagnosed more than 12 months after diagnosis of the index thyroid cancer. With an average of 7.8 years of followup, 8.7 percent of patients who received RAI developed a second primary malignancy versus 3.2 percent of patients who did not receive RAI (p=0.004).

Two additional studies examined the incidence of specific subtypes of second primary malignancies—breast[114] and leukemia[115] diagnoses—in persons with thyroid cancer. The study examining the risk of developing breast cancer (n=10,361) included persons with thyroid cancer of any histology from Taiwan who were diagnosed from 2000 to 2008.[114] Cases were frequency matched to four controls each from national health insurance data based on year of index diagnosis and age. Breast cancer outcomes were included if they were diagnosed after the thyroid index date or completion of RAI treatment, if RAI was received. With a median 6.5 years of followup (69,554 person-years), the excess risk of breast cancer among persons who received a cumulative RAI dose greater than 4.44 GBq was 2.7 cancer cases per 10,000 person-years compared with controls. The excess risk was 7.9 cancer cases per 10,000 person-years among persons who received a cumulative RAI dose of 4.44 GBq or less, and 4.6 cancer cases per 10,000 person-years among persons who did not receive RAI, compared with the same controls. The other study, examining the risk of developing leukemia (n=211,360), included persons with thyroid cancer of any histologic type as reported by the South Korean national health insurance claims database and diagnosed from 2008 to 2013.[115] Leukemia diagnoses were included if they occurred after the index thyroid cancer or after completion of RAI treatment, if RAI was received. With a median 2.4 years of followup (542,845 person-years), the incidence of leukemia was elevated among persons who received the highest cumulative doses of RAI (2.1 cancer cases per 10,000 person-years among those who received >5.5 GBq and 3.0 cancer cases per 10,000 person-years among those who received 3.7 to 5.5 GBq); incidence was 1.0 case per 10,000 person-years among persons who did not receive RAI (p <0.001 for trend).

One fair-quality retrospective[121] and five fair-quality prospective studies (n=830) assessed the permanent harms of RAI on the salivary glands.[117-120, 122] The studies were generally small and had an average followup of 1 to 8.4 years. The mean radiation dose from RAI ranged from 1.1 to 5.3 GBq. The most common adverse effect of RAI to the salivary glands was xerostomia (dry mouth), which ranged from 2.3 to 35 percent. Dry mouth can adversely affect quality of life and vocal function and increase the risk of dental disease. One good-quality retrospective study (n=8,946), which used national data from Taiwan from 1997 to 2008, found no notable difference in the incidence of hyperparathyroidism between persons with papillary or follicular thyroid cancer who had received RAI and those who did not over an average followup of about 5 years.[123] One fair-quality retrospective study (n=18,850) including a U.S. cohort of persons with papillary or follicular thyroid cancer found no notable difference in the birthrate between women who had received RAI and those who had not.[124]

Limitations

Studies evaluating the harms of RAI using SEER data prior to 1987 may include radiation from other modalities, such as brachytherapy. Studies using SEER data did not account for the dose of radiation exposure. Studies reporting dose of radiation exposure varied in study design and ranges/thresholds of radiation doses, limiting direct comparisons. Studies that evaluated the harms of RAI on second primary malignancy and on salivary glands used different study methods, including how adverse outcomes were defined and adjustment (if any) for important known confounders. In addition, most of the studies that evaluated harms to salivary glands did not use a comparator arm (i.e., persons not exposed to RAI).

Chapter 4. Discussion

Summary of Evidence

In theory, screening for thyroid cancer could result in early detection of malignant nodules that can be treated more effectively, and with less harm, than if detected later or with symptomatic identification of thyroid cancer. However, we found no direct evidence to support this logic. To date there are no trials evaluating the (net) benefit of thyroid cancer screening (KQ 1) and, because most cases of thyroid cancer have a long latency period, screening trials of the benefit on patient health outcomes (i.e., morbidity and mortality) are unlikely to be conducted.

Well-designed studies evaluating the diagnostic accuracy of palpation or ultrasound in screening relevant populations (e.g., unselected or asymptomatic persons) are extremely limited (KQ 2). Two older Finnish studies, which were included in the prior review to support the 1996 USPSTF recommendation, demonstrated very low sensitivity of the neck examination to detect thyroid nodules, but these studies were limited to a single examiner.[55, 56] Two small South Korean studies evaluated the diagnostic accuracy of various sonographic features with ultrasound in a screening population.[57, 58] In those studies, using any one of several malignant sonographic characteristics (i.e., microcalcification, taller rather than wider, irregular shape, ill-defined or spiculated margin, a solid component with marked hypoechogenicity) could have high sensitivity (94.3%) but not specificity (and thus false-positive results) to detect cancer, whereas using a combination of two or more of these characteristics could have both high sensitivity (94.8%) and specificity (86.6%). These two studies, however, did not provide followup on most patients without malignant sonographic characteristics and thus likely overestimate the true sensitivity. Many other studies with similar study designs were excluded because they were not conducted or not reported to be conducted in a screening population. These two studies confirmed that these sonographic characteristics are most predictive of thyroid cancer but that the precision regarding the diagnostic accuracy of each characteristic varies (see "Diagnostic Accuracy of Ultrasound and FNA" below).

Potential harms of thyroid cancer screening are due primarily to subsequent diagnostic procedures and treatment. The major concerns for harms in thyroid cancer screening are "unnecessary" diagnostic procedures and treatments resulting from a false-positive finding and, more important, overdiagnosis (i.e., persons diagnosed with indolent cancer that would have never caused any suffering or death). We found very limited evidence to evaluate the potential harms of screening or FNA (KQ 3). One study suggested that, in practice, many persons (24%) with abnormal ultrasound findings go on to receive unnecessary FNA (i.e., do not meet current-day criteria and thus would not be expected to have a high risk of malignancy). Two studies suggested that there are no major harms of FNA, even though the procedure can result in localized hematomas or, very rarely, implantation of cancer along the needle tract.[66, 67] Nonetheless, FNA is generally regarded as a safe procedure when performed by an experienced clinician;[33-35, 37] the main potential harm is diagnostic inaccuracy or nondiagnostic samples leading to repeat procedures or unnecessary surgery (see "Diagnostic Accuracy of Ultrasound and FNA" below). We found no direct evidence (i.e., studies comparing screening with no screening) to evaluate the magnitude or effect of thyroid cancer screening on overdiagnosis.

However, because this is such an important issue for thyroid cancer screening—and for many, the main reason in the argument against thyroid cancer screening—we have included a discussion of the supporting evidence below (see "Overdiagnosis").

We found no studies that evaluated if treatment of earlier-stage or screen-detected cancer compared with symptomatic cancer improves patient health outcomes (KQ 4). It is still unclear if immediate surgery, versus observation, improves patient health outcomes for small, well-differentiated thyroid cancer. We found one large study using SEER data that found very good 20-year survival rates in both treated and untreated persons with papillary thyroid cancer, albeit higher in treated persons.[69] In this study, the untreated group was a self-selected minority (1% of the studied population) that differed in measured (and likely unmeasured) potential confounders for which the study did not adjust. It is therefore unclear if differences in survival were due to treatment rather than a case mix of patients who self-selected to be treated (or not). Nonetheless, this study demonstrates that the overwhelming majority of persons diagnosed with papillary cancer in the United States will get surgery. One Japanese study found no deaths after an average of 6 years of followup among persons who opted for observation of papillary microcarcinoma compared with two deaths among persons who opted for immediate surgery.[70, 72] Ultimately, 56 out of 162 persons in the observation group had surgical treatment.[71] Again, this study did not adjust for confounders.

In contrast, we found a relatively large body of observational literature describing harms of treatment with surgery and RAI (KQ 5). These studies generally included a mixture of patients, likely not from screening alone. Limited data from included screening studies, however, suggest that a substantial proportion of screen-detected cancer cases include extrathyroidal extension[61] or lymph node metastases[54, 59-61] at the time of detection, therefore warranting various interventions comparable with those in the treatment studies we identified. In addition, the rate of surgical harms did not appear to vary by study-level averages of proxies for prognosis (e.g., age, tumor size, tumor stage). We found that permanent surgical complications were not uncommon. Our pooled analysis showed that thyroidectomies were associated with 2 to 6 cases of permanent hypoparathyroidism and 1 to 2 cases of permanent recurrent laryngeal nerve palsy per 100 surgeries. The rate of hypoparathyroidism appears to be more variable with lymph node dissection. Our review is generally consistent with findings of existing systematic reviews. Jeannon et al[126] reviewed 27 studies and estimated the incidence of permanent recurrent laryngeal nerve palsy at 2.3 percent, and Shan et al[127] reviewed 16 studies and found no substantive increased risk of permanent hypoparathyroidism or recurrent laryngeal nerve palsy due to thyroidectomy with lymph node dissection compared with thyroidectomy alone. Limitations in the included primary literature did not allow for assessment of the effect of surgical volume on the variation of surgical harms across studies. However, evidence from nonincluded studies (not specific to thyroid cancer) suggests that surgeons with higher case volumes have lower rates of case complications, but even experienced surgeons have complication rates consistent with estimates in our review.[5, 128, 129] Other serious harms may include death, airway injury, cardiopulmonary events, wound complications, and infection but are not commonly reported.

RAI is not routinely employed as treatment of thyroid cancer but is considered for persons with high-risk cancer.[5] Radiation doses vary and generally correspond to the indication for RAI, such that lower doses (1.11 GBq or 30 mCi) are used for ablation and higher doses (≤5.5 GBq or 150 mCi) are used for adjuvant therapy for known or suspected residual disease.[5] Two studies using SEER data found an excess cancer risk of about 12 or 13 cancer cases per 10,000 person-years; however, neither reported the radiation dose. Smaller studies that reported radiation dose demonstrated an association with excess cancer risk at clinically used doses of RAI; however, differences in study designs and variable reporting on radiation dose limits our understanding of the magnitude and precision of this small excess risk. Our findings are consistent with older excluded literature. A 2009 systematic review by Sawka et al[46] that estimated the risk of second primary malignancies after RAI treatment of thyroid cancer included two large studies, one by Brown et al[130] using a U.S. cohort (included in our review) and another by Rubino et al[131] using three European cohorts (n=6,841) (excluded because treatment dates were as early as 1934). The average radiation dose reported in the European cohorts was approximately 6 GBq (or 162 mCi), and the calculated excess absolute risk of secondary malignancies with approximately 1 GBq or 27 mCi was about 15 cancer cases (14.4 solid and 0.8 hematologic) per 100,000 person-years. Six studies showed that RAI (mean dose, 2.96 to 5.3 GBq or 80 to 142 mCi) is associated with permanent dry mouth (2.3% to 35%), which can adversely affect quality of life and increase the risk of dental disease.[117-122] Although RAI can affect gonadal function, we found no evidence (including three older excluded studies) to suggest that lower doses of radiation from RAI result in male or female infertility. Our findings are consistent with existing systematic reviews that have examined the effects of RAI on gonadal function in men and women.[132, 133]

Key Contextual Issues

Diagnostic Accuracy of Ultrasound and FNA

Ultrasound

Our review was limited to diagnostic accuracy studies of screening the thyroid by ultrasound in unselected or asymptomatic persons, in which all or a random subset of screen-negative persons also received a reference standard (i.e., histology). Therefore, many studies evaluating the diagnostic accuracy of thyroid ultrasound (e.g., studies limited to persons with known thyroid nodules) and a rather large body of literature on the diagnostic accuracy of various ultrasound characteristics (e.g., nodule shape, margins, echogenicity, calcifications) for malignancy were excluded. Several studies have shown that certain ultrasound characteristics, in combination with nodule size, could help to determine the risk of malignancy and therefore potentially reduce unnecessary FNA testing.[40, 134-138]

Brito et al[137] reviewed 31 studies on diagnostic accuracy (not in screening populations) published from 1985 to 2012 and showed that the three ultrasound characteristics most predictive of thyroid cancer malignancy were taller than wide shape, internal calcifications, and infiltrative margins.[137] Taller than wide shape had a sensitivity of 0.53 (95% CI, 0.50 to 0.56) and specificity of 0.93 (95% CI, 0.91 to 0.94), internal calcifications had a sensitivity of 0.54 (95% CI, 0.52 to 0.56) and specificity of 0.81 (95% CI, 0.80 to 0.82), and infiltrative margins had a sensitivity of 0.56 (95% CI, 0.50 to 0.60) and specificity of 0.79 (95% CI, 0.77 to 0.80). Brito also showed that nodules with spongiform or cystic features (though present in only about 2% of nodules) were most likely benign. Nodule size alone was not an accurate predictor of malignancy, and the review did not evaluate accuracy based on multiple characteristics. Smith-Bindman et al[40] conducted a retrospective case-control study of 11,618 thyroid ultrasounds done at the University of California, San Francisco from 2000 to 2005. In a multivariable model, only three characteristics remained statistically significant predictors of thyroid cancer: microcalcifications (odds ratio [OR], 8.1 [95% CI, 3.8 to 17.3]), nodule size 2 cm or larger (OR, 3.6 [95% CI, 1.7 to 7.6]), and entirely solid composition (OR, 4.0 [95% CI, 1.7 to 9.2]). Additional large studies out of Korea,[136, 138] Turkey,[135] and Italy[134] demonstrated that nodules with calcifications, taller than wide shape, irregular margins, and hypoechoic patterns are the most predictive of thyroid cancer malignancy. The sensitivity of each of these characteristics to characterize malignant nodules varied widely between studies, from 44 to 86 percent for microcalcifications, 40 to 76 percent for taller than wide shape, 48 to 90 percent for irregular margins, and 41 to 87 percent for hypoechogenicity.[134, 135, 138] Specificity ranged from 54 to 90 percent for microcalcifications, 60 to 91 percent for taller than wide shape, 81 to 92 percent for irregular margins, and 47 to 92 percent for hypoechogenicity.[134, 135, 138] Several, but not all, sensitivity and specificity results from our two included studies for KQ 2[57, 58, 139] fall within these wide ranges, further emphasizing the wide variability in diagnostic accuracy for these characteristics.[57, 58]

Published in 2015, the ATA's evidence-based guidelines on the management of thyroid nodules and differentiated thyroid cancer strongly recommends FNA for nodules larger than 1 cm with highly suspicious sonographic patterns, including a solid hypoechoic nodule or a solid hypoechoic component in a partially cystic nodule with either irregular margins, microcalcifications, taller than wide shape, or disrupted rim calcifications with small extrusive hypoechoic soft tissue component or extrathyroidal extension.[5] The ATA guidelines also strongly recommend FNA for nodules at least 1 cm in size with intermediate suspicious sonographic patterns, including a hypoechoic solid nodule with a smooth regular margin and without microcalcifications, extrathyroidal extension, or taller than wide shape, although this latter recommendation was based on lower-quality evidence.

FNA

FNA is a quick, low-risk, and reliable procedure and currently the best method available for determining which thyroid nodules should be surgically removed or observed over time. Nonetheless, FNA is not perfect. The 2015 ATA guidelines recommend that FNA cytology be classified using the Bethesda System to reduce variability in reporting.[5] The Bethesda System categories are 1) nondiagnostic or unsatisfactory, 2) benign, 3) AUS/FLUS, 4) follicular neoplasm or suspicious for follicular neoplasm, 6) suspicious for malignancy, or 6) malignant. Patients who have nodules with initial nondiagnostic results should have a repeat FNA with ultrasound guidance. Patients with malignant nodules should be recommended for thyroid surgery. Management of indeterminate nodules (AUS/FLUS, follicular neoplasm, or suspicious for malignancy) is more controversial and may involve molecular testing, repeat FNA, and/or surgical excision depending on the patient's risk factors, the ultrasound characteristics of the nodules, and patient preference.

A 2012 systematic review of eight studies reported diagnostic accuracy among 25,445 FNAs of thyroid nodules.[140] Overall, 6,362 (25%) FNAs resulted in surgery, with the proportion varying from 11.8 to 45.1 percent across the studies. The overall sensitivity and specificity of FNA for detecting malignancy were 97.0 and 50.7 percent, respectively,[140] when considering the Bethesda System categories of follicular neoplasm, suspicious for malignancy, and malignant as positive. The sensitivity and specificity increased to 97.2 and 60.2 percent, respectively, when also including AUS/FLUS results (9.6% of all FNAs) as positive. The positive predictive value for AUS/FLUS alone was 15.9 percent, and 39.2 percent of these cases ultimately went on to surgery. The 2015 ATA guidelines state that only 7 percent of all thyroid FNAs[5, 141] are expected to have this result; however, Bongiovonni[140] showed that the percentage of FNAs with AUS/FLUS results from eight studies ranged widely, from 0.8 to 27.2 percent. Large percentages of indeterminate FNA results as well as variability in the management of these indeterminate findings could ultimately result in unnecessary surgery and overtreatment of thyroid nodules. In the United States alone, 59,478 persons underwent thyroidectomy in an inpatient setting in 2009.[142] While 18,008 (30.3%) of those operations were for thyroid cancer, the remainder were benign conditions, including nontoxic nodular goiter (36.0%) and benign neoplasms (11.2 %).

Overdiagnosis

Overdiagnosis of thyroid cancer occurs when a thyroid malignancy is diagnosed but would not have caused symptoms or death during a patient's lifetime.[143] Overdiagnosis occurs because some thyroid tumors grow so slowly that the cancer never progresses (and sometimes regresses) or progresses at such a slow pace that the person dies of other causes before the cancer is symptomatic. Welch and Black[144] proposed two prerequisites for overdiagnosis, both of which are met by thyroid cancer: 1) the existence of a disease reservoir or a substantial number of subclinical cancer cases, and 2) a method to detect these subclinical cancer cases via screening. One of the major harms from overdiagnosis is overtreatment, or the overuse of procedures that may result in treatment harms without (or only marginally) improving patient outcomes. According to SEER data, 98.8 percent of persons with thyroid cancer diagnosed from 1973 to 2005 underwent definitive treatment.[69] Overdiagnosis may also lead to preventable harms, such as increased patient anxiety, potential complications or adverse effects from treatment (as we reported), and increased health care costs[145] without benefit to the patient. However, at present, there is no clear way to determine which cases of thyroid cancer would actually require treatment to improve patient survival and which would not.

Although overdiagnosis is arguably the most important harm of thyroid cancer screening, it is not addressed by our review of harms of screening (KQ 3) due to limitations in the evidence base. To accurately estimate overdiagnosis, studies must compare screened and unscreened groups.[143] We found no studies that compared screened and unscreened groups with incidence or overdiagnosis of thyroid cancer as an outcome. A recent review by Carter et al[143] provided an overview of the types of study designs needed to accurately quantify overdiagnosis in cancer screening, none of which is available for thyroid cancer. The four types of study designs are modeling studies, pathological and imaging studies, ecological and cohort studies, and followup of RCTs. Modeling studies compare the way cancer would hypothetically occur with and without screening. Biases may limit the quality of modeling studies and include a lack of direct evidence to support modeling assumptions, validation analyses, or generalizability. Pathology and imaging studies determine the extent of overdiagnosis-based characteristics seen in imaging or pathology studies, such as tumor growth rate. These studies assume that pathology or imaging characteristics are strongly correlated with cancer morbidity or mortality, which may be a difficult assumption to apply to thyroid cancer because it has not been determined which tumor characteristics are more predictive of mortality than others, particularly for papillary carcinomas. Ecological and cohort studies typically follow persons through cancer screening programs and compare the cancer incidence with unscreened control groups. These studies are subject to selection bias and confounding from control group selection (studies typically use historical controls or controls from different geographic areas without screening programs) or lead-time bias from insufficient followup time. Followup from RCTs comparing screening with no screening may be the least-biased study design for assessing overdiagnosis; however, this type of study is rare, even for other types of cancer.

Incidence and Mortality Data

The best evidence we have to suggest that overdiagnosis is a problem with thyroid cancer comes from studies showing a rising incidence in thyroid cancer detection over time with no corresponding change in the mortality rate.[2, 47, 69, 146-148] Several studies by Davies and Welch[2, 69, 148] have used SEER data to estimate the incidence of thyroid cancer and cancer-related mortality in the United States since 1973. The most recent estimates, published in 2014, showed that the incidence of thyroid cancer increased from 4.9 cases per 100,000 persons in 1975 to 14.3 cases per 100,000 persons in 2009, representing an absolute increase of 9.4 (95% CI, 8.9 to 9.9) cases per 100,000 persons.[2] When only cases of papillary cancer were examined, the absolute increase over the same time period was 9.1 (95% CI, 8.6 to 9.6) cases per 100,000 persons[2]; thus, cases of papillary cancer have accounted for the majority of the increased incidence among all cases of thyroid cancer. These increases were 3 to 4 times greater in women than in men. The size distribution of diagnosed tumors has shifted toward smaller lesions, with the proportion of tumors smaller than 1 cm that were diagnosed increasing from 25 percent in 1988 to 1989 to 39 percent in 2008 to 2009.[2] During the same time period, the rate of thyroid cancer mortality remained stable (approximately 0.5 deaths per 100,000 persons).[2, 148] Ho et al[147] conducted a similar analysis using SEER data and found nearly identical thyroid cancer incidence and mortality rates over time. They also noted that the 10-year disease-specific survival for patients diagnosed from 1983 to 1999 increased from 95.4 to 98.6 percent (p=0.002), which may reflect, in part, that small, asymptomatic cancer accounts for most new diagnoses. Neither of these studies reported mortality by histologic type, which is an important element to consider given that patients with medullary and anaplastic cancer have much higher mortality rates than patients with differentiated cancer.[1]

Data from other countries have shown similar findings. A summary report using data from the Cancer Incidence in Five Continents database showed steady increases in thyroid cancer incidence in 12 selected countries from 1960 to 2007, which, again, was primarily driven by a rise in papillary carcinoma diagnoses.[146] Mortality data from the World Health Organization showed that the mortality rate from 2000 to 2010 either stabilized around 0.2 deaths per 100,000 men and 0.6 deaths per 100,000 women or declined by 2 to 3 percent per year for men and 2 to 5 percent per year for women. The declines are likely related to changes in both risk factors (due to improvements in diet, reductions in iodine deficiency, and medical use of ionizing radiation over the last couple of decades in some countries) and cancer detection (resulting in overdiagnosis of cancer with a favorable prognosis). The best example that illustrates the problem of overdiagnosis of thyroid cancer comes from South Korea, which has had an organized cancer screening program since 1999.[47] Although the program did not officially include thyroid cancer screening, providers frequently offered thyroid screening with ultrasound for a small additional cost. In 2011, the rate of thyroid cancer diagnoses was 15 times the rate in 1993,[47] while the rate of thyroid cancer mortality remained stable. In 2011 alone, more than 40,000 persons were diagnosed with thyroid cancer, whereas fewer than 400 died. Nearly every person diagnosed with thyroid cancer underwent surgical treatment. One study noted that the tumors excised decreased in size over time: the proportion of tumors excised that were smaller than 1 cm increased from 14 percent in 1995 to 56 percent in 2005.[61] Increases in thyroid cancer incidence ranging from 3.2 to 6.2 percent per year in men and 3.5 to 8.1 percent in women were noted in France, Australia, and Canada from the early 1980s to the late 1990s, although none of these countries implemented thyroid cancer screening as did South Korea.[149-151] These studies also noted that the majority of the increase in incidence was due to an increase in cases of papillary thyroid carcinoma or microcarcinoma.

Several studies have evaluated whether the increased incidence in thyroid cancer is a result of increased detection (e.g., through increased imaging) or a true increase in risk factors for thyroid cancer (e.g., due to exposure to ionizing radiation). Davies et al[152] conducted a small (n=279) study to identify examinations that led to detecting cases of asymptomatic cancer. The results showed that 46 percent (n=44 of 95) of identified cases of cancer were first noted on surgical evaluation following detection of a nodule during a routine examination (i.e., asymptomatic), imaging for an unrelated cause, or diagnostic workup for other problems where the thyroid might be involved (e.g., patient complaining of fatigue). The majority of these cases of "asymptomatic" cancer were papillary (n=37), and the mean tumor size was 1.9 cm (range, 0.2 to 10 cm), whereas the mean tumor size of cases of symptomatic papillary cancer was 2.4 cm (range, 0.2 to 8 cm). These results are consistent with the epidemiologic studies described above that noted that the increased incidence of thyroid cancer was due to increased diagnoses of small papillary tumors.

However, a review by Pellegriti et al[18] noted that while the largest increase in thyroid cancer incidence occurred among tumors smaller than 1 cm, smaller increases have occurred among larger tumors. For example, a study using SEER data showed that the incidence of thyroid tumors 2 to 4 cm in size increased 4.6 percent (95% CI, 3.5 to 5.7) per year from 1995 to 2006 and that of larger tumors increased 4.1 percent (95% CI, 3.4 to 4.8) per year from 1983 to 2006.[153] A second SEER study showed that from 1983 to 2006, papillary thyroid tumors smaller than 1 cm, 1.1 to 2 cm, 2.1 to 5 cm, and larger than 5 cm increased by 19.3, 12.3, 10.3, and 12.0 percent per year, respectively.[41] A third SEER study showed that from 1992 to 2005, approximately 50 percent of the overall increase in papillary cancer incidence was from tumors 1 cm or smaller, 30 percent from tumors 1.1 to 2 cm, and 20 percent from larger tumors.[154]

Pellegriti et al[18] also pointed out that an increase in incidence solely due to increased detection should have affected all histologic types and sexes equally. As we noted above, prior studies primarily noted increases among cases of papillary cancer and larger increases in incidence in women than men.[2, 147, 149-151] Additional studies, such as the study by Chen et al,[155] used SEER data to demonstrate that increases in incidence by tumor size differed between men and women.

From 1988 to 2005, the incidence of tumors smaller than 1 cm increased by 4 percent (95% CI, 0.8 to 7.3) per year in men and by 8.6 percent (95% CI, 7.8 to 9.5) per year in women. During the same time period, the incidence of thyroid tumors 1.0 to 2.9 cm in size increased by 5.5 percent (95% CI, 4.2 to 6.8) in men and by 0.4 percent (95% CI, -3.0 to 3.8) in women. Enewold et al,[154] also using SEER data, demonstrated that the incidence rate of thyroid cancer varied by race/ethnicity, sex, and histology. Papillary cancer was the only histologic type to see a significant increase in the rate from 1980 to 2005, but the increase differed by race/ethnicity and sex (8.0%, 2.7%, 3.80%, and 1.16% per 100,000 person-years for white women, white men, black women, and black men, respectively).

In the United States, the increased incidence of thyroid cancer over time may also be related to increased access to care. This hypothesis is supported by a study that used SEER data from 1973 to 2009 linked to U.S. Census data from 2000 to demonstrate that thyroid cancer incidence was positively correlated with income level, education, and employment.[156] Another study, which used data from 1999 to 2009 from the U.S. Cancer Statistics Report linked to Lifescript doctor review data and administrative patient claims data, showed that the incidence of thyroid cancer was significantly correlated with the density of endocrinologists.[43] Incidence varied from 4.7 per 100,000 person-years in Oklahoma to 9.1 per 100,000 person-years in Rhode Island, and much of the variation in incidence by U.S. State could be explained by the density of endocrinologists and general surgeons as well as the use of neck ultrasounds.

Pellegriti et al[18] also reviewed whether changes in potential risk factors for thyroid carcinoma are related to thyroid cancer incidence, which could suggest that some of the increased incidence is real and not related to overdiagnosis. Pellegriti et al noted that in the United States, the use of medical imaging such as CT scans and x-ray has increased dramatically and that individual doses of ionizing radiation from these examinations doubled from 1980 to 2006. Additional elements of diet, lifestyle, and pollution (e.g., iodine intake, food or environmental contaminants) may influence the risk of thyroid cancer, but these aspects have not been studied carefully.[18] Thus, limited evidence exists for an external cause of increased thyroid cancer incidence beyond increased detection and diagnosis.

Autopsy Data

Autopsy studies have provided additional evidence on overdiagnosis of thyroid cancer. A 2014 review by Lee et al[30] summarized 15 studies published from 1969 to 2005 on latent thyroid cancer discovered at autopsy. Of 8,619 thyroid glands obtained at autopsy, 989 (11.5%) were positive for papillary thyroid carcinoma. The proportion of cases of papillary thyroid cancer varied widely, from 1.0 to 35.6 percent. The majority of the tumors were tiny (diameter <1 to 3 mm), and women and men were equally likely to have papillary cancer diagnosed on autopsy. The authors compared the autopsy diagnoses with 1,355 papillary microcarcinomas diagnosed clinically at their institution; most patients diagnosed clinically (67.3%) had tumors larger than 0.5 cm, and women were 11 times more likely than men to be diagnosed. Comparisons between the latent cancer cases diagnosed on autopsy and the papillary microcarcinomas diagnosed clinically are likely subject to selection bias, but the autopsy studies clearly demonstrate that a proportion of thyroid cancer cases would likely never result in symptoms or mortality.

Natural History Data

Studies describing the natural history of thyroid nodules and malignancies also lend evidence to the problem of overdiagnosis in thyroid cancer. The 2015 ATA guidelines note that benign nodule growth has been variably defined across studies and that there is no good cutoff to use for percent change in size when determining whether to conduct repeat FNA on nodules previously diagnosed as benign.[5] Durante et al[157] describe 5-year followup of 992 patients with benign thyroid nodules (size, 0.4 to 4 cm). In 686 patients (69%), the size of the nodules remained stable; in 184 patients (18.5%), the size of one or more nodules decreased; and in 153 patients (15.4%), the size of one or more nodules increased by 20 percent or more (the groups were not mutually exclusive because some persons had more than one nodule). Ultimately, only five patients were diagnosed with thyroid malignancy. There are currently no studies with followup of benign nodules beyond 5 years. Studies with longer followup are needed to help determine whether indefinite followup of nodules is necessary.

Nodule growth was evaluated in persons with thyroid cancer by Ito et al.[71] Among 162 persons with papillary microcarcinoma who opted for observation instead of immediate surgical treatment, within 1 year the tumor increased in size by 2 mm or more in 20 patients (15.3%), decreased in size by 2 mm or more in 18 patients (13.8%), or did not change in 92 patients (70.8%). After 5 years of followup, 72.3 percent of tumors did not increase in size. Ultimately, 56 patients went on to have surgery, only 13 of whom had an increase in tumor size of 2 mm or more.

Another study, of 2,070 patients with papillary microcarcinoma, looked at recurrence-free survival up to 35 years after diagnosis and found that the survival rate was 96.7 percent for patients with tumors 5 mm or smaller and 86.0 percent for patients with tumors 6 to 10 mm in size ($p<0.0001$).[158] In a multivariable survival model, neither patient age nor sex was predictive of disease-free survival. A total of 73 patients experienced recurrence at a median time of 10.3 years. A large SEER study evaluated recurrence and mortality outcomes among 18,445 patients with papillary microcarcinoma; at 15 years, the overall survival rate was 90.7 percent and the disease-specific survival rate was 99.3 percent. In multivariable survival models, patient characteristics related to poorer overall survival included age older than 45 years (hazard ratio [HR], 6.18 [95% CI, 4.80 to 7.97]), male sex (HR, 1.74 [95% CI, 1.44 to 2.11]), and African American race (HR, 2.56 [95% CI, 1.88 to 3.47]).[159] A total of 49 patients died of thyroid cancer. Using SEER data, Davies et al[69] estimated the rate of papillary thyroid cancer–specific survival by whether the patients received definitive treatment. The 10-year survival rate was 99 percent among 29,789 persons who had received definitive treatment and 97 percent among 440 persons who did not. In the United States, data from single institutions have demonstrated that the overwhelming majority of thyroid cancer diagnoses are stage I papillary cancer, with 20-year survival approximating 100 percent.[160] These data highlight the slow-growing nature of thyroid tumors and the low potential for recurrence or mortality due to thyroid cancer, particularly papillary tumors and microcarcinoma. However, data on the survival of patients who never receive treatment are very limited. As Ho et al[147] pointed out, the high survival rates of patients with thyroid cancer may be a result of length bias as increasing numbers of subclinical thyroid cancer cases are diagnosed, thereby shifting survival curves toward longer survival.

Limitations of the Review

Our review was designed to support the USPSTF in making a recommendation regarding screening for thyroid cancer such that our inclusion criteria reflected decisions about identifying the most applicable evidence for our primary stakeholder. We did not include studies primarily focused on cohorts exposed to high doses of radiation due to environmental disasters. In addition, we did not review the diagnostic accuracy of ultrasound or ultrasound characteristics to detect thyroid cancer in nonscreening populations, primarily due to referral bias, although we provide a summary of this literature (see "Diagnostic Accuracy of Ultrasound"). For our review of overdiagnosis, our inclusion criteria required studies that compared screened versus unscreened persons. However, because these types of studies do not exist, we summarize the supporting literature (see "Overdiagnosis").

Because our review focused on the benefit of treatment versus observation or the treatment of asymptomatic versus symptomatic disease, we excluded studies evaluating the comparative benefits and harms of treatment (i.e., the most effective or safest treatment). We also excluded harms not directly related to surgery or RAI (e.g., subsequent harms from suppressive doses of thyroxine). We excluded older studies that examined harms of RAI, as radiation doses have changed over time. Nonetheless, we acknowledge that, over time, surgical techniques, RAI doses, and the case mix of persons undergoing surgery and/or RAI have changed; such included studies still may not accurately reflect modern-day practice. Given our primary audience and resource limitations, we limited our review to evidence conducted in countries with the most appropriate applicability to U.S. practice and to articles published in English. We do not believe these criteria resulted in omission of any key evidence.

Due to the sparse data for most of the KQs, we were limited to nonquantitative analyses. Our meta-analyses to pool surgical harms had high statistical heterogeneity for outcomes of hypoparathyroidism, which we could not explain by using several study-level characteristics.

Evidence Gaps and Future Research Needs

Overall, there is very little evidence examining the benefit of screening for thyroid cancer. No professional society recommends population-based thyroid cancer screening. Additionally, there is little evidence to support screening in persons with an elevated risk of thyroid cancer. Previously, the USPSTF stated there was insufficient evidence to recommend screening in persons with a personal history of irradiation (and we found no new studies in this review), and the ATA stated in 2015 that there was insufficient evidence to support screening persons with a family history of differentiated thyroid cancer. Although population-based screening trials for thyroid cancer are unlikely, trials or well-designed observational studies to address the benefit of screening in higher-risk populations (e.g., those with a personal history of irradiation or a family history of differentiated thyroid cancer) would be helpful to understand if there is any role at all for screening for thyroid cancer. The use of radiation to treat benign conditions in childhood ended several decades ago, so questions about best practices for screening in this population may not be a priority, but there are smaller subpopulations who have received radiation for diagnostic (e.g., CT scans) or therapeutic (e.g., treatment of hematologic cancer) purposes in childhood, adolescence, or early adulthood, for whom assessing best practices may be relevant.

Given the indolent nature of many cases of thyroid cancer and the risks associated with treatment, trials or well-designed observational studies examining the benefit of early treatment versus observation or surveillance for patients with (smaller) well-differentiated thyroid cancer are also needed. In addition, we need studies to determine which set of prognostic indicators predict aggressive versus indolent disease. Over the past decade, better understanding of the genetic mechanisms of thyroid cancer and the creation of molecular tests to aide in cancer diagnosis have made molecular markers a very promising area of research to help derive a prognosis of thyroid cancer.[5]

Conclusions

Although an ultrasound of the neck using high-risk sonographic characteristics plus followup cytology from FNA can reasonably identify thyroid cancer, it is still unclear if population-based or targeted screening can decrease mortality rates or improve important patient health outcomes. Screening results in the identification of indolent thyroid cancer which would not have resulted in any morbidity or mortality in a person’s lifetime. Treatment of these cases of overdiagnosed cancer can pose real harms, including complications from surgical and RAI treatment. There is a lack of evidence to understand the true magnitude of overdiagnosis as well as the risk markers that predict indolent versus progressive thyroid cancer.

References

1. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines)2014.
2. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 2014 Apr;140(4):317-22. PMID: 24557566.
3. Eden K, Mahon S, Helfand M. Screening high-risk populations for thyroid cancer. Med Pediatr Oncol. 2001 May;36(5):583-91. PMID: 11340616.
4. Dean DS, Gharib H. Epidemiology of thyroid nodules. Best practice & research Clinical endocrinology & metabolism. 2008 Dec;22(6):901-11. PMID: 19041821.
5. Haugen BRM, Alexander EK, Bible KC, Doherty G, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015 Oct 14. PMID: 26462967.
6. SEER Stat Fact Sheets: Thyroid Cancer. http://seer.cancer.gov/statfacts/html/thyro.html: Surveillance, Epidemiology and End Results Program; 2014 [cited 2014 November 30, 2015].
7. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. CA Cancer J Clin. 2013 Nov-Dec;63(6):374-94. PMID: 23797834.
8. What are the key statistics about thyroid cancer? : American Cancer Society 2015 [cited 2015 November 30, 2015]; Available from: http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-key-statistics.
9. Aschebrook-Kilfoy B, Schechter RB, Shih YC, Kaplan EL, Chiu BC, Angelos P, et al. The clinical and economic burden of a sustained increase in thyroid cancer incidence. Cancer Epidemiol Biomarkers Prev. 2013 Jul;22(7):1252-9. PMID: 23677575.
10. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer.[Erratum appears in Thyroid. 2010 Aug;20(8):942 Note: Hauger, Bryan R [corrected to Haugen, Bryan R]], [Erratum appears in Thyroid. 2010 Jun;20(6):674-5]. Thyroid. 2009 Nov;19(11):1167-214. PMID: 19860577.
11. Hughes DT, Doherty GM. Central neck dissection for papillary thyroid cancer. Cancer Control. 2011 Apr;18(2):83-8. PMID: 21451450.
12. Xing MM. Thyroid carcinoma. 2012 [updated September 10, 2012; cited August 5 2014]; Available from: https://www.clinicalkey.com/#!/content/medical_topic/21-s2.0-1014684.
13. Malchoff CD, Malchoff DM. Familial nonmedullary thyroid carcinoma. Cancer Control. 2006 Apr;13(2):106-10. PMID: 16735984.
14. World Health Organization. International classification of diseases for oncology (ICD-O)–3rd edition, 1st revision. 2013. PMID.
15. Pelizzo M, Boschin I, Bernante P, Toniato A, Piotto A, Pagetta C, et al. Natural history, diagnosis, treatment and outcome of medullary thyroid cancer: 37 years experience on 157 patients. European Journal of Surgical Oncology (EJSO). 2007;33(4):493-7. PMID.
16. Saad MF, Ordonez NG, Rashid RK, Guido JJ, Hill CS, Jr., Hickey RC, et al. Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161 patients. Medicine (Baltimore). 1984 Nov;63(6):319-42. PMID: 6503683.

17. Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer. 2000 Mar 1;88(5):1139-48. PMID: 10699905.
18. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. Journal of cancer epidemiology. 2013;2013:965212. PMID: 23737785.
19. Schonfeld SJ, Lee C, Berrington de Gonzalez A. Medical exposure to radiation and thyroid cancer. Clin Oncol (R Coll Radiol). 2011 May;23(4):244-50. PMID: 21296564.
20. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. 1995. Radiat Res. 2012 Aug;178(2):AV43-60. PMID: 22870979.
21. Little MP, Wakeford R, Tawn EJ, Bouffler SD, Berrington de Gonzalez A. Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do. Radiology. 2009 Apr;251(1):6-12. PMID: 19332841.
22. Safety Xray and CT exams. http://www.radiologyinfo.org/en/safety/?pg=sfty_xray2014 [cited October 7, 2014].
23. Oakley GM, Curtin K, Layfield L, Jarboe E, Buchmann LO, Hunt JP. Increased melanoma risk in individuals with papillary thyroid carcinoma. JAMA Otolaryngol Head Neck Surg. 2014 May;140(5):423-7. PMID: 24626334.
24. Pal T, Vogl FD, Chappuis PO, Tsang R, Brierley J, Renard H, 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 Nov;86(11):5307-12. PMID: 11701697.
25. Jasperson KW, Burt RW. APC-Associated Polyposis Conditions. In: Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong CT, et al., editors. GeneReviews(R). Seattle WA: University of Washington, Seattle; 1993.
26. Krampitz GW, Norton JA. RET gene mutations (genotype and phenotype) of multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma. Cancer. 2014 Jul 1;120(13):1920-31. PMID: 24699901.
27. Quadbeck B, Pruellage J, Roggenbuck U, Hirche H, Janssen OE, Mann K, et al. Long-term follow-up of thyroid nodule growth. Exp Clin Endocrinol Diabetes. 2002 Oct;110(7):348-54. PMID: 12397534.
28. Sciuto R, Romano L, Rea S, Marandino F, Sperduti I, Maini C. Natural history and clinical outcome of differentiated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution. Annals of oncology. 2009;20(10):1728-35. PMID: 19773250.
29. Sipos JA, Mazzaferri EL. Thyroid cancer epidemiology and prognostic variables. Clin Oncol (R Coll Radiol). 2010 Aug;22(6):395-404. PMID: 20627675.
30. Lee YS, Lim H, Chang H-S, Park CS. Papillary Thyroid Microcarcinomas Are Different from Latent Papillary Thyroid Carcinomas at Autopsy. J Korean Med Sci. 2014 04/25;29(5):676-9. PMID: PMC4024958.
31. Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery. 2008 Dec;144(6):1070-7; discussion 7-8. PMID: 19041020.
32. Ort S, Goldenberg D. Management of regional metastases in well-differentiated thyroid cancer. Otolaryngol Clin North Am. 2008 Dec;41(6):1207-18, xi. PMID: 19040980.

33. Norman J. Papillary Cancer: Symptoms, Treatments and Prognosis for Papillary Thyroid Carcinoma. Endocrineweb2012 [cited 2014 October 27]; Available from: http://www.endocrineweb.com/conditions/thyroid-cancer/papillary-cancer.
34. Barbet J, Campion L, Kraeber-Bodere F, Chatal J-F, Group GTES. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab. 2005 Nov;90(11):6077-84. PMID: 16091497.
35. Laure Giraudet A, Al Ghulzan A, Auperin A, Leboulleux S, Chehboun A, Troalen F, et al. Progression of medullary thyroid carcinoma: assessment with calcitonin and carcinoembryonic antigen doubling times. Eur J Endocrinol. 2008 Feb;158(2):239-46. PMID: 18230832.
36. Pelizzo MR, Boschin IM, Toniato A, Piotto A, Pagetta C, Gross MD, et al. Papillary thyroid carcinoma: 35-year outcome and prognostic factors in 1858 patients. Clinical nuclear medicine. 2007 Jun;32(6):440-4. PMID: 17515749.
37. 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 Jan-Feb;17(1):41-7; discussion 7-8. PMID: 7883548.
38. McIver B, Hay ID, Giuffrida DF, Dvorak CE, Grant CS, Thompson GB, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. Surgery. 2001 Dec;130(6):1028-34. PMID: 11742333.
39. Tennvall J, Lundell G, Wahlberg P, Bergenfelz A, Grimelius L, Akerman M, et al. Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. Br J Cancer. 2002 Jun 17;86(12):1848-53. PMID: 12085174.
40. Smith-Bindman R, Lebda P, Feldstein VA, Sellami D, Goldstein RB, Brasic N, et al. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. JAMA Intern Med. 2013 Oct 28;173(19):1788-96. PMID: 23978950.
41. Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry. Surgery. 2010 Dec;148(6):1147-52; discussion 52-3. PMID: 21134545.
42. Hughes DT, Haymart MR, Miller BS, Gauger PG, Doherty GM. The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. Thyroid. 2011 Mar;21(3):231-6. PMID: 21268762.
43. Udelsman R, Zhang Y. The epidemic of thyroid cancer in the United States: the role of endocrinologists and ultrasounds. Thyroid. 2014 Mar;24(3):472-9. PMID: 23937391.
44. Baloch ZW, Cibas ES, Clark DP, Layfield LJ, Ljung B-M, Pitman MB, et al. The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation. Cytojournal. 2008 04/07;5:6-. PMID: PMC2365970.
45. 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 Oct 1;117(19):4439-46. PMID: 21432843.
46. Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, et al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid. 2009 May;19(5):451-7. PMID: 19281429.
47. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"--screening and overdiagnosis. New England journal of medicine. 2014 Nov 6;371(19):1765-7. PMID: 25372084.

48. United Nations Development Programme. Human Development Index: 2013 Rankings. United Nations Development Programme; 2013 [cited 2014]; Available from: http://hdr.undp.org/en/2013-report.
49. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the US Preventive Services Task Force: a review of the process. American journal of preventive medicine. 2001 Apr;20(3 Suppl):21-35. PMID: 11306229.
50. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
51. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36. PMID: 22007046.
52. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003 Nov 10;3(1):25. PMID: 14606960.
53. Bucci A, Shore-Freedman E, Gierlowski T, Mihailescu D, Ron E, Schneider AB. Behavior of small thyroid cancers found by screening radiation-exposed individuals. J Clin Endocrinol Metab. 2001 Aug;86(8):3711-6. PMID: 11502800.
54. Ishida O, Izuo M, Ogawa T, Kurebayashi J, Satoh K. Evaluation of mass screening for thyroid cancer. Jpn J Clin Oncol. 1988 Dec;18(4):289-95. PMID: 3204679.
55. Brander A, Viikinkoski P, Nickels J, Kivisaari L. Thyroid gland: US screening in a random adult population. Radiology. 1991 Dec;181(3):683-7. PMID: 1947082.
56. Brander A, Viikinkoski P, Nickels J, Kivisaari L. Thyroid gland: US screening in middle-aged women with no previous thyroid disease. Radiology. 1989 Nov;173(2):507-10. PMID: 2678263.
57. Kim SJ, Moon WK, Cho N. Sonographic criteria for fine-needle aspiration cytology in a Korean female population undergoing thyroid ultrasound screening. Acta Radiol. 2010 Jun;51(5):475-81. PMID: 20235746.
58. Kim JY, Lee CH, Kim SY, Jeon WK, Kang JH, An SK, et al. Radiologic and pathologic findings of nonpalpable thyroid carcinomas detected by ultrasonography in a medical screening center. Journal of ultrasound in medicine. 2008 Feb;27(2):215-23. PMID: 18204012.
59. Suehiro F. Thyroid cancer detected by mass screening over a period of 16 years at a health care center in Japan. Surgery today. 2006;36(11):947-53. PMID: 17072713.
60. Chung WY, Chang HS, Kim EK, Park CS. Ultrasonographic mass screening for thyroid carcinoma: a study in women scheduled to undergo a breast examination. Surgery today. 2001;31(9):763-7. PMID: 11686552.
61. Lee HK, Hur MH, Ahn SM. Diagnosis of occult thyroid carcinoma by ultrasonography. Yonsei medical journal. 2003 Dec 30;44(6):1040-4. PMID: 14703614.
62. Ron E, Lubin E, Modan B. Screening for early detection of radiation-associated thyroid cancer: a pilot study. Isr J Med Sci. 1984 Dec;20(12):1164-8. PMID: 6519948.
63. Shimaoka K, Bakri K, Sciascia M, Razack M, Rao U, Mettlin C, et al. Thyroid screening program; follow-up evaluation. N Y State J Med. 1982 Jul;82(8):1184-7. PMID: 6957738.
64. Ron E, Modan B, Preston D, Alfandary E, Stovall M, Boice JD, Jr. Thyroid neoplasia following low-dose radiation in childhood. Radiat Res. 1989 Dec;120(3):516-31. PMID: 2594972.

65. Hobbs HA, Bahl M, Nelson RC, Eastwood JD, Esclamado RM, Hoang JK. Applying the Society of Radiologists in Ultrasound recommendations for fine-needle aspiration of thyroid nodules: effect on workup and malignancy detection. AJR American Journal of Roentgenology. 2014 Mar;202(3):602-7. PMID: 24555597.
66. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Needle tract implantation of papillary thyroid carcinoma after fine-needle aspiration biopsy. World journal of surgery. 2005 Dec;29(12):1544-9. PMID: 16311845.
67. Abu-Yousef MM, Larson JH, Kuehn DM, Wu AS, Laroia AT. Safety of ultrasound-guided fine needle aspiration biopsy of neck lesions in patients taking antithrombotic/anticoagulant medications. Ultrasound Q. 2011 Sep;27(3):157-9. PMID: 21873852.
68. Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, Coleman BG, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology. 2005 Dec;237(3):794-800. PMID: 16304103.
69. Davies L, Welch HG. Thyroid cancer survival in the United States: observational data from 1973 to 2005. Arch Otolaryngol Head Neck Surg. 2010 May;136(5):440-4. PMID: 20479371.
70. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World journal of surgery. 2010 Jan;34(1):28-35. PMID: 20020290.
71. Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid. 2003 Apr;13(4):381-7. PMID: 12804106.
72. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014 Jan;24(1):27-34. PMID: 24001104.
73. Oda H, Miyauchi A, Ito Y, Yoshioka K, Nakayama A, Sasai H, et al. Incidences of Unfavorable Events in the Management of Low-Risk Papillary Microcarcinoma of the Thyroid by Active Surveillance Versus Immediate Surgery. Thyroid. 2016 Jan;26(1):150-5. PMID: 26426735.
74. Tartaglia F, Blasi S, Giuliani A, Sgueglia M, Tromba L, Carbotta S, et al. Central neck dissection in papillary thyroid carcinoma: results of a retrospective study. Int J Surg. 2014;12 Suppl 1:S57-62. PMID: 24862662.
75. Hyun SM, Song HY, Kim SY, Nam SY, Roh JL, Han MW, et al. Impact of combined prophylactic unilateral central neck dissection and hemithyroidectomy in patients with papillary thyroid microcarcinoma. Annals of surgical oncology. 2012 Feb;19(2):591-6. PMID: 21837525.
76. Son YI, Jeong HS, Baek CH, Chung MK, Ryu J, Chung JH, et al. Extent of prophylactic lymph node dissection in the central neck area of the patients with papillary thyroid carcinoma: comparison of limited versus comprehensive lymph node dissection in a 2-year safety study. Annals of surgical oncology. 2008 Jul;15(7):2020-6. PMID: 18459004.
77. Viola D, Materazzi G, Valerio L, Molinaro E, Agate L, Faviana P, et al. Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study. J Clin Endocrinol Metab. 2015 Jan 15:jc20143825. PMID: 25590215.
78. Conzo G, Calo PG, Sinisi AA, De Bellis A, Pasquali D, Iorio S, et al. Impact of prophylactic central compartment neck dissection on locoregional recurrence of

differentiated thyroid cancer in clinically node-negative patients: a retrospective study of a large clinical series. Surgery. 2014 Jun;155(6):998-1005. PMID: 24856120.
79. Chang YW, Kim HS, Kim HY, Lee JB, Bae JW, Son GS. Should central lymph node dissection be considered for all papillary thyroid microcarcinoma? Asian journal of surgery / Asian Surgical Association. 2015 Apr 22. PMID: 25913730.
80. Del Rio P, Maestroni U, Sianesi M, Viani L, Vicente D, Stojadinovic A, et al. Minimally invasive video-assisted thyroidectomy for papillary thyroid cancer: a prospective 5-year follow-up study. Tumori. 2015 Mar-Apr;101(2):144-7. PMID: 25791536.
81. Donatini G, Castagnet M, Desurmont T, Rudolph N, Othman D, Kraimps JL. Partial Thyroidectomy for Papillary Thyroid Microcarcinoma: Is Completion Total Thyroidectomy Indicated? World J Surg. 2015 Nov 6. PMID: 26546190.
82. Kwan WY, Chow TL, Choi CY, Lam SH. Complication rates of central compartment dissection in papillary thyroid cancer. ANZ J Surg. 2015 Apr;85(4):274-8. PMID: 23890372.
83. Ahn D, Sohn JH, Park JY. Surgical complications and recurrence after central neck dissection in cN0 papillary thyroid carcinoma. Auris, nasus, larynx. 2014 Feb;41(1):63-8. PMID: 23886706.
84. Boute P, Merlin J, Biet A, Cuvelier P, Strunski V, Page C. Morbidity of central compartment dissection for differentiated thyroid carcinoma of the follicular epithelium. Eur Ann Otorhinolaryngol Head Neck Dis. 2013 Nov;130(5):245-9. PMID: 23835075.
85. Caliskan M, Park JH, Jeong JS, Lee CR, Park SK, Kang SW, et al. Role of prophylactic ipsilateral central compartment lymph node dissection in papillary thyroid microcarcinoma. Endocrine journal. 2012;59(4):305-11. PMID: 22240889.
86. Calo PG, Medas F, Pisano G, Boi F, Baghino G, Mariotti S, et al. Differentiated thyroid cancer: indications and extent of central neck dissection--our experience. Int J Surg Oncol. 2013;2013:625193. PMID: 24282633.
87. Chaplin JM, O'Brien CJ, McNeil EB, Haghighi K. Application of prognostic scoring systems in differentiated thyroid carcinoma. Aust N Z J Surg. 1999 Sep;69(9):625-8. PMID: 10515332.
88. Cirocchi R, Boselli C, Guarino S, Sanguinetti A, Trastulli S, Desiderio J, et al. Total thyroidectomy with ultrasonic dissector for cancer: multicentric experience. World journal of surgical oncology. 2012;10:70. PMID: 22540914.
89. Giordano D, Valcavi R, Thompson GB, Pedroni C, Renna L, Gradoni P, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid. 2012 Sep;22(9):911-7. PMID: 22827494.
90. Hartl DM, Mamelle E, Borget I, Leboulleux S, Mirghani H, Schlumberger M. Influence of prophylactic neck dissection on rate of retreatment for papillary thyroid carcinoma. World journal of surgery. 2013 Aug;37(8):1951-8. PMID: 23677562.
91. Lee YS, Nam KH, Chung WY, Chang HS, Park CS. Postoperative complications of thyroid cancer in a single center experience. J Korean Med Sci. 2010 Apr;25(4):541-5. PMID: 20357995.
92. Moo TA, Umunna B, Kato M, Butriago D, Kundel A, Lee JA, et al. Ipsilateral versus bilateral central neck lymph node dissection in papillary thyroid carcinoma. Annals of surgery. 2009 Sep;250(3):403-8. PMID: 19661784.

93. Palestini N, Borasi A, Cestino L, Freddi M, Odasso C, Robecchi A. Is central neck dissection a safe procedure in the treatment of papillary thyroid cancer? Our experience. Langenbecks Arch Surg. 2008 Sep;393(5):693-8. PMID: 18592264.
94. Raffaelli M, De Crea C, Sessa L, Giustacchini P, Revelli L, Bellantone C, et al. Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma. Surgery. 2012 Dec;152(6):957-64. PMID: 23158170.
95. Raj MD, Grodski S, Martin SA, Yeung M, Serpell JW. The role of fine-needle aspiration cytology in the surgical management of thyroid cancer. ANZ J Surg. 2010 Nov;80(11):827-30. PMID: 20969692.
96. Shindo ML, Sinha UK, Rice DH. Safety of thyroidectomy in residency: a review of 186 consecutive cases. Laryngoscope. 1995 Nov;105(11):1173-5. PMID: 7475870.
97. Sim R, Soo KC. Surgical treatment of thyroid cancer: the Singapore General Hospital experience. J R Coll Surg Edinb. 1998 Aug;43(4):239-43. PMID: 9735646.
98. So YK, Son YI, Hong SD, Seo MY, Baek CH, Jeong HS, et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. Surgery. 2010 Sep;148(3):526-31. PMID: 20189620.
99. Spear SA, Theler J, Sorensen DM. Complications after the surgical treatment of malignant thyroid disease. Mil Med. 2008 Apr;173(4):399-402. PMID: 18472632.
100. Sywak M, Cornford L, Roach P, Stalberg P, Sidhu S, Delbridge L. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery. 2006 Dec;140(6):1000-5; discussion 5-7. PMID: 17188149.
101. Yassa L, Cibas ES, Benson CB, Frates MC, Doubilet PM, Gawande AA, et al. Long-term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. Cancer. 2007 Dec 25;111(6):508-16. PMID: 17999413.
102. Kim BS, Kang KH, Kang H, Park SJ. Central neck dissection using a bilateral axillo-breast approach for robotic thyroidectomy: comparison with conventional open procedure after propensity score matching. Surgical laparoscopy, endoscopy & percutaneous techniques. 2014 Feb;24(1):67-72. PMID: 24487161.
103. Kim WW, Kim JS, Hur SM, Kim SH, Lee SK, Choi JH, et al. Is robotic surgery superior to endoscopic and open surgeries in thyroid cancer? World journal of surgery. 2011 Apr;35(4):779-84. PMID: 21253726.
104. Shah MD, Witterick IJ, Eski SJ, Pinto R, Freeman JL. Quality of life in patients undergoing thyroid surgery. J Otolaryngol. 2006 Aug;35(4):209-15. PMID: 17176794.
105. Francis D, Pearce E, Ni S, Garrett C, Penson D. Epidemiology of vocal fold paralyses after total thyroidectomy for well-differentiated thyroid cancer in a Medicare population. Otolaryngol Head Neck Surg. 2014 Apr;150(4):548-57. PMID: 24482349.
106. Kwan WY, Chow TL, Choi CY, Lam SH. Complication rates of central compartment dissection in papillary thyroid cancer. ANZ J Surg. 2013 Jul 26. PMID: 23890372.
107. Zerey M, Prabhu AS, Newcomb WL, Lincourt AE, Kercher KW, Heniford BT. Short-term outcomes after unilateral versus complete thyroidectomy for malignancy: a national perspective. American surgeon. 2009 Jan;75(1):20-4. PMID: 19213391.
108. Hundahl SA, Cady B, Cunningham MP, Mazzaferri E, McKee RF, Rosai J, et al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the united states during 1996. U.S. and German Thyroid Cancer Study Group. An American

College of Surgeons Commission on Cancer Patient Care Evaluation study. Cancer. 2000 Jul 1;89(1):202-17. PMID: 10897019.

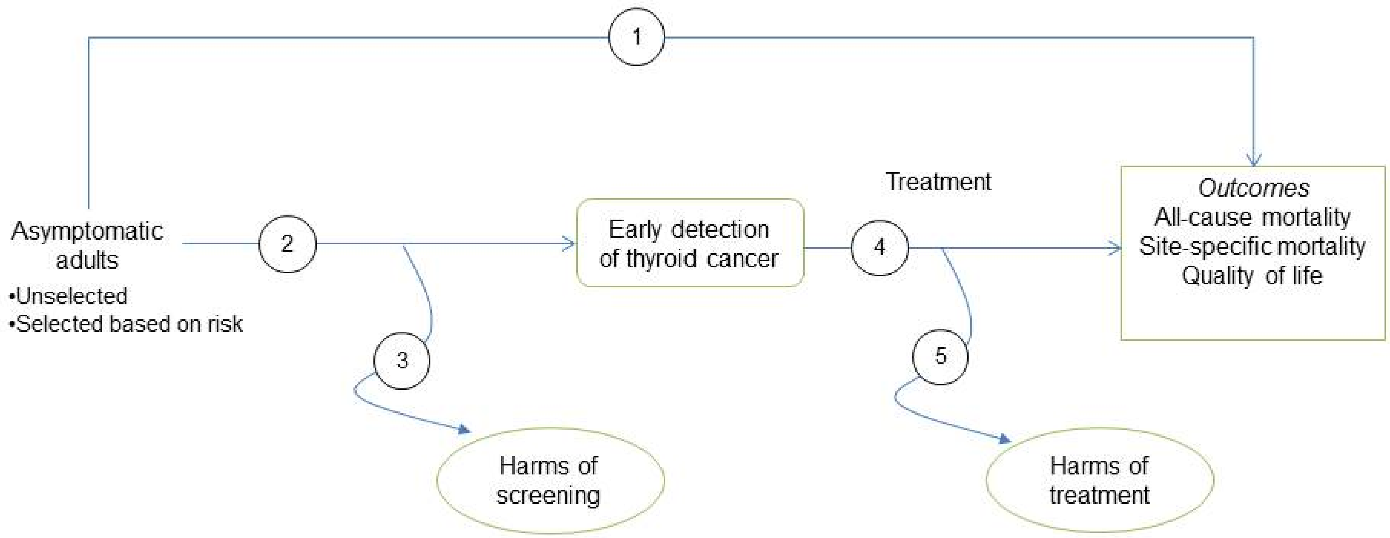
109. Holzer S, Reiners C, Mann K, Bamberg M, Rothmund M, Dudeck J, et al. Patterns of care for patients with primary differentiated carcinoma of the thyroid gland treated in Germany during 1996. U.S. and German Thyroid Cancer Group. Cancer. 2000 Jul 1;89(1):192-201. PMID: 10897018.
110. Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. J Clin Endocrinol Metab. 2008 Feb;93(2):504-15. PMID: 18029468.
111. Lang BH, Wong IO, Wong KP, Cowling BJ, Wan KY. Risk of second primary malignancy in differentiated thyroid carcinoma treated with radioactive iodine therapy. Surgery. 2012 Jun;151(6):844-50. PMID: 22341041.
112. Hakala TT, Sand JA, Jukkola A, Huhtala HS, Metso S, Kellokumpu-Lehtinen PL. Increased risk of certain second primary malignancies in patients treated for well-differentiated thyroid cancer. Int J Clin Oncol. 2015 Sep 26. PMID: 26410770.
113. Khang AR, Cho SW, Choi HS, Ahn HY, Yoo WS, Kim KW, et al. The risk of second primary malignancy is increased in differentiated thyroid cancer patients with a cumulative (131)I dose over 37 GBq. Clinical endocrinology. 2015 Jul;83(1):117-23. PMID: 25115234.
114. Lin CY, Lin CL, Huang WS, Kao CH. Risk of Breast Cancer in Patients With Thyroid Cancer Receiving or Not Receiving I-131 Treatment: A Nationwide Population-based Cohort Study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2015 Dec 30. PMID: 26719377.
115. Seo GH, Cho YY, Chung JH, Kim SW. Increased Risk of Leukemia After Radioactive Iodine Therapy in Patients with Thyroid Cancer: A Nationwide, Population-Based Study in Korea. Thyroid. 2015 Aug;25(8):927-34. PMID: 26133388.
116. Ronckers CM, McCarron P, Ron E. Thyroid cancer and multiple primary tumors in the SEER cancer registries. Int J Cancer. 2005 Nov 1;117(2):281-8. PMID: 15880372.
117. Hyer S, Kong A, Pratt B, Harmer C. Salivary gland toxicity after radioiodine therapy for thyroid cancer. Clin Oncol (R Coll Radiol). 2007 Feb;19(1):83-6. PMID: 17305259.
118. Ish-Shalom S, Durleshter L, Segal E, Nagler RM. Sialochemical and oxidative analyses in radioactive I131-treated patients with thyroid carcinoma. European journal of endocrinology / European Federation of Endocrine Societies [serial on the Internet]. 2008; (5): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/362/CN-00631362/frame.html.
119. Jeong SY, Kim HW, Lee SW, Ahn BC, Lee J. Salivary gland function 5 years after radioactive iodine ablation in patients with differentiated thyroid cancer: direct comparison of pre- and postablation scintigraphies and their relation to xerostomia symptoms. Thyroid. 2013 May;23(5):609-16. PMID: 23153322.
120. Solans R, Bosch JA, Galofre P, Porta F, Rosello J, Selva-O'Callagan A, et al. Salivary and lacrimal gland dysfunction (sicca syndrome) after radioiodine therapy. Journal of nuclear medicine. 2001 May;42(5):738-43. PMID: 11337569.
121. Grewal RK, Larson SM, Pentlow CE, Pentlow KS, Gonen M, Qualey R, et al. Salivary gland side effects commonly develop several weeks after initial radioactive iodine ablation. Journal of nuclear medicine. 2009 Oct;50(10):1605-10. PMID: 19759114.

122. Ryu CH, Ryu J, Ryu YM, Lee YJ, Lee EK, Kim SK, et al. Administration of Radioactive Iodine Therapy Within 1 Year After Total Thyroidectomy Does Not Affect Vocal Function. Journal of nuclear medicine. 2015 Oct;56(10):1480-6. PMID: 26272814.
123. Lin CM, Doyle P, Tsan YT, Lee CH, Wang JD, Chen PC, et al. 131I treatment for thyroid cancer and risk of developing primary hyperparathyroidism: a cohort study. Eur J Nucl Med Mol Imaging. 2014 Feb;41(2):253-9. PMID: 23982456.
124. Wu JX, Young S, Ro K, Li N, Leung AM, Chiu HK, et al. Reproductive outcomes and nononcologic complications after radioactive iodine ablation for well-differentiated thyroid cancer. Thyroid. 2015 Jan;25(1):133-8. PMID: 25289542.
125. Lang BH, Wong KP. Risk factors for nonsynchronous second primary malignancy and related death in patients with differentiated thyroid carcinoma. Annals of surgical oncology. 2011 Dec;18(13):3559-65. PMID: 21573833.
126. Jeannon JP, Orabi AA, Bruch GA, Abdalsalam HA, Simo R. Diagnosis of recurrent laryngeal nerve palsy after thyroidectomy: a systematic review. International journal of clinical practice. 2009 Apr;63(4):624-9. PMID: 19335706.
127. Shan CX, Zhang W, Jiang DZ, Zheng XM, Liu S, Qiu M. Routine central neck dissection in differentiated thyroid carcinoma: a systematic review and meta-analysis. Laryngoscope. 2012 Apr;122(4):797-804. PMID: 22294492.
128. Loyo M, Tufano RP, Gourin CG. National trends in thyroid surgery and the effect of volume on short-term outcomes. The Laryngoscope. 2013;123(8):2056-63. PMID.
129. Gourin CG, Tufano RP, Forastiere AA, Koch WM, Pawlik TM, Bristow RE. Volume-based trends in thyroid surgery. Archives of Otolaryngology–Head & Neck Surgery. 2010;136(12):1191-8. PMID.
130. Brown T, Sidhu S, Gill A, Robinson B, Learoyd D, Sywak M, et al. Increasing incidence of thyroid cancer is due to increased pathologic detection. Surgery. 2008 Dec;144(6):1038-43; discussion 43. PMID: 19041015.
131. Rubino C, de Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, et al. Second primary malignancies in thyroid cancer patients. Br J Cancer. 2003 Nov 3;89(9):1638-44. PMID: 14583762.
132. Sawka AM, Lakra DC, Lea J, Alshehri B, Tsang RW, Brierley JD, et al. A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors. Clinical endocrinology. 2008 Sep;69(3):479-90. PMID: 18284643.
133. Sawka AM, Lea J, Alshehri B, Straus S, Tsang RW, Brierley JD, et al. A systematic review of the gonadal effects of therapeutic radioactive iodine in male thyroid cancer survivors. Clinical endocrinology. 2008 Apr;68(4):610-7. PMID: 17973944.
134. Cappelli C, Castellano M, Pirola I, Gandossi E, De Martino E, Cumetti D, et al. Thyroid nodule shape suggests malignancy. European Journal of Endocrinology. 2006 Jul;155(1):27-31. PMID: 16793946.
135. Gul K, Ersoy R, Dirikoc A, Korukluoglu B, Ersoy PE, Aydin R, et al. Ultrasonographic evaluation of thyroid nodules: comparison of ultrasonographic, cytological, and histopathological findings. Endocrine. 2009 Dec;36(3):464-72. PMID: 19859839.
136. Seo H, Na DG, Kim JH, Kim KW, Yoon JW. Ultrasound-Based Risk Stratification for Malignancy in Thyroid Nodules: A Four-Tier Categorization System. Eur Radiol. 2015 Feb 14. PMID: 25680723.

137. Brito JP, Gionfriddo MR, Al Nofal A, Boehmer KR, Leppin AL, Reading C, et al. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab. 2014 Apr;99(4):1253-63. PMID: 24276450.
138. Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, et al. Benign and malignant thyroid nodules: US differentiation--multicenter retrospective study. Radiology. 2008 Jun;247(3):762-70. PMID: 18403624.
139. Kim JY, Lee CH, Kim SY, Jeon WK, Kang JH, An SK, et al. Radiologic and pathologic findings of nonpalpable thyroid carcinomas detected by ultrasonography in a medical screening center. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2008 Feb;27(2):215-23. PMID: 18204012.
140. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. Acta Cytol. 2012;56(4):333-9. PMID: 22846422.
141. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol. 2009;132(5):658-65. PMID.
142. Vashishta R, Mahalingam-Dhingra A, Lander L, Shin EJ, Shah RK. Thyroidectomy outcomes: a national perspective. Otolaryngol Head Neck Surg. 2012 Dec;147(6):1027-34. PMID: 22807486.
143. Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. Bmj. 2015;350:g7773. PMID.
144. Welch HG, Black WC. Overdiagnosis in cancer. J Natl Cancer Inst. 2010 May 5;102(9):605-13. PMID: 20413742.
145. Brito JP, Morris JC, Montori VM. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. Bmj. 2013;347:f4706. PMID.
146. La Vecchia C, Bosetti C, Malvezzi M, Garavello W, Bertuccio P, Levi F, et al. Author's reply to thyroid cancer: An epidemic of disease or an epidemic of diagnosis? Int J Cancer. 2014 Nov 1. PMID: 25363708.
147. Ho AS, Davies L, Nixon IJ, Palmer FL, Wang LY, Patel SG, et al. Increasing diagnosis of subclinical thyroid cancers leads to spurious improvements in survival rates. Cancer. 2015 Feb 24. PMID: 25712809.
148. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. Jama. 2006 May 10;295(18):2164-7. PMID: 16684987.
149. Leenhardt L, Grosclaude P, Cherie-Challine L, Thyroid Cancer C. Increased incidence of thyroid carcinoma in france: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. Thyroid. 2004 Dec;14(12):1056-60. PMID: 15650358.
150. Burgess JR. Temporal trends for thyroid carcinoma in Australia: an increasing incidence of papillary thyroid carcinoma (1982-1997). Thyroid. 2002 Feb;12(2):141-9. PMID: 11916283.
151. Liu S, Semenciw R, Ugnat AM, Mao Y. Increasing thyroid cancer incidence in Canada, 1970-1996: time trends and age-period-cohort effects. Br J Cancer. 2001 Nov 2;85(9):1335-9. PMID: 11720471.
152. Davies L, Ouellette M, Hunter M, Welch HG. The increasing incidence of small thyroid cancers: where are the cases coming from? Laryngoscope. 2010 Dec;120(12):2446-51. PMID: 21108428.

153. Morris LG, Myssiorek D. Improved detection does not fully explain the rising incidence of well-differentiated thyroid cancer: a population-based analysis. Am J Surg. 2010 Oct;200(4):454-61. PMID: 20561605.
154. Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev. 2009 Mar;18(3):784-91. PMID: 19240234.
155. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer. 2009 Aug 15;115(16):3801-7. PMID: 19598221.
156. Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. Thyroid. 2013 Jul;23(7):885-91. PMID: 23517343.
157. Durante C, Costante G, Lucisano G, Bruno R, Meringolo D, Paciaroni A, et al. The natural history of benign thyroid nodules. Jama. 2015 Mar 3;313(9):926-35. PMID: 25734734.
158. Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. World journal of surgery. 2008 May;32(5):747-53. PMID: 18264828.
159. Yu XM, Wan Y, Sippel RS, Chen H. Should all papillary thyroid microcarcinomas be aggressively treated? An analysis of 18,445 cases. Annals of surgery. 2011 Oct;254(4):653-60. PMID: 21876434.
160. Tuttle M. Clinicopathologic staging of differentiated thyroid cancer. [Internet] UpToDate2011 [cited 2016 April 6]; Available from: http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?10/39/10879?source=related_link.
161. Son EJ, Kim E-K, Kwak JY, Hong SW, Chang H-S. Positive predictive values of sonographic features of solid thyroid nodule. Clinical imaging. 2010 Mar-Apr;34(2):127-33. PMID: 20189077.
162. Lang BH-H. Incidental thyroid carcinoma by FDG-PET/CT: a study of clinicopathological characteristics. Annals of surgical oncology. 2011 Feb;18(2):472-8. PMID: 20740320.

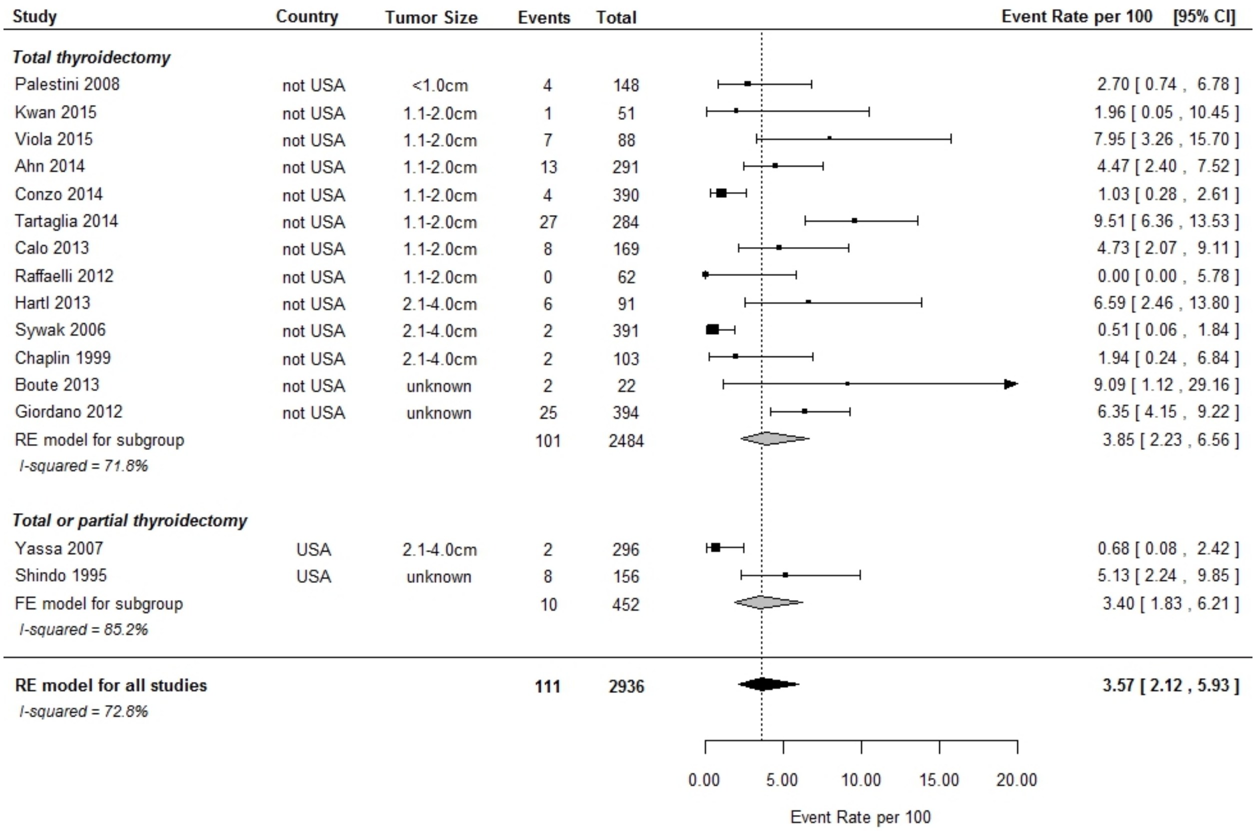
Figure 1. Analytic Framework and Key Questions



Key Questions

1. Compared with not screening, does screening adults for thyroid cancer lead to a reduced risk of thyroid-specific mortality or morbidity, reduced all-cause mortality, and/or improved quality of life?
2. What are the test performance characteristics of screening tests for detecting malignant thyroid nodules in adults?
3. What are the harms of screening adults for thyroid cancer?
4. Does treatment of screen-detected thyroid cancer reduce thyroid-specific mortality or morbidity, reduce all-cause mortality, and/or improve quality of life?
5. What are the harms of treating screen-detected thyroid cancer?

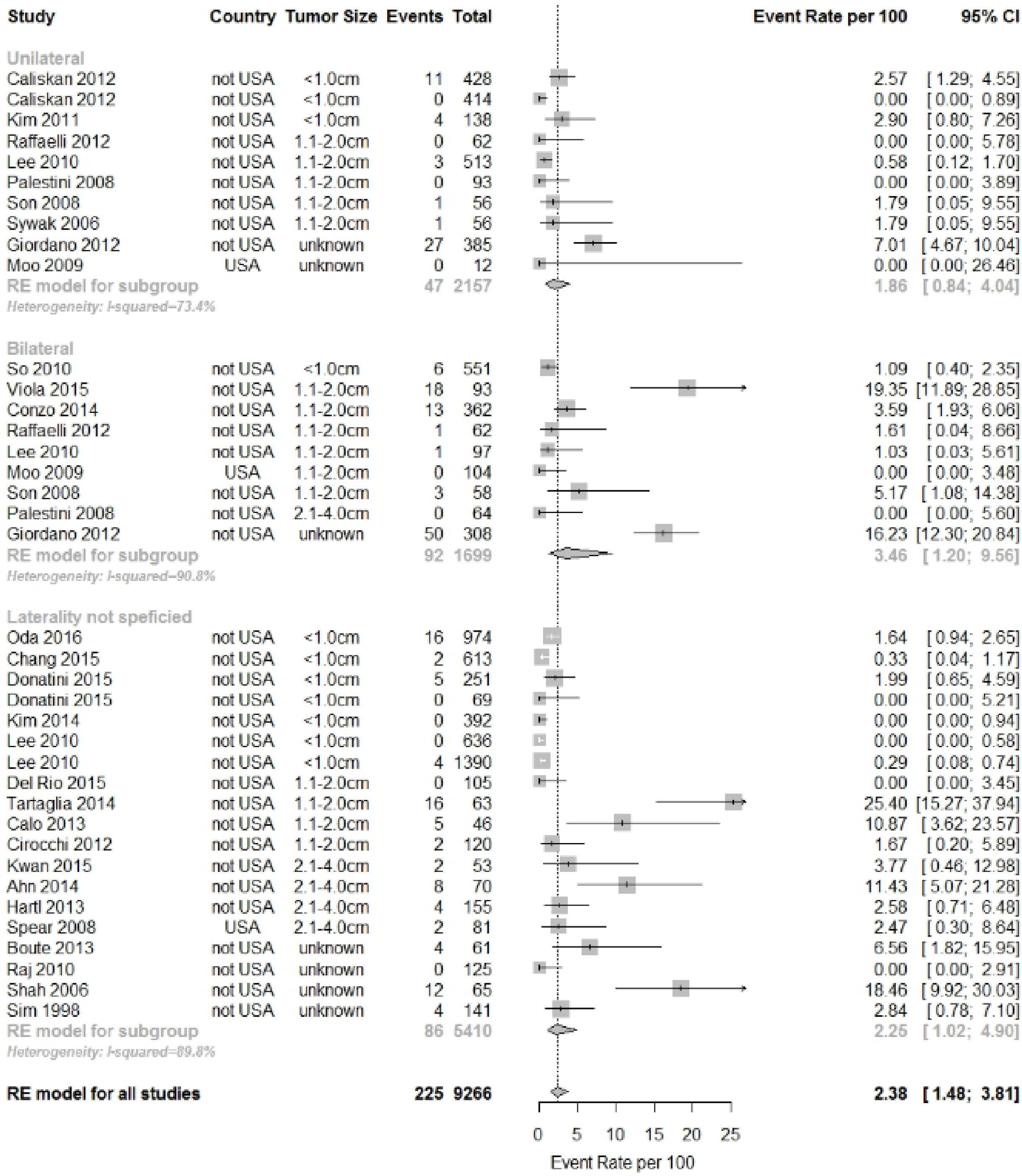
Figure 2. Key Question 5 Results: Permanent Hypoparathyroidism From Surgery, Stratified by Type of Thyroidectomy



Note: Tumor size=calculated mean tumor size.

Abbreviations: CI=confidence interval; RE=random effects; FE=fixed effects.

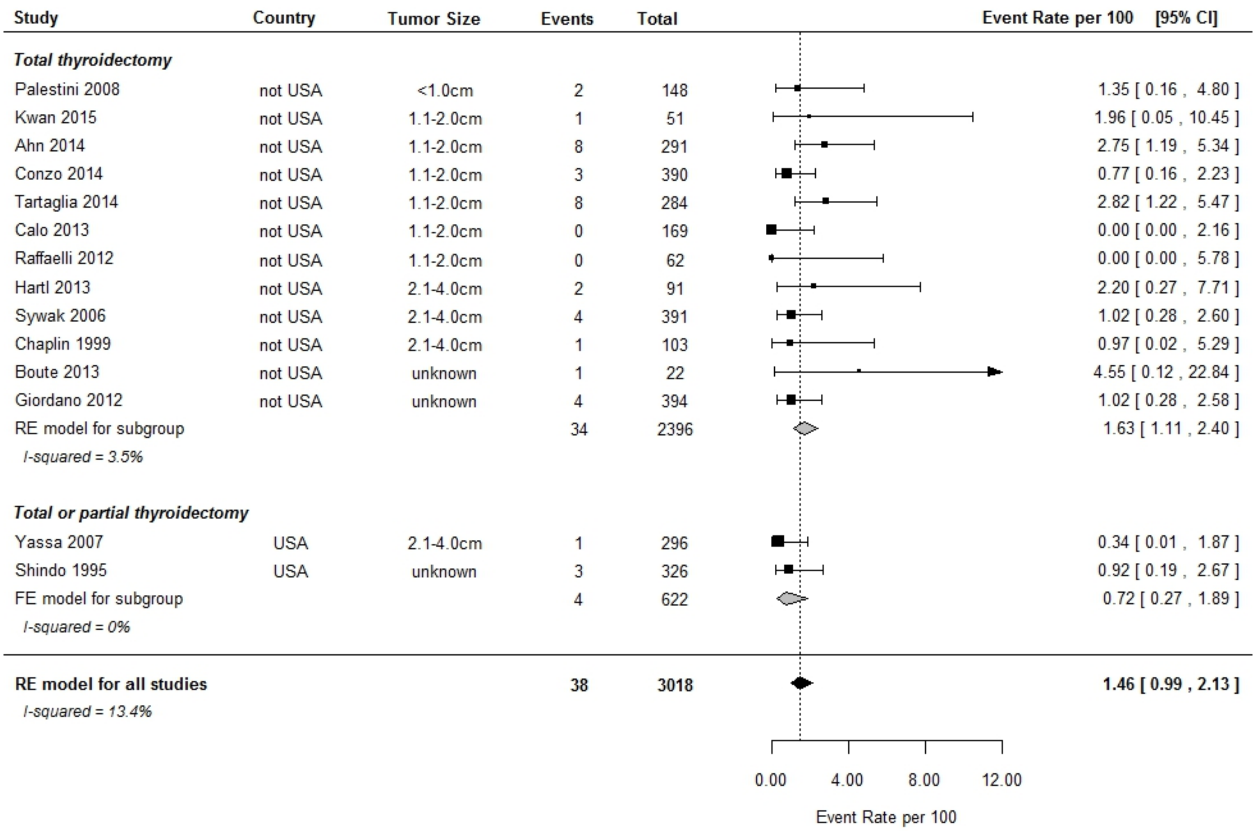
Figure 3. Key Question 5 Results: Permanent Hypoparathyroidism From Surgery, Stratified by Type of Lymph Node Dissection



Note: Tumor size=calculated mean tumor size.

Abbreviations: CI=confidence interval; RE=random effects; FE=fixed effects.

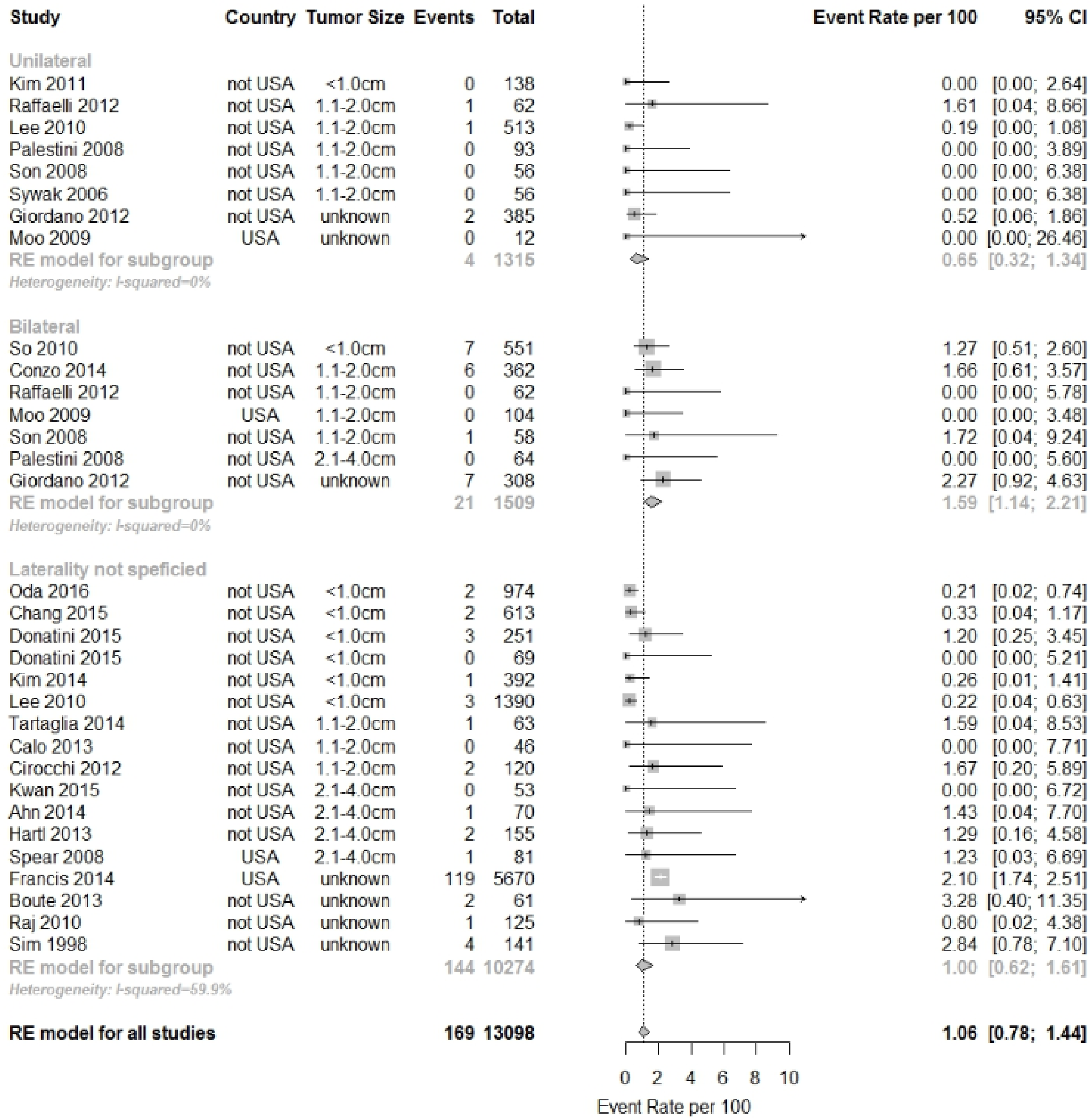
Figure 4. Key Question 5 Results: Permanent Recurrent Laryngeal Nerve Palsy From Surgery, Stratified by Type of Thyroidectomy



Note: Tumor size=calculated mean tumor size.

Abbreviations: CI=confidence interval; RE=random effects; FE=fixed effects.

Figure 5. Key Question 5 Results: Permanent Recurrent Laryngeal Nerve Palsy From Surgery, Stratified by Type of Lymph Node Dissection



Note: Tumor size=calculated mean tumor size.

Abbreviations: CI=confidence interval; RE=random effects; FE=fixed effects.

Table 1. Included Studies for Key Question 2: Test Performance Characteristics of Screening Tests for Detecting Malignant Thyroid Nodules in Adults

Screening Method								
Palpation	Suehiro, 2006[59] Fair	Japan 1989-2005	Retrospective	46,433	49	45*		X
Palpation	Brander, 1991[55] Fair	Finland 1989-1990	Prospective	253	35	51	X	X
Palpation	Brander, 1989[56] Fair	Finland 1988	Prospective	101	52	100	X	X
Palpation	Ishida, 1988[54] Fair	Japan 1980-1986	Prospective	152,651	NR	100		X
US	Kim, 2010[57] Fair	South Korea 2005-2007	Prospective	2,079	43	100	X	
US	Kim, 2008[58] Fair	South Korea 2004-2006	Retrospective	16,352	53	67	X	
US	Lee, 2003[61] Fair	South Korea 2003	Prospective	697	43	100		X
US	Chung, 2001[60] Fair	South Korea 1997-1998	Prospective	1,401	47	100		X
Palpation + diagnostic followup†	Ron, 1984[62] Fair	Israel Years NR	Prospective	443	29	49		X
Palpation + diagnostic followup‡	Shimaoka, 1982[63] Fair	USA 1977-1980	Prospective	1,500	39	64		X

* Percentage of exam visits that were women (calculated).
† Diagnostic followup consisted of technitium-99m thyroid scan and thyroid function tests.
‡ Diagnostic followup consisted of iodine 123 thyroid scan, blood tests, and indirect laryngoscopy.

Abbreviations: KQ=key question; NR=not reported; X=reported; US=ultrasound.

Table 2. Key Question 2 Results: Diagnostic Accuracy of Screening Ultrasound

Study, Year, Quality				
Kim, 2010[57] Fair	113 persons	≥1 characteristics:		
		Microcalcification		
		Irregular shape		
		Taller-than-wide shape		
		Ill-defined or microlobulated margin		
		Marked hypoechogenicity		
Kim, 2008[58] Fair	140 nodules	≥2 characteristics:	94.8%	86.6%
		Microcalcification	70.7% (57.3-81.9)	98.8% (93.4-99.8)
		Taller-than-wide or irregular shape	55.2% (41.5-68.3)	89% (80.2-94.8)
		Spiculated margin	48.3% (35-61.8)	97.6% (91.4-99.6)
		Marked hypoechogenicity	55.2% (41.5-68.3)	96.3% (89.7-99.2)
		Solid	93.1% (83.3-98)	51.2% (39.9-62.4)

* Calculated confidence intervals.
Note: Both studies report accuracy only among patients who had at least one study-defined malignant ultrasound characteristic, providing no followup on the vast majority (n=18,188) of screened individuals who did not have these characteristics.

Abbreviations: KQ=key question; CI=confidence interval.

Table 3. Key Question 2 Results: Cancer Yield From Thyroid Cancer Screening

Screening Method						
Palpation	Suehiro, 2006[59] Fair	46,433	4.3	Papillary, follicular	Based on surgical pathology or metastatic disease on clinical followup	Men: 58 Women: 38
	Brander, 1991[55] Fair	253	0	NA	Based on FNA cytology	NA
	Brander, 1989[56] Fair	99	0	NA	Based on FNA cytology	NA
	Ishida, 1988[54] Fair	152,651	1.4	Papillary, follicular, and 1 medullary	Based on surgical pathology	63
US	Kim, 2010[57] Fair	2,079	25.5	Papillary only	Based on FNA cytology	NR
	Kim, 2008[58] Fair	16,352	9.2	Papillary only	Based on FNA cytology	NR
	Lee, 2003[61] Fair	693	30.3	Papillary only	Based on surgical pathology	33
	Chung, 2001[60] Fair	1,397	26.5	Papillary and 1 insular	Malignant on FNA biopsy and confirmed with surgical pathology	41
Palpation + diagnostic followup*	Ron, 1984[62] Fair	443	0	NA	Based on surgical pathology	NA
Palpation + diagnostic followup[†]	Shimaoka, 1982[63] Fair	1,500	11.3	NR	Based on surgical pathology	NR

* Diagnostic followup consisted of thyroid scan with technetium-99m and thyroid function tests.
[†] Diagnostic followup consisted of thyroid imaging by iodine 123 thyroid scan, blood tests, and indirect laryngoscopy.

Abbreviations: KQ=key question; US=ultrasonography; FNA=fine-needle aspiration; NA=not applicable; NR=not reported.

Table 4. Included Studies and Results for Key Question 3: Harms of Screening and Diagnostic Fine-Needle Aspiration

Study, Year, Quality							
Hobbs, 2014[65] Fair	USA 2010-2011	Retrospective	400	55	83	To determine the proportion of thyroid nodules undergoing ultrasound-guided FNA that do not meet Society of Radiologists in Ultrasound recommendations from 2005*	Persons undergoing FNA not meeting Society of Radiologists in Ultrasound recommendations: 96/400 (24.0%)
Abu-Yousef, 2011[67] Fair	USA 2006-2007	Retrospective	582†	56	71	To determine whether there is a significantly increased incidence of bleeding complications from ultrasound-guided FNA of neck masses in patients on antithrombotic or anticoagulant therapy (compared to patients not on therapy)	Major complications (hospitalization or intervention required): 0/582 (0%) Post-procedural hematoma: 5/582‡ (0.9%)
Ito, 2005[66] Fair	Japan 1990-2002	Retrospective	4,912	NR§	NR§	To investigate the relationship between needle tract implantation of papillary thyroid cancer and clinicopathological characteristics	Tumor implantation: 7/4,912 (0.14%)

* FNA is appropriate for nodules that have a maximum diameter of 1 cm or larger and have microcalcifications; nodules that are 1.5 cm or larger and are solid or have coarse calcifications; nodules that are 2 cm or larger and are mixed solid and cystic; and nodules with substantial growth since the prior ultrasound.

† n for thyroid masses only.

‡ Difference in incidence of hematomas between persons who were on antiplatelet or anticoagulant therapy versus persons not on therapy not statistically significant.

§ Data reported for 10 persons with outcomes: mean age 65 years and 90% female.

Abbreviations: FNA=fine-needle aspiration; KQ=key question; NR=not reported.

Table 5. Included Studies and Results for Key Question 4: Treatment Effectiveness of Screen-Detected Thyroid Cancer on Patient Health Outcomes

Study, Year, Quality									
Davies, 2010[69] Fair	USA 1973-2005	Retrospective observational Papillary	IG	35,223	46	77	7.6 (0-32)	161/35,223 (0.45%)	20-year survival: 99% (93% to 100%) *10-year survival: Recommended: 99.5% (99.4% to 99.6%)
			CG	440	51	81	5.9 (0-31)	6/440 (1.4%) *Recommended: 4/216 (1.9%) *Not recommended: 1/165 (0.6%) (p=0.10)	20-year survival: 97% (96% to 100%) 10-year survival: *Recommended: 98.1% (95.9% to 100%) *Not recommended: 99.3% (97.8% to 100%)
			IG vs. CG		p<0.001	p=0.06	p<0.001	p=0.09	20-year p<0.001
Oda, 2016[73] Ito, 2014[72†] Ito, 2010[70] Ito, 2003[71] Fair	Japan 1993-2004	Prospective observational Papillary microcarcinomas	IG	1,055	52	91	6.3 (0.08-15.3)	2/1,055 (0.2%)	NR
			CG	340	NR	92	6.2 (1.5-15.6)	0/340 (0%)	NR
	Japan 2005-2013	Prospective observational Papillary microcarcinomas	IG	974	55‡	88	3.9‡ (1.0-9.7)	0/974 (0%)	NR
			CG	1179	57‡	88	3.9‡ (1.0-9.7)	0/1179 (0%)	NR

* Subset of population (1988-2005) that had treatment recommendation as a variable and refers to SEER classification: Recommended=recommended to be treated; Not recommended (NR)=not recommended to be treated.
[†] Recurrence in the observation group is reported in this study.
[‡] Median.

Abbreviations: CG=control or comparator group, no (immediate) surgical treatment; IG=intervention group, surgical treatment; KQ=key question.

Table 6. Included Studies for Key Question 5: Harms of Surgical Treatment of Screen-Detected Thyroid Cancer

Author, Year, Quality	Country, Recruiting Years	Study Design	N	Mean Age (years)	Women (%)	Permanent Hypoparathyroidism	Permanent RLN Palsy	Other Serious Harms
Oda, 2016[73] Fair	Japan 2005-2013	Prospective observational	974*	56	88	X	X	Wound infection
Chang, 2015[79] Fair	South Korea 2002-2013	Retrospective observational	613	46	91	X	X	Hematoma requiring reoperation
Del Rio, 2015[80] Fair	Italy 2005-2007	Prospective observational	105	59	82	X	NR	NR
Donatini, 2015[81] Fair	France 1991-2015	Prospective observational	880	48	81	X	X	NR
Kwan, 2015[82] Fair	Hong Kong 1995-2011	Retrospective observational	105	51	78	X	X	Airway injury
Viola, 2015[77] Fair	Italy 2008-2010	RCT	181	45	75	X	NR	NR
Ahn, 2014[83] Fair	South Korea 2000-2007	Retrospective observational	361	48	85	X	X	NR
Conzo, 2014[78] Fair	Italy 1998-2005	Retrospective observational	752	45	80	X	X	Hematoma requiring reoperation
Francis, 2014[105] Fair	USA 1991-2009	Retrospective observational	5,670	74	69	NR	X	NR
Kim, 2014[102] Fair	South Korea 2011-2012	Retrospective observational	515	46	82	X	X	Wound infection
Tartaglia, 2014[74] Fair	Italy 2000-2010	Retrospective observational	347	48	78	X	X	NR
Boute, 2013[84] Fair	France 1998-2009	Retrospective observational	83	51	55	X	X	NR
Calo, 2013[86] Fair	Italy 2002-2008	Retrospective observational	215	51	81	X	X	Hematoma requiring reoperation
Hartl, 2013[90] Fair	France 1995-2010	Retrospective observational	246	46	78	X	X	NR
Caliskan, 2012[85] Fair	South Korea 2000-2005	Retrospective observational	842	46	91	X	NR	Tracheal injury
Cirocchi, 2012[88] Fair	Italy 2009-2010	CCT	321	NR	55	X	X	Wound infection
Giordano, 2012[89] Fair	Italy 1997-2010	Retrospective observational	1,087	NR	NR	X	X	NR
Hyun, 2012[75‡] Fair	South Korea 2002-2009	Retrospective observational	152	47	81	X	NR	NR
Raffaelli, 2012[94] Fair	Italy 2008-2010	CCT	186	43	80	X	X	NR
Kim 2011[103] Fair	South Korea 2008-2009	Retrospective observational	302	52	75	X	X	Wound infection, chyle fistula
Lee, 2010[91] Fair	South Korea 2006-2007	Retrospective observational	2,636	47	86	X	X	NR

Table 6. Included Studies for Key Question 5: Harms of Surgical Treatment of Screen-Detected Thyroid Cancer

Author, Year, Quality	Country, Recruiting Years	Study Design	N	Mean Age (years)	Women (%)	Permanent Hypoparathyroidism	Permanent RLN Palsy	Other Serious Harms
Raj, 2010[95] Fair	Australia 1993-2008	Retrospective observational	125	48	76	X	X	NR
So, 2010[98] Fair	South Korea 2005-2009	Retrospective observational	551	50	80	X	X	Hematoma requiring reoperation
Moo, 2009[92] Fair	USA 2003-2009	Prospective observational	116	47	76	X	X	NR
Zerey, 2009[§107] Fair	USA 1999-2003	Retrospective observational	13,854	48	76	NR	NR	Wound infection, tracheal or laryngeal perforation, esophageal perforation, adverse cardiopulmonary event (i.e., MI, CVA, PE), pneumonia, renal failure, same-stay mortality
Palestini, 2008[93] Fair	Italy 2000-2006	Retrospective observational	305	47	73	X	X	NR
Son, 2008[76] Fair	South Korea 2003-2005	Retrospective observational	114	48	75	X	X	NR
Spear, 2008[99] Fair	USA 1996-2000	Retrospective observational	82	42[†]	70	X	X	Phrenic nerve injury
Yassa, 2007[101] Fair	USA 1995-2004[‡]	Retrospective observational	2,587	50	88	X	X	NR
Shah, 2006§[104] Fair	Canada 2002-2003	Prospective observational	76	46	82	X	NR	NR
Sywak, 2006[100] Fair	Australia 1995-2005	Retrospective observational	447	42	72	X	X	Wound infection
Holzer, 2000[109§] Fair	Germany 1996	Prospective observational	2,376	51[†]	77	NR	NR	Wound infection
Hundahl, 2000[108§] Fair	USA 1996	Prospective observational	5,584	45[†]	75	NR	NR	Wound infection, airway problem, postoperative death
Chaplin, 1999[87] Fair	Australia NR	Retrospective observational	175	45[†]	70	X	X	NR
Sim, 1998[97] Fair	Singapore 1988-1994	Retrospective observational	149	45[†]	75	X	X	NR
Shindo, 1995[96] Fair	USA 1989-1994	Retrospective observational	181	NR	90	X	X	NR

* N analyzed for persons evaluated for surgical harms; total study population was 2,153.
[†] Median or calculated based on median.
[‡] 2002-2004 for surgical harms data.
[§] Not included in meta-analysis because study does not report permanent hypoparathyroidism or RLN palsy, or it does not clearly define outcomes as permanent or temporary.

Abbreviations: CCT=controlled clinical trial; CVA=cerebrovascular accident; KQ=key question; NR=not reported; RCT=randomized, controlled trial; RLN=recurrent laryngeal nerve; MI=myocardial infarction; PE=pulmonary embolus; X=reported.

Table 7. Included Studies for Key Question 5: Harms of RAI Treatment of Screen-Detected Thyroid Cancer

Hakala, 2015[112] Fair	Finland 1981-2002	Retrospective observational	910	49	82	X	NR	NR
Khang, 2015[113] Fair	South Korea 1976-2010	Retrospective observational	2,468	46	84	X	NR	NR
Lin, 2015[114] Fair	Taiwan 2000-2008	Prospective observational	10,361	46	100	X	NR	NR
Seo, 2015[115] Fair	South Korea 2008-2013	Retrospective observational	211,360	48	82	X	NR	NR
Lang, 2012[111] Lang, 2011[125] Fair	Hong Kong 1971-2009	Retrospective observational	895	47	81	X	NR	NR
Iyer, 2011[45] Fair	USA 1973-2006	Retrospective observational	37,176	NR	NR	X	NR	NR
Brown, 2008[110] Fair	USA 1973-2002	Retrospective observational	28,286*	42[†]	76	X	NR	NR
Ronckers, 2005[116] Fair	USA 1973-2000	Prospective observational	29,456	43[†]	75	X	NR	NR
Ryu, 2015 [122] Fair	South Korea 2010	Prospective observational	160	49	81	NR	X	NR
Jeong, 2013[119] Fair	South Korea 2003-2006	Prospective observational	213	47	91	NR	X	NR
Grewal, 2009[121] Fair	USA 1995-2003	Retrospective observational	262	45	66	NR	X	NR
Ish-Shalom, 2008[118] Fair	Israel NR	Prospective observational	40	48	100	NR	X	NR
Hyer, 2007[117] Fair	UK NR	Prospective observational	76	51	75	NR	X	NR
Solans, 2001[120] Fair	Spain 1990-1995	Prospective observational	79	46	86	NR	X[‡]	NR
Wu, 2015[124] Fair	USA 1999-2008	Retrospective observational	18,850[§]	47	100	NR	NR	Reproductive outcomes[‖]
Lin, 2014[123] Good	Taiwan 1997-2008	Retrospective observational	8,946	44	81	NR	NR	Hyperparathyroidism

* 28,286 is the total number included in the RAI analysis; total n for the study is 30,278.
[†] Median.
[‡] Study also reported dry eyes.
[§] Total cohort included 25,333 persons; the reproductive outcomes subset included 18,850 women.
[‖] Birthrate and median time to first delivery.

Abbreviations: KQ=key question; NR=not reported; X=reported.

Table 8. Results for Key Question 5: Harms of Surgical Treatment of Screen-Detected Thyroid Cancer

Study, Year, Quality	Treatment Arm	LN Indication	LN Side	Histology	Mean Tumor Size Category (cm)	Lymph Node Metastases (%)	N	N (%) Hypoparathyroidism	N (%) RLN Palsy
Oda, 2016*[73] Fair	All	NR	NR	Micropapillary	0-1.0	0	974	16 (2)	2 (0.2)
Chang, 2015[79] Fair	All	NR	Ipsilateral and bilateral	Micropapillary	0-1.0	39	613	2 (0)	2 (0)
Del Rio, 2015[80] Fair	All	NR	NR	Papillary	1.1-2.0	NR	105	0 (0)	NR
Donatini, 2015[81] Fair	Less than TT	NR	NR	Micropapillary	0-1.0	1	69	0 (0)	0 (0)
	TT	NR	NR	Micropapillary	0-1.0	14	251	5 (2)	3 (1)
Kwan, 2015[82] Fair	TT	NA	NA	Papillary	1.1-2.0‡	NR	51	1 (2)	1 (2)
	TT+ LND	Prophylactic	Ipsilateral and bilateral	Papillary	2.1-4.0‡	NR	53	2 (4)	0 (0)
Viola, 2015[77] Fair	TT	NA	NA	Papillary	1.1-2.0	7	88	7 (8)	NR
	TT+ LND	Prophylactic	Bilateral	Papillary	1.1-2.0	46	93	18 (19)	NR
Ahn, 2014[83] Fair	TT	NA	NA	Papillary	1.1-2.0	NR	291	13 (4)	8 (3)
	TT+ LND	Prophylactic	NR	Papillary	2.1-4.0	64	70	8 (11)	1 (1)
Conzo, 2014[78] Fair	TT	NA	NA	Differentiated	1.1-2.0	NR	390	4 (1)	3 (1)
	TT+ LND	Prophylactic	Bilateral	Differentiated	1.1-2.0	NR	362	13 (4)	6 (2)
Francis, 2014[105] Fair	TT	NA	NA	Mixed (all)	Unable to determine	NR	5,670†	NR	119 (2) †
Kim, 2014[102] Fair	TT+ LND	Prophylactic and therapeutic	Ipsilateral and bilateral	Papillary	0-1.0	42	392	0 (0)	1 (0)
Tartaglia, 2014[74] Fair	TT	NA	NA	Papillary	1.1-2.0	NR	284	27 (10)	8 (3)
	TT+ LND	NR	NR	Papillary	1.1-2.0	NR	63	16 (25)	1 (2)
Boute, 2013[84] Fair	TT	NA	NA	Differentiated	Unable to determine	44	22	2 (9)	1 (5)
	TT+ LND	NR	NR	Differentiated	Unable to determine	44	61	4 (7)	2 (3)
Calo, 2013[86] Fair	TT	NA	NA	Differentiated	1.1-2.0	NR	169	8 (5)	0 (0) †
	TT+ LND	Prophylactic	NR	Differentiated	1.1-2.0	NR	46	5 (11)	0 (0) †
Hartl, 2013[90] Fair	TT	NA	NA	Papillary	2.1-4.0‡	NR	91	6 (7) †	2 (2) †
	TT+ LND	Prophylactic	Ipsilateral and bilateral	Papillary	2.1-4.0‡	52	155	4 (3) †	2 (1) †
Caliskan, 2012[85] Fair	Less than TT+ LND	Prophylactic	Ipsilateral	Micropapillary	0-1.0‡	26	414	0 (0)	NR
	TT+ LND	Prophylactic	Ipsilateral	Micropapillary	0-1.0‡	26	428	11 (3)	NR
Cirocchi, 2012[88] Fair	TT+ LND	NR	NR	Differentiated	1.1-2.0‡	NR	120	2 (2)	2 (2)

Table 8. Results for Key Question 5: Harms of Surgical Treatment of Screen-Detected Thyroid Cancer

Study, Year, Quality	Treatment Arm	LN Indication	LN Side	Histology	Mean Tumor Size Category (cm)	Lymph Node Metastases (%)	N	N (%) Hypoparathyroidism	N (%) RLN Palsy
Giordano, 2012[89] Fair	TT	NA	NA	Papillary	Unable to determine	NR	394	25 (6)	4 (1)
	TT+ LND	Prophylactic	Ipsilateral	Papillary	Unable to determine	NR	385	27 (7)	2 (1)
	TT+ LND	Prophylactic	Bilateral	Papillary	Unable to determine	NR	308	50 (16)	7 (2)
Hyun, 2012[75] Fair	Less than TT	NA	NA	Micropapillary	0-1.0	NR	87	0 (0)[¶]	NR
	Less than TT+ LND	Prophylactic	Ipsilateral	Micropapillary	0-1.0	29	65	0 (0)[¶]	NR
Raffaelli, 2012[94] Fair	TT	NA	NA	Papillary	1.1-2.0	10	62	0 (0)[†]	0 (0)[†]
	TT+LND	Prophylactic	Ipsilateral	Papillary	1.1-2.0	29	62	0 (0)[†]	1 (2)[†]
	TT+LND	Prophylactic	Bilateral	Papillary	1.1-2.0	42	62	1 (2)[†]	0 (0)[†]
Kim, 2011[103] Fair	TT+LND	Prophylactic	Ipsilateral	Micropapillary	0-1.0	NR	138	4 (3)	0 (0)
Lee, 2010[91] Fair	Less than TT+LND	Prophylactic and therapeutic	NR	Mixed (all)	0-1.0	NR	636	0 (0)	NR
	TT+LND	Prophylactic and therapeutic	NR	Mixed (all)	0-1.0	NR	1,390	4 (0)	3 (0)
	TT+LND	Therapeutic	Ipsilateral	Mixed (all)	1.1-2.0	NR	513	3 (1)	1 (0)
	TT+LND	Therapeutic	Bilateral	Mixed (all)	1.1-2.0	NR	97	1 (1)	NR
Raj, 2010[95] Fair	All	NR	NR	Mixed (all)	Unable to determine	1	125	0 (0)[†]	1 (1)[†]
So, 2010[98] Fair	All	Prophylactic	Bilateral	Micropapillary	0-1.0	37	551	6 (1)	7 (1)
Moo, 2009[92] Fair	TT+LND	Prophylactic	Ipsilateral	Papillary	Unable to determine	NR	12	0 (0)	0 (0)
	TT+LND	Prophylactic	Bilateral	Papillary	1.1-2.0	45	104	0 (0)	0 (0)
Zerey, 2009[107] Fair	Less than TT	NA	NA	NR	Unable to determine	NR	4,238	NR[¶]	NR[¶]
	TT	NA	NA	NR	Unable to determine	NR	9,616	NR[¶]	NR[¶]
Palestini, 2008[93] Fair	TT	NA	NA	Papillary	0-1.0	NR	148	4 (3)	2 (1)[†]
	TT+LND	Prophylactic	Ipsilateral	Papillary	1.1-2.0	22	93	0 (0)	0 (0)[†]
	TT+LND	Therapeutic	Bilateral	Papillary	2.1-4.0	72	64	0 (0)	0 (0)[†]
Son, 2008[161] Fair	TT+LND	Prophylactic	Ipsilateral	Papillary	1.1-2.0	NR	56	1 (2)	0 (0)
	TT+LND	Prophylactic	Bilateral	Papillary	1.1-2.0	NR	58	3 (5)	1 (2)
Spear, 2008[99] Fair	All	NR	NR	Mixed (all)	2.1-4.0[‡]	13	81	2 (2)	1 (1)
Yassa, 2007[101] Fair	Less than TT	NA	NA	NR	2.1-4.0	NR	296	2 (1)[†]	1 (0)[†]

Table 8. Results for Key Question 5: Harms of Surgical Treatment of Screen-Detected Thyroid Cancer

Study, Year, Quality	Treatment Arm	LN Indication	LN Side	Histology	Mean Tumor Size Category (cm)	Lymph Node Metastases (%)	N	N (%) Hypoparathyroidism	N (%) RLN Palsy
Shah, 2006[104] Fair	All	NR	Ipsilateral and bilateral	Mixed (all)	Unable to determine	9	65	12 (18)[¶]	NR
Sywak, 2006[100] Fair	TT	NA	NA	Papillary	2.1-4.0	NR	391	2 (1)	4 (1)[†]
	TT+LND	Prophylactic	Ipsilateral	Papillary	1.1-2.0	NR	56	1 (2)	0 (0)[†]
Holzer, 2000[109] Fair	All	NR	NR	Differentiated	2.1-4.0[‡]	NR	2,376	NR[¶]	NR[¶]
Hundahl, 2000[108] Fair	Less than TT (lobectomy)	NA	NA	Mixed (all)	1.1-2.0[‡]	NR	903	NR[¶]	NR[¶]
	Less than TT (near-total)	NA	NA	Mixed (all)	1.1-2.0[‡]	NR	840	NR[¶]	NR[¶]
	TT	NA	NA	Mixed (all)	1.1-2.0[‡]	NR	1,928	NR[¶]	NR[¶]
	TT+LND	NR	NR	Mixed (all)	1.1-2.0[‡]	NR	1,464	NR[¶]	NR[¶]
Chaplin, 1999[87] Fair	TT	NA	NA	Differentiated	2.1-4.0[‡]	NR	103	2 (2)[†]	1 (1)[†]
Sim, 1998[97] Fair	All	NR	NR	Mixed (all)	Unable to determine	NR	141	4 (3)	4 (3)
Shindo, 1995[96] Fair	All	NA	NA	NR	Unable to determine	NR	156	8 (5) [§]	NR
	All	NA	NA	NR	Unable to determine	NR	326	NR	3 (1)[†]

* N analyzed for persons evaluated for surgical harms; total study population was 2,153.
[†] Followup not defined.
[‡] Calculated.
[§] Followup ≤6 months.
[¶] Not included in meta-analysis because study does not report permanent hypoparathyroidism or RLN palsy, or it does not clearly define outcomes as permanent or temporary.

Note: Studies with "All" for treatment arm indicate mixed surgery types ranging from less than total thyroidectomy to total thyroidectomy with or without lymph node dissection, and outcomes were not reported separately by surgery type.

Abbreviations: KQ=key question; LND=lymph node dissection; NA=not applicable; NR=not reported; RLN=recurrent laryngeal nerve; TT=total thyroidectomy.

Table 9. Results for Key Question 5: Harms of RAI Treatment of Screen-Detected Thyroid Cancer

Author, Year, Quality	Country, Recruiting Years	N	Radiation Dose (mean or median)	Followup Duration (years)	Permanent Outcomes
Second Primary Malignancy					**N outcomes/N population; incidence per 10,000 person-years; excess risk per 10,000 person-years compared with controls without thyroid cancer**
Hakala, 2015[112] Fair	Finland 1981-2002	910*	Median: 3.7 GBq (100 mCi) Mean: 5.3 GBq (143.2 mCi)	Mean: 16.2	Second primary malignancy diagnosed at least 12 months after thyroid cancer diagnosis: N / Incidence / Excess risk‡ All: 109/910; 77.3; N/A Stratified by RAI dose: >3.7 GBq RAI: 27/214; 93.8; 25.3 ≤3.7 GBq RAI: 56/526; 67.4; -4.6 No RAI: 26/170; 89.1; 29.2 p=NR; p=NR; p=NR Rate ratio for second primary malignancy at any site vs. controls‡ without thyroid cancer: >3.7 GBq RAI: 1.37 (95% CI, 0.90 to 2.09) ≤3.7 GBq RAI: 0.94 (95% CI, 0.70 to 1.25) No RAI: 1.49 (95% CI, 0.96 to 2.30)
Khang, 2015[113] Fair	South Korea 1976-2010	2468	Mean: 5.1 GBq (137.8 mCi)	Median: 7.0	Nonthyroid second primary malignancy diagnosed ≥12 months after thyroid cancer diagnosis or RAI treatment: N / Incidence / Excess risk‡ All: 61/2468; 27.9†; N/A Stratified by RAI dose: ≥37 GBq RAI: 11/69; 131.4; 101.4 22.3–36.9 GBq RAI: 2/44; 54.6; 24.6 5.56–22.2 GBq RAI: 6/302; 19.0; -11.1 1.1–5.55 GBq RAI: 18/981; 23.7; -6.4 No RAI: 24/1072; 30.9; 0.9 p=NR; p=NR; p=NR Adjusted odds ratio‡ for second primary malignancy at any site: ≥37 GBq RAI: 5.54 (95% CI, 2.64 to 11.63) 22.3–36.9 GBq RAI: 2.04 (95% CI, 0.48 to 8.70) 5.56–22.2 GBq RAI: 0.67 (95% CI, 0.27 to 1.66) 1.1-5–55 GBq RAI: 0.87 (95% CI, 0.47 to 1.62) No RAI: reference p<0.001
Lin, 2015[114] Fair	Taiwan 2000-2008	10,361	NR	Median: 6.5	Breast cancer diagnosed after thyroid cancer diagnosis: N / Incidence / Excess risk‡ All: 129/10,361; 18.6; N/A Stratified by RAI dose: >4.44 GBq RAI: 30/2848; 15.8; 2.7 ≤4.44 GBq RAI: 61/4221; 21.0; 7.9 No RAI: 38/3,292; 17.7; 4.6 p=NR; p=NR; p=NR

Table 9. Results for Key Question 5: Harms of RAI Treatment of Screen-Detected Thyroid Cancer

Author, Year, Quality	Country, Recruiting Years	N	Radiation Dose (mean or median)	Followup Duration (years)	Permanent Outcomes
					Adjusted hazard ratio[§] for breast cancer diagnosis: >4.44 GBq RAI: 0.90 (95% CI, 0.56 to 1.46) ≤4.44 GBq RAI: 1.18 (95% CI, 0.79 to 1.77) No RAI: reference
Seo, 2015[115] Fair	South Korea 2008-2013	211,360	Mean: 3.7 GBq (100 mCi)	Median:2.4[†]	Leukemia diagnosed after thyroid cancer surgery or RAI treatment: N / Incidence[‡] / Excess risk All: 72/211,360 / 1.3 / N/A Stratified by RAI dose: >5.5 GBq RAI: 15/23,356 / 2.1 / NR 3.7–5.5 GBq RAI: 21/28,441 / 3.0 / NR 1.1–3.7 GBq RAI: 6/28,397 / 0.9 / NR ≤1.1 GBq RAI: 4/23,547 / 0.6 / NR No RAI: 26/107,619 / 1.0 / NR p=NR / p=0.001 / p=NR Adjusted hazard ratios[¶] for leukemia diagnosis: >5.5 GBq RAI: 2.08 (95% CI, 1.09 to 3.94) 3.7–5.5 GBq RAI: 3.09 (95% CI, 1.74 to 5.51) 1.1–3.7 GBq RAI: 0.88 (95% CI, 0.36 to 2.14) ≤1.1 GBq RAI: 0.62 (95% CI, 0.22 to 1.77) No RAI: reference
Lang, 2012[111] Lang, 2011[162] Fair	Hong Kong 1971-2009	895	3 GBq[‖] (80 mCi)	Median: 7.8	Nonthyroid second primary malignancy diagnosed ≥12 months after thyroid cancer diagnosis: N / Incidence / Excess risk All: 64/895 / 61.5[†] / N/A Stratified by RAI use: RAI: 56/643 / NR / NR No RAI: 8/252 / NR / NR p=0.004 / p=NR / p=NR Standardized incidence ratio[¶] for second primary malignancy at any site vs. the general population: RAI: 1.51 (95% CI, 1.14 to 1.96) No RAI: 0.84 (95% CI, 0.36 to 1.66)
Iyer, 2011[45] Fair	USA 1973-2006	37,176	NR	Mean: 11[†]	Second primary malignancy diagnosed ≥6 months after thyroid cancer diagnosis: N / Incidence / Excess risk All: 3,223/37,176 / 67.0[†] / N/A Stratified by RAI use: RAI: NR / NR / 11.9 No RAI: NR / NR / NR p=NR / p=NR / p=NR

Table 9. Results for Key Question 5: Harms of RAI Treatment of Screen-Detected Thyroid Cancer

Author, Year, Quality	Country, Recruiting Years	N	Radiation Dose (mean or median)	Followup Duration (years)	Permanent Outcomes
					Standardized incidence ratio** for second primary malignancy at any site vs. a reference cohort of identical age, sex, race, and time: RAI: 1.18 (95% CI, 1.10 to 1.25) No RAI: 1.02 (95% CI, 0.98 to 1.06)
Brown, 2008[110] Fair	USA 1973-2002	28,286	NR	Mean: 10	Nonthyroid second primary malignancy diagnosed ≥2 months after thyroid cancer diagnosis: N / Incidence / Excess risk All: 2,191/28,286 / 74.9[†] / N/A Stratified by RAI: RAI: 618/10,257 / 75.8 / 13.3 No RAI: 1,573/18,029 / 74.6 / 3.5 p=NR / p=NR / p≤0.05 Standardized incidence ratio[††] for second primary malignancy at any site vs. the general population: RAI: 1.21 (95% CI, 1.12 to 1.31) No RAI: 1.05 (95% CI, 1.00 to 1.10)
Ronckers, 2005[116] Fair	USA 1973-2000	29,456	NR	Median: 7.9	Second primary malignancy diagnosed ≥2 months after thyroid cancer diagnosis: N / Incidence / Excess risk All: 2,214/29,456 / 78.9[†] / 7.6 Stratified by RAI from 1988–2000 only (N=17,055): RAI: 236/6,745 / NR / NR No RAI: 394/8,951 / NR / NR p<0.05 / p=NR / p=NR Standardized incidence ratio[‡‡] for second primary malignancy at any site vs. the general population: RAI: 1.14 (95% CI, NR) No RAI: 1.19 (95% CI, NR but excludes 1)
Salivary gland					
Ryu, 2015[122] Fair	South Korea 2010	160	Range: Low dose: 1.1-2.2 GBq (29.7-59.5 mCi) High dose: ≥3.7 GBq (≥100 mCi)	Minimum: 1	RAI treatment and dose had no effect on vocal function (as a result of salivary gland dysfunction).
Jeong, 2013[119] Fair	South Korea 2003-2006	213	Mean[‖]: 5.1 GBq (138 mCi)	Mean: 5	RAI: dry mouth 35/213 (16.4%) No RAI: NA

Table 9. Results for Key Question 5: Harms of RAI Treatment of Screen-Detected Thyroid Cancer

Author, Year, Quality	Country, Recruiting Years	N	Radiation Dose (mean or median)	Followup Duration (years)	Permanent Outcomes
Grewal, 2009[121] Fair	USA 1995-2003	262	Mean[\\]: 5.3 GBq (142 mCi)	Mean: 7	RAI: Any: 13/262 (15%) Dry mouth: 6/262 (2%) Salivary gland swelling: 2/262 (1%) Alterations in taste: 3/262 (1%) Salivary gland pain: 1/262 (0%) Tear-duct blockage: 2/262 (1%)[§§] No RAI: NA
Ish-Shalom, 2008[118] Fair	Israel NR	40	Mean[\\†]: 4.0 GBq (109 mCi)	Mean: 8.4	RAI: Dry mouth complaints: 8/23 (35%) (p=0.21) Difficulty swallowing: 5/23 (22%) (p=0.05) Alterations in taste: 3/23 (13%) (p=0.18) No RAI: Dry mouth complaints: 3/17 (18%) Difficulty swallowing: 0/17 (0%) Alterations in taste: 0/17 (0%)
Hyer, 2007[117] Fair	UK NR	76	3 GBq[\\] (80 mCi)	Minimum: 2	RAI: Dry mouth: 16/76 (21%) No RAI: NA
Solans, 2001[120] Fair	Spain 1990-1995	79	Range[\\]: 925 MBq to 18.5 GBq (25-500 mCi)	3	RAI: Dry mouth: 12/79 (15%) Dry eyes: 11/79 (14%) No RAI: NA
Other					
Wu, 2015[124] Fair	USA 1999-2008	18,850	NR (California Cancer Registry)	Median: 4	Birthrate[¶¶]: Did not differ overall between groups (p=0.81) by age (adjusted p-value reported) per 1,000 women-years Median time to first delivery following initial presentation: RAI: 34.5 months No RAI: 26.1 months p<0.0001
Lin, 2014[123] Good	Taiwan 1997-2008	8,946	Median[†]: 3.7 GBq (100 mCi)	Mean: 5	Primary hyperparathyroidism: RAI: 4/6,153 patients or 27,318 person-years No RAI: 4/2,793 patients or 10,930 person-years Hazard ratio: 0.35 (95% CI, 0.09 to 1.42)

* 910 analyzed; 920 originally included in study.
† Calculated.
‡ Adjusted for age at thyroid cancer diagnosis, sex, years of diagnosis, pathology, and RAI dose.
§ Adjusted for age, all comorbidities, hormone therapy, mammography, ultrasonography, radiotherapy, chemotherapy, and thyroxine supplement.
¶ Adjusted for age and sex.
\\ Standard radiation dose of initial treatment, subsequent therapy administered as needed.
** Adjusted for age, sex, race, and time.
†† Adjusted for age, sex, and race.

Table 9. Results for Key Question 5: Harms of RAI Treatment of Screen-Detected Thyroid Cancer

[‡‡] Adjusted for ethnic group, sex, age, and time.
[§§] Corrected with surgery at 2 and 4 years after surgery.
[¶¶] Study also reported rates of nasolacrimal duct stenosis.

Abbreviations: KQ=key question; RAI=radioactive iodine ablation; NA=not applicable; NR=not reported.
Note: 1 GBq=27.03 mCi.

Table 10. Summary of Evidence, by Key Question

Test or intervention	# Studies (k), Sample size (n), Design	Summary of Findings*	Body of Evidence Limitations[†]	Quality	Applicability
KQ 1: Effectiveness					
NA	k=0	No trials have evaluated the impact of screening for thyroid cancer on patient morbidity or mortality.	NA	NA	NA
KQ 2: Diagnostic accuracy					
Palpation	k=2 n=354 Prospective diagnostic accuracy k=4 n=201,027 Pro/retrospective cohort	2 older Finnish studies found that neck palpation was not sensitive (11.6% to 27.8%) in detecting nodules compared with ultrasound. 4 studies found the yield of cancer ranged from 0 to 4.3 cases per 1,000 persons. 2 additional studies in adults with a history of irradiation found the yield of cancer ranged from 0 to 11.3 cases per 1,000 persons.	Only 2 small studies reported diagnostic accuracy; 1 study did not follow up all persons with neck palpations. No evidence of reporting bias.	Fair	Poor: diagnostic accuracy studies are old and use a single examiner
Ultrasound	k=2 n=243 Pro/retrospective diagnostic accuracy k=2 n=2,094 Pro/retrospective cohort	2 South Korean studies found that using any 1 of several malignant sonographic characteristics can be highly sensitive (94.3%) in detecting cancer and that using a combination (≥2) of these characteristics can be both highly sensitive (94.8%) and specific (86.6%). In 4 South Korean studies, the yield of cancer ranged from 9.2 to 30.3 cases per 1,000 persons.	Only 2 small studies reported diagnostic accuracy, neither of which followed up with the vast majority of screened individuals, such that the reported sensitivities are likely overestimates. No evidence of reporting bias.	Fair	Fair: both diagnostic accuracy studies conducted in South Korea by the same investigators, 1 of which included women only
KQ 3: Screening harms					
Ultrasound	k=1 n=400 Retrospective cohort	1 U.S. study found that 24% of persons underwent FNA of a nodule that did not meet the Society of Radiologists in Ultrasound criteria for FNA.	Only 1 study.	Fair	Poor: single-institution; standards for referral to FNA have changed
Ultrasound-guided FNA	k=2 n=5,494 Retrospective cohort	1 Japanese study (n=4,912) observed 7 cases of needle tract implantation of papillary thyroid cancer with FNA. It is unclear what impact, if any, this had on patient outcomes. 1 U.S. study observed hematomas from FNA but no major bleeding complications requiring hospitalization.	One study for each type of harm. Possible reporting bias.	Fair	Fair: both single-institution studies

Table 10. Summary of Evidence, by Key Question

Test or intervention	# Studies (k), Sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
KQ 4: Treatment benefit					
Surgery	k=2 n=39,211 Pro/retrospective cohort	1 U.S. study using SEER data found that, overall, untreated persons with papillary thyroid cancer had a slightly worse 20-year survival rate (97%) than did treated persons (99%) (p<0.001). 1 Japanese study found no deaths in persons with papillary microcarcinoma who opted for ultrasound observation vs. 2 deaths in persons who opted for immediate surgery.	Studies were not designed to evaluate the comparative benefit of treatment vs. no or delayed treatment. Lack of adjustment for confounders such that it is unclear if differences in survival are due to differences in treatment vs. case mix of persons. No evidence of reporting bias.	Fair to poor	Fair: U.S. study includes persons treated in 1970s and 1980s; Japanese study includes persons with papillary microcarcinoma
KQ 5: Treatment harms					
Surgery	k=36 n=43,295 Pro/retrospective cohort	The rate of permanent hypoparathyroidism varied widely; best estimates were 2 to 6 events per 100 thyroidectomies and were more variable with lymph node dissection. The rate of recurrent laryngeal nerve palsy was less variable, estimated at 1 to 2 events per 100 surgeries (with or without lymph node dissection).	Possible publication bias for hypoparathyroidism but not recurrent laryngeal nerve palsy outcomes. The driver of the wide variation of estimates is unclear.	Fair	Fair: indication for type of surgery and case mix of patients going on to surgery have changed over time
RAI	k=16 n=291,796‡ Pro/retrospective cohort	Treatment with RAI for differentiated thyroid cancer is associated with a small increase in primary second malignancies: approximately 12 to 13 excess cancers per 10,000 patients. Smaller studies demonstrate an association of excess cancers at clinically used doses. Other commonly reported permanent harms from RAI include dry mouth, ranging from 2.3 to 35% of persons.	Differences in study designs and variable reporting on radiation doses limits our understanding of the magnitude and precision around risk of second primary malignancies. No evidence-reporting bias for commonly reported adverse outcomes.	Fair	Fair: indication and radiation dose of RAI have changed over time

* Includes consistency and precision.
† Includes reporting bias.
‡ Calculated sample size includes only the largest study using SEER data so as to avoid double-counting studies with overlapping populations.

Abbreviations: CI=confidence interval; FNA=fine-needle aspiration; k=number of studies; n=number; NA=not applicable; RAI=radioactive iodine.

Appendix A. Search Strategy

Databases searched:
OVID MEDLINE
PubMed, publisher-supplied
Cochrane Central Register of Controlled Trials (CENTRAL)

Key:
/ = MeSH subject heading
? = wildcard
ti = word in title
ab = word in abstract
pt = publication type
* = truncation
kw = keyword
adj# = adjacent within # number of words
fs = floating subheading
us = ultrasonography
dt = drug therapy
rt = radiotherapy
su = surgery
th = therapy

MEDLINE
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid MEDLINE(R) Daily Update <January 12, 2016>
Search Strategy:
----
1 Thyroid Neoplasms/
2 Thyroid Nodule/
3 Thyroid Carcinoma, Anaplastic/
4 Carcinoma/
5 Carcinoma, Papillary/
6 Carcinoma, Medullary/
7 Carcinoma, Papillary, Follicular/
8 Adenocarcinoma, Follicular/
9 Adenocarcinoma, Papillary/
10 Adenocarcinoma/
11 Thyroid Gland/
12 11 and (4 or 5 or 6 or 7 or 8 or 8 or 10)
13 (thyroid adj3 (cancer* or carcinoma* or adenoma* or nodule* or tumo?r* or neoplasm* or lymphoma* or adenocarcinoma* or sarcoma* or papillar* or follicular* or hurthle* or oxyphil* or medullar* or anaplast* or malignan*)).ti.
14 1 or 2 or 3 or 12 or 13
15 Ultrasonography/
16 Elasticity Imaging Techniques/
17 Elasticity/
18 Mass Screening/
19 Multiphasic Screening/
20 "Early Detection of Cancer"/
21 early diagnosis/
22 Palpation/

23 Population Surveillance/
24 Sentinel Surveillance/
25 (screen* or surveil*).ti,ab.
26 (test* or exam* or detect* or predict* or identif* or discover* or diagnos*).ti.
27 case finding.ti,ab.
28 ultrasound*.ti,ab.
29 ultrasonograph*.ti,ab.
30 elastogra*.ti,ab.
31 echotomograph*.ti,ab.
32 echograph*.ti,ab.
33 ultrasonic*.ti,ab.
34 sonograph*.ti,ab.
35 sonogram*.ti,ab.
36 (palpat* or palpab*).ti,ab.
37 Thyroid Neoplasms/us [Ultrasonography]
38 Thyroid Nodule/us [Ultrasonography]
39 Carcinoma/us [Ultrasonography]
40 Carcinoma, Papillary/us [Ultrasonography]
41 Carcinoma, Medullary/us [Ultrasonography]
42 Carcinoma, Papillary, Follicular/us [Ultrasonography]
43 Adenocarcinoma, Follicular/us [Ultrasonography]
44 Adenocarcinoma, Papillary/us [Ultrasonography]
45 Adenocarcinoma/us [Ultrasonography]
46 37 or 38
47 11 and (39 or 40 or 41 or 42 or 43 or 44 or 45)
48 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
49 Clinical Trials as Topic/
50 Controlled Clinical Trials as Topic/
51 Randomized Controlled Trials as Topic/
52 Meta-Analysis as Topic/
53 Control Groups/
54 Double-Blind Method/
55 Single-Blind Method/
56 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
57 random*.ti,ab.
58 clinical trial*.ti,ab.
59 controlled trial*.ti,ab.
60 meta analy*.ti,ab.
61 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62 (14 and 48) or 46 or 47
63 61 and 62
64 remove duplicates from 63
65 "Sensitivity and Specificity"/
66 "Predictive Value of Tests"/
67 ROC Curve/
68 False Negative Reactions/
69 False Positive Reactions/
70 Diagnostic Errors/
71 "Reproducibility of Results"/
72 Reference Values/

73 Reference Standards/
74 Observer Variation/
75 receiver operat*.ti,ab.
76 roc curv*.ti,ab.
77 sensitivit*.ti,ab.
78 specificit*.ti,ab.
79 predictive value.ti,ab.
80 accuracy.ti,ab.
81 false positive*.ti,ab.
82 false negative*.ti,ab.
83 miss rate*.ti,ab.
84 error rate*.ti,ab.
85 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84
86 (14 and 48) or 46 or 47
87 85 and 86
88 remove duplicates from 87
89 Mortality/
90 Morbidity/
91 Death/
92 "Drug-Related Side Effects and Adverse Reactions"/
93 Fatal Outcome/
94 "Quality of Life"/
95 Stress, Psychological/
96 Anxiety/
97 Reoperation/
98 Recurrence/
99 Neoplasm Recurrence, Local/
100 Hypocalcemia/
101 Voice Disorders/
102 Voice Quality/
103 Voice/ (6278)
104 Hypesthesia/
105 safety.ti,ab.
106 harm*.ti,ab.
107 mortality.ti,ab.
108 complication*.ti,ab.
109 (death or deaths or die or dying).ti,ab.
110 (adverse adj2 (interaction* or response* or effect* or event* or reaction* or outcome* or feature*)).ti,ab.
111 adverse effects.fs.
112 mortality.fs.
113 overdiagnos*.ti,ab.
114 over diagnos*.ti,ab.
115 unnecessary exam*.ti,ab.
116 unnecessary procedure*.ti,ab.
117 unnecessary test*.ti,ab.
118 unneeded exam*.ti,ab.
119 unneeded procedure*.ti,ab.
120 unneeded test*.ti,ab.
121 unneeded surger*.ti,ab.

122 unnecessary surger*.ti,ab.
123 reoperation*.ti,ab.
124 recur*.ti,ab.
125 overtreat*.ti,ab.
126 over treat*.ti,ab.
127 (secondary adj3 malignan*).ti,ab.
128 psychosocial*.ti,ab.
129 (anxiet* or anxious* or distress* or nervous*).ti,ab.
130 (burden* or challenge*).ti,ab.
131 side effect*.ti,ab.
132 hypocalcem*.ti,ab.
133 hypocalcaem*.ti,ab.
134 voice.ti,ab.
135 numb*.ti,ab.
136 hypesthes*.ti,ab.
137 incidence/
138 Time Factors/
139 Prognosis/
140 Autopsy/
141 (incidence or prognos* or natural histor* or autopsy or autopsies).ti,ab.
142 ((time or temporal) adj3 trend*).ti,ab.
143 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142
144 Clinical Trials as Topic/
145 Controlled Clinical Trials as Topic/
146 Randomized Controlled Trials as Topic/
147 Meta-Analysis as Topic/
148 Control Groups/
149 Double-Blind Method/
150 Single-Blind Method/
151 Cohort Studies/
152 Longitudinal Studies/
153 Follow-Up Studies/
154 Prospective Studies/
155 Retrospective Studies/
156 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
157 random*.ti,ab.
158 clinical trial*.ti,ab.
159 controlled trial*.ti,ab.
160 meta analy*.ti,ab.
161 cohort.ti,ab.
162 longitudinal.ti,ab.
163 (follow up or followup).ti,ab.
164 case-control studies/
165 (case adj2 (control* or base* or comparison* or referrent or referent or compeer*)).ti,ab.
166 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165
167 (14 and 48) or 46 or 47
168 143 and 166 and 167

169 remove duplicates from 168
170 Thyroidectomy/
171 Lymph Node Excision/
172 Neck Dissection/
173 Iodine Radioisotopes/
174 Iodine Isotopes/
175 surgery.ti,ab.
176 surgical.ti,ab.
177 treat*.ti.
178 thyroidect*.ti,ab.
179 lobect*.ti,ab.
180 ((thyroid or neck or lymph) adj3 (remov* or dissect* or excis* or extract*)).ti,ab.
181 lymphadenect*.ti,ab.
182 radioactive iodin*.ti,ab.
183 radioiodin*.ti,ab.
184 radio iodin*.ti,ab.
185 radio nuclide*.ti,ab.
186 radionuclide*.ti,ab.
187 (iodine adj2 ablat*).ti,ab.
188 i-131.ti,ab.
189 131-i.ti,ab.
190 Thyroid Neoplasms/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
191 Thyroid Nodule/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
192 Thyroid Carcinoma, Anaplastic/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
193 Carcinoma/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
194 Carcinoma, Papillary/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
195 Carcinoma, Medullary/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
196 Carcinoma, Papillary, Follicular/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
197 Adenocarcinoma, Follicular/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
198 Adenocarcinoma, Papillary/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
199 Adenocarcinoma/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
200 190 or 191 or 192
201 11 and (193 or 194 or 195 or 196 or 197 or 198 or 199)
202 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189
203 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163
204 (14 and 202) or 200 or 201
205 203 and 204
206 (14 and 202) or 200 or 201
207 143 and 166 and 206
208 64 or 88 or 169 or 205 or 207
209 limit 208 to yr="1966 -Current"
210 limit 209 to english language
211 animals/ not (humans/ and animals/)
212 210 not 211

Appendix A. Search Strategy

PubMed [publisher supplied references only]

Search	Query
#44	Search **#41 AND #42 AND #43**
#43	Search **English[language]**
#42	Search **publisher[sb]**
#41	Search **#18 OR #40**
#40	Search **#3 AND #39**
#39	Search **#19 OR #20 OR # 21 OR #22 OR #23 OR #26 OR # 27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38**
#38	Search **iodine radio isotope*[tiab]**
#37	Search **iodine radioisotope*[tiab]**
#36	Search **iodine isotope*[tiab]**
#35	Search **131 I[tiab]**
#34	Search **I 131[tiab]**
#33	Search **ablat*[ti]**
#32	Search **radionuclide*[tiab]**
#31	Search **radio nuclide*[tiab]**
#30	Search **radio iodin*[tiab]**
#29	Search **radioiodin*[tiab]**
#28	Search **radioactive iodin*[tiab]**
#27	Search **lymphadenect*[tiab]**
#26	Search **#24 AND #25**
#25	Search **remov*[ti] OR dissect*[ti] OR excis*[ti] OR extract*[ti]**
#24	Search **thyroid[ti] OR neck[ti] OR lymph[ti]**
#23	Search **lobect*[tiab]**
#22	Search **thyroidect*[tiab]**
#21	Search **treat*[ti]**
#20	Search **surgical[tiab]**
#19	Search **surger*[tiab]**
#18	Search **#3 AND #17**
#17	Search **#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16**
#16	Search **elastic imag*[tiab]**
#15	Search **palpat*[tiab] or palpab*[tiab]**
#14	Search **sonogram*[tiab]**
#13	Search **sonograph*[tiab]**
#12	Search **ultrasonic*[tiab]**
#11	Search **echograph*[tiab]**
#10	Search **echotomograph*[tiab]**
#9	Search **elastogra*[tiab]**

Appendix A. Search Strategy

Search	Query
#8	Search **ultrasonograph*[tiab]**
#7	Search **ultrasound*[tiab]**
#6	Search **case finding*[tiab]**
#5	Search **test*[ti] OR exam*[ti] OR detect*[ti] OR predict*[ti] OR identif*[ti] OR discover*[ti] OR diagnos*[ti]**
#4	Search **screen*[tiab] OR surveil*[tiab]**
#3	Search **#1 AND #2**
#2	Search **cancer*[ti] OR carcinoma*[ti] OR adenoma*[ti] OR nodule*[ti] OR tumor*[ti] OR tumour*[ti] OR neoplasm*[ti] OR lymphoma*[ti] OR adenocarcinoma*[ti] OR sarcoma*[ti] OR papillar*[ti] OR follicular*[ti] OR hurthle*[ti] OR oxyphil*[ti] OR medullar*[ti] OR anaplast*[ti] OR malignan*[ti]**
#1	Search **thyroid[ti]**

Cochrane Central Register of Controlled Clinical Trials (CENTRAL)

#1 (thyroid):ti,ab,kw near/3 (cancer* or carcinoma* or adenoma* or nodule* or tumo?r* or neoplasm* or lymphoma* or adenocarcinoma* or sarcoma* or papillar* or follicular* or hurthle* or oxyphil* or medullar* or anaplast* or malignan*):ti,ab,kw
#2 (screen* or surveil*):ti,ab,kw
#3 (test* or exam* or detect* or predict* or identif* or discover* or diagnos*):ti
#4 "case finding":ti,ab,kw
#5 ultrasound*:ti,ab,kw
#6 ultrasonograph*:ti,ab,kw
#7 elastogra*:ti,ab,kw
#8 echotomograph*:ti,ab,kw
#9 echograph*:ti,ab,kw
#10 ultrasonic*:ti,ab,kw
#11 sonograph*:ti,ab,kw
#12 sonogram*:ti,ab,kw
#13 (palpat* or palpab*):ti,ab,kw
#14 (elasti*):ti,ab,kw near/3 (image or imaging):ti,ab,kw
#15 #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 #1 and #15
#17 "receiver operat*":ti,ab,kw
#18 "roc curv*":ti,ab,kw
#19 sensitivit*:ti,ab,kw
#20 specificit*:ti,ab,kw
#21 "predictive value*":ti,ab,kw
#22 accuracy:ti,ab,kw
#23 "false positive*":ti,ab,kw
#24 "false negative*":ti,ab,kw
#25 "miss rate*":ti,ab,kw
#26 "error rate*":ti,ab,kw
#27 reference near/3 standard*:ti,ab,kw
#28 reference near/3 value*:ti,ab,kw
#29 "observer variation*":ti,ab,kw
#30 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 58443
#31 #16 and #30
#32 safety:ti,ab,kw
#33 harm*:ti,ab,kw

#34	mortality:ti,ab,kw
#35	complication*:ti,ab,kw
#36	(death or deaths or die or dying or fatal*):ti,ab,kw
#37	adverse:ti,ab,kw near/2 (interaction* or response* or effect* or event* or reaction* or outcome* or feature*):ti,ab,kw
#38	overdiagnos*:ti,ab,kw
#39	"over diagnos*":ti,ab,kw
#40	"unnecessary exam*":ti,ab,kw
#41	"unnecessary procedure*":ti,ab,kw
#42	"unnecessary test*":ti,ab,kw
#43	"unneeded exam*":ti,ab,kw
#44	"unneeded procedure*":ti,ab,kw
#45	"unneeded test*":ti,ab,kw
#46	"unneeded surger*":ti,ab,kw
#47	"unnecessary surger*":ti,ab,kw
#48	reoperation*:ti,ab,kw
#49	recur*:ti,ab,kw
#50	overtreat*:ti,ab,kw
#51	"over treat*":ti,ab,kw
#52	(secondary near/3 malignan*):ti,ab,kw
#53	psychosocial*:ti,ab,kw
#54	(anxiet* or anxious* or distress* or nervous*):ti,ab,kw
#55	(burden* or challenge*):ti,ab,kw
#56	"side effect*":ti,ab,kw
#57	hypocalcem*:ti,ab,kw
#58	hypocalcaem*:ti,ab,kw
#59	voice:ti,ab,kw
#60	numb*:ti,ab,kw
#61	hypesthes*:ti,ab,kw
#62	(incidence or prognos* or "natural histor*" or autopsy or autopsies):ti,ab,kw
#63	(time or temporal):ti,ab,kw near/3 (trend* or factor*):ti,ab,kw
#64	morbidit*:ti,ab,kw
#65	"quality of life":ti,ab,kw
#66	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65
#67	#16 and #66
#68	(surger* or surgical):ti,ab,kw
#69	treat*:ti
#70	thyroidect*:ti,ab,kw
#71	lobect*:ti,ab,kw
#72	(thyroid or neck or lymph*):ti,ab,kw near/3 (remov* or dissect* or excis* or extract*):ti,ab,kw 1757
#73	lymphadenect*:ti,ab,kw
#74	"radioactive iodin*":ti,ab,kw
#75	radioiodin*:ti,ab,kw
#76	"radio iodin*":ti,ab,kw
#77	iodin*:ti,ab,kw near/3 (isotope* or radioisotope* or "radio isotope*"):ti,ab,kw
#78	"radio nuclide*":ti,ab,kw
#79	radionuclide*:ti,ab,kw
#80	(iodine near/2 ablat*):ti,ab,kw

Appendix A. Search Strategy

#81 "i-131":ti,ab,kw
#82 "131-i":ti,ab,kw
#83 #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82
#84 #1 and #83
#85 #1 and #83 and #66
#86 #16 or #31 or #67 or #84 or #85 in Trials

Appendix A Table 1. Quality Assessment Criteria

Study Design	Quality Criteria
Randomized controlled trials USPSTF methods[49]	• Valid random assignment? • Was allocation concealed? • Was eligibility criteria specified? • Were groups similar at baseline? • Were measurements equal, valid, and reliable? • Was there intervention fidelity? • Was there adequate adherence to the intervention? • Were outcome assessors blinded? • Was there acceptable followup? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there evidence of selective reporting of outcomes? • Was the device calibration and/or maintenance reported?
Observational studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottawa Scale (NOS)[50]	• Was the cohort systematically selected to avoid bias? • Was eligibility criteria specified? • Were groups similar at baseline? • Was the outcome of interest not present at baseline? • Were measurements equal, valid, and reliable? • Were outcome assessors blinded? • Was there acceptable followup? • Were the statistical methods acceptable? • Was the handling of missing data appropriate?
Diagnostic accuracy studies adapted from QUADAS I and II [51, 52]	• Screening test relevant, available for primary care, and adequately described • Study uses a credible reference standard performed regardless of test results • Reference standard interpreted independently of screening test • Handles indeterminate results in a reasonable manner • Spectrum of patients included in study • Sample size reported • Administration of reliable screening test

Abbreviations: USPSTF=U.S. Preventive Services Task Force; QUADAS=Quality Assessment of Diagnostic Accuracy Studies.

Appendix A Table 2. Inclusion and Exclusion Criteria

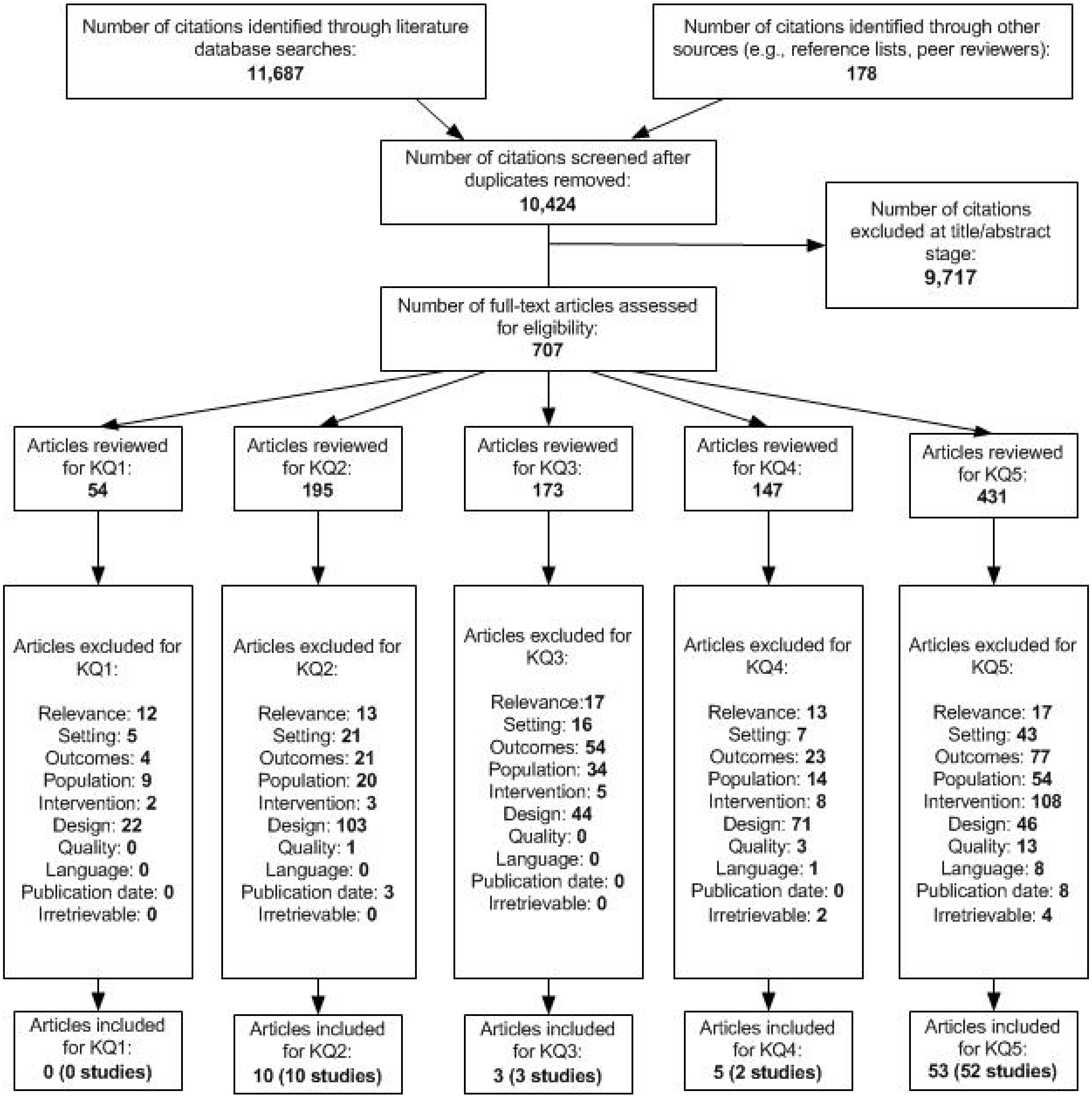
	Include	Exclude
Populations	• Asymptomatic adults age ≥18 years • High-risk populations (those with a history of radiation exposure or family history of thyroid cancer)	• Persons who are already under surveillance for thyroid cancer because of previous thyroid cancer • Persons who have symptoms that may lead to thyroid evaluation • Persons with known inherited genetic syndromes, such as multiple endocrine neoplasia type II, as selection criteria for studies • Persons with thyroid disease • Children and adolescents
Screening tests	**KQs 1–3:** Palpation or ultrasound of the neck conducted by primary care providers or specialists as part of a routine well care visit	• Enhanced ultrasound methods, such as elastography or ultrasound with contrast media • Diagnostic procedures (e.g., fine needle aspiration) will be excluded as screening tests but reviewed under harms of screening • Other imaging tests (e.g., magnetic resonance imaging, positron emission tomography) that incidentally identify thyroid nodules • Blood tests (e.g., calcitonin, thyroid-stimulating hormone) • Self-examination • Diagnostic accuracy studies in persons with known nodules
Treatment interventions	**KQs 4, 5:** Surgery, including lobectomy, near-total thyroidectomy, total thyroidectomy, and lymphadenectomy; radioactive iodine ablation	• Chemotherapy • External beam radiation therapy • Nonsurgical ablative treatment, such as thermal ablation, radiofrequency ablation, or ultrasound-guided percutaneous ethanol injection • Older treatment studies pre-1990
Comparisons	**KQs 1–3:** No screening **KQs 4, 5:** No treatment	
Outcomes	**KQs 1, 4:** Reduced morbidity associated with any thyroid cancer (including papillary, follicular, medullary, and anaplastic), including: • Improved quality of life • Decreased thyroid cancer mortality • Decreased all-cause mortality **KQ 2:** Sensitivity, specificity, positive predictive value, false-positives, false-negatives, nodule detection rates, and cancer detection rates **KQs 3, 5:** Any harm from screening or treatment, including overdiagnosis,* diagnostic tests, overtreatment,** psychosocial harms, secondary malignancies, or procedure-related adverse events	Incidentally identified thyroid nodules
Settings	• U.S. primary care settings • Nations categorized as “High” on the Human Development Index (as defined by the World Health Organization)	Nations with environmental disasters that lead to very high radiation exposure (e.g., Ukraine, Japan)

Appendix A Table 2. Inclusion and Exclusion Criteria

	Include	Exclude
Study designs	Fair- to good-quality studies published between January 1, 1966 and March 31, 2015 **KQ 1:** Randomized, controlled trials **KQ 2:** Diagnostic accuracy studies with a reference standard, systematic evidence reviews **KQs 3, 5:** Randomized, controlled trials; controlled clinical trials; cohort studies; case-control studies **KQ 4:** Randomized, controlled trials; controlled clinical trials; cohort studies	Poor-quality studies with a fatal flaw; studies outside of the publication window; case reports and case series; decision analyses

*Diagnosis of nonpalpable nodules measuring <1 cm and/or fine needle aspiration of nodules not meeting revised 2009 American Thyroid Association criteria for fine needle aspiration.
**Including treatment of an overdiagnosed nodule and extended followup of benign nodules.

Appendix A Figure 1. Literature Flow Diagram



Abbreviation: KQ=key question.

Appendix B. Ongoing Studies

We searched selected grey literature sources, including ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), for ongoing trials. From these sources no screening focused studies were identified. Multiple studies found focus on the effectiveness of surgery in people with low risk papillary carcinomas. The majority of these focus on people with low-risk papillary thyroid cancer or microcarcinomas of the thyroid. There are two randomized trials addressing efficacy and safety of prophylactic central lymph node dissection, both of which are still in the recruiting phase; the South Korean based study is expected to be completed in 2022[155]and the U.S. based study is expected to be completed in 2020.[156] Outcomes will include harms of surgery. For papillary microcarcinomas there are three ongoing studies that would contribute to the evidence around overdiagnosis or harms of treatment. Two studies from South Korea on the comparative effectiveness of surgical treatment of papillary microcarcinomas may report the harms.[157, 158] Another study will evaluate why patients with papillary microcarcinoma choose treatement versus active surveillance.[159]

Appendix C. Excluded Studies

Exclusion Codes

E Codes

E1. Study relevance
E1a. Primary aim technology improvements
E2. Study design
E2a. Case report or case series
E2b. Comparative effectiveness only, no control (untreated arm)
E2c. Diagnostic accuracy studies in persons with known nodules
E3. Setting
E3a. Not a very high HDI country
E3b. Nation with environmental disaster with very high radiation exposure
E4. Population
E4a. Previous thyroid cancer
E4b. Symptomatic
E4c. Inherited genetic syndromes
E4d. Thyroid disease
E4e. Children $\leq$ 18
E5. No relevant outcomes or incomplete outcomes
E5a. No additional relevant data (primary article included)
E5b. Incidentally identified thyroid nodules
E6. Intervention (including outdated technology)
E6a. Imaging other than ultrasound
E6b. Blood tests
E6c. Self-exam
E6d. Chemotherapy
E6e. External beam radiation therapy
E6f. Non-surgical ablative treatment other than Radioactive Iodine Ablation
E6g. older treatment study – pre 1980
E6h. Single-surgeon practice
E7. Poor Study Quality
E8. Key existing SER with out of date MA
E9. Not in English
E10. Unable to retrieve

1. Abboud B, Sleilaty G, Tannoury J, Daher R, Abadjian G and Ghorra C. Cervical neck dissection without drains in well-differentiated thyroid carcinoma. American surgeon2011. p. 1624-8.PMID: 22273220. **KQ5e3a**
2. Abboud B, Tannoury J, Sleilaty G, Daher R, Abadjian G and Ghorra C. Cervical neck dissection without drainage in papillary thyroid carcinoma. Journal of Laryngology & Otology2013. p. 299-302.PMID: 23374592. **KQ5e3a**
3. Abel SM, Noyek AM, Freeman JL and Chapnik JS. Nonpalpable occult and metastatic papillary thyroid carcinoma. Laryngoscope1993. p. 149-55.PMID: 8426505. **KQ2E1**
4. Abu-Eshy SA, Khan AR, Khan GM, al-Humaidi MA, al-Shehri MY and Malatani TS. Thyroid malignancy in multinodular goitre and solitary nodule. Journal of the Royal College of Surgeons of Edinburgh1995. p. 310-2.PMID: 8523308. **KQ3E4**
5. Acun Z, Cihan A, Ulukent SC, Comert M, Ucan B, Cakmak GK and Cesur A. A randomized prospective study of complications between general surgery residents and attending surgeons in near-total thyroidectomies. Surg Today. 2004/12/08 ed2004. p. 997-1001.PMID: 15580380. **KQALLE3A**
6. Adwok JA. Evaluation and surgical treatment of solitary thyroid nodules. East African Medical Journal1995. p. 191-3.PMID: 7796774. **KQ5E6H**

7. Agrawal C, Guthrie L, Sturm MS, Stanek J, Martin L, Henwood-Finley M, Aldrink JH, Olshefski R and O'Brien SH. Comparison of Thyroid Nodule Prevalence by Ultrasound in Childhood Cancer Survivors With and Without Thyroid Radiation Exposure. Journal of Pediatric Hematology/Oncology2016. p. 43-8.PMID: 26583623. **KQ2E4E**
8. Ahn HS, Kim HJ and Welch HG. Korea's thyroid-cancer "epidemic"--screening and overdiagnosis. New England journal of medicine2014. p. 1765-7.PMID: 25372084. **KQALLE2**
9. Ahn HY, Kang AR, Bo YH, Kim KW, Park YJ and Park DJ. The risk of breast cancer is reduced in thyroid cancer patients after radioactive iodine therapy. Boston, MA: Endocr Rev; 2011**KQ5E7 (only abstract available)**
10. Ahn HY, Min HS, Yeo Y, Ma SH, Hwang Y, An JH, Choi HS, Keam B, Im SA, Park do J, Park IA, Noh DY, Youn YK, Chung JK, Cho BY, Park SK and Park YJ. Radioactive Iodine Therapy Did Not Significantly Increase the Incidence and Recurrence of Subsequent Breast Cancer. Journal of Clinical Endocrinology & Metabolism2015. p. 3486-93.PMID: 26147607. **KQ5E7**
11. Ahuja AT, Evans RM, Chick W, King WW, Metreweli C and Li AK. Role of ultrasound in the management of thyroid nodules. American journal of surgery1992. p. 654-7.PMID: 1463118. **KQ2E2C, KQ3E4**
12. Akgul O, Ocak S, Keskek M, Koc M and Tez M. Risk of malignancy in non-diagnostic thyroid fine-needle aspiration biopsy in multinodular goitre patients. Endocrine Regulations2011. p. 9-12.PMID: 21314205. **KQ5e1**
13. Akslen LA, Haldorsen T, Thoresen SO and Glattre E. Survival and causes of death in thyroid cancer: a population-based study of 2479 cases from Norway. Cancer Research. 1991/02/15 ed1991. p. 1234-41.PMID: 1997164. **KQ1E2, KQ4E2**
14. Alexander C, Bader JB, Schaefer A, Finke C and Kirsch CM. Intermediate and long-term side effects of high-dose radioiodine therapy for thyroid carcinoma. Journal of nuclear medicine1998. p. 1551-4.PMID: 9744341. **KQ5E7**
15. Alexander EK, Heering JP, Benson CB, Frates MC, Doubilet PM, Cibas ES and Marqusee E. Assessment of nondiagnostic ultrasound-guided fine needle aspirations of thyroid nodules. Journal of Clinical Endocrinology & Metabolism2002. p. 4924-7.PMID: 12414851. **KQ3e5**
16. Almeida JP, Sanabria AE, Lima EN and Kowalski LP. Late side effects of radioactive iodine on salivary gland function in patients with thyroid cancer. Head & neck2011. p. 686-90.PMID: 21484917. **KQ5e3a**
17. Almeida JP, Vartanian JG and Kowalski LP. Clinical predictors of quality of life in patients with initial differentiated thyroid cancers.[Erratum appears in Arch Otolaryngol Head Neck Surg. 2009 Jul;135(7):636 Note: Almeida, Juliana [corrected to Almeida, Juliana Pereira]]. Archives of Otolaryngology -- Head & Neck Surgery2009. p. 342-6.PMID: 19380354. **KQ5e3a**
18. Al-Qahtani KH, Al Asiri M, Tunio MA, Aljohani NJ, Bayoumi Y, Fatani H and AlHadab A. "Adjuvant Radioactive iodine 133 ablation in papillary microcarcinoma of thyroid: Saudi Arabian experience". Journal of Otolaryngology: Head and Neck Surgery2015. p. 51.PMID: 26621255. **KQ4E2B, KQ5E5**
19. An JH, Song KH, Kim SK, Park KS, Yoo YB, Yang JH, Hwang TS and Kim DL. RAS mutations in indeterminate thyroid nodules are predictive of the follicular variant of papillary thyroid carcinoma. Clin Endocrinol (Oxf). 2014/08/12 ed2014.PMID: 25109485. **KQ2E2C, KQ3E5**
20. An YS, Yoon JK, Lee SJ, Song HS, Yoon SH and Jo KS. Symptomatic late-onset sialadenitis after radioiodine therapy in thyroid cancer. Annals of nuclear medicine2013. p. 386-91.PMID: CN-00965525. **kq5e4**
21. Ansari-Lari MA and Westra WH. The prevalence and significance of clinically unsuspected neoplasms in cervical lymph nodes. Head & neck2003. p. 841-7.PMID: 12966508. **KQ5e5**
22. Appetecchia M and Solivetti FM. The association of colour flow Doppler sonography and conventional ultrasonography improves the diagnosis of thyroid carcinoma. Hormone Research2006. p. 249-56.PMID: 17016052. **KQ2e2c**
23. Ardito G, Revelli L, Giustozzi E, Salvatori M, Fadda G, Ardito F, Avenia N, Ferretti A, Rampin L, Chondrogiannis S, Colletti PM and Rubello D. Aggressive papillary thyroid microcarcinoma: prognostic factors and therapeutic strategy. Clinical nuclear medicine2013. p. 25-8.PMID: 23242040. **KQ4e5**
24. Ashcraft MW and Van Herle AJ. Management of thyroid nodules. II: Scanning techniques, thyroid suppressive therapy, and fine needle aspiration. Head & Neck Surgery. 1981/03/01 ed1981. p. 297-322.PMID: 6163751. **KQALLE2**

25. Atli M, Akgul M, Saryal M, Daglar G, Yasti AC and Kama NA. Thyroid incidentalomas: prediction of malignancy and management. International surgery2006. p. 237-44.PMID: 16967687. **KQ2E4**
26. Auer G, Backdahl M, Falkmer U, Grimelius L, Lundell G and Wallin G. Follicular tumors of the thyroid gland: diagnosis, clinical aspects and nuclear DNA analysis. World journal of surgery1992. p. 589-94.PMID: 1413829. **KQ5E2**
27. Ayala C, Navarro E, Rodriguez JR, Silva H, Venegas E and Astorga R. Conception after iodine-131 therapy for differentiated thyroid cancer. Thyroid1998. p. 1009-11.PMID: 9848714. **KQ5E6G**
28. Azizi G, Keller JM, Mayo ML, Piper K, Puett D, Earp KM and Malchoff CD. Thyroid Nodules and Shear Wave Elastography: A New Tool in Thyroid Cancer Detection. Ultrasound in medicine & biology2015. p. 2855-65.PMID: 26277203. **KQ2E2C**
29. Bae U, Dighe M, Dubinsky T, Minoshima S, Shamdasani V and Kim Y. Ultrasound thyroid elastography using carotid artery pulsation: preliminary study. Journal of ultrasound in medicine2007. p. 797-805.PMID: 17526611. **KQ2e6a**
30. Baier ND, Hahn PF, Gervais DA, Samir A, Halpern EF, Mueller PR and Harisinghani MG. Fine-needle aspiration biopsy of thyroid nodules: experience in a cohort of 944 patients. AJR. American Journal of Roentgenology2009. p. 1175-9.PMID: 19770344. **KQ3e5**
31. Baloch Z, LiVolsi VA, Jain P, Jain R, Aljada I, Mandel S, Langer JE and Gupta PK. Role of repeat fine-needle aspiration biopsy (FNAB) in the management of thyroid nodules. Diagnostic Cytopathology2003. p. 203-6.PMID: 14506672. **KQ3E5**
32. Barczynski M, Konturek A, Stopa M and Nowak W. Prophylactic central neck dissection for papillary thyroid cancer. British journal of surgery2013. p. 410-8.PMID: 23188784. **KQ4E2B, KQ5E6H**
33. Bellantone R, Lombardi CP, Raffaelli M, Traini E, De Crea C, Rossi ED and Fadda G. Management of cystic or predominantly cystic thyroid nodules: the role of ultrasound-guided fine-needle aspiration biopsy. Thyroid2004. p. 43-7.PMID: 15009913. **KQ3e5**
34. Bergenfelz A, Jansson S, Kristoffersson A, Martensson H, Reihner E, Wallin G and Lausen I. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbecks Archives of Surgery2008. p. 667-73.PMID: 18633639. **KQ5e4b**
35. Bergholm U, Adami HO, Bergstrom R, Johansson H, Lundell G, Telenius-Berg M and Akerstrom G. Clinical characteristics in sporadic and familial medullary thyroid carcinoma. A nationwide study of 249 patients in Sweden from 1959 through 1981. Cancer. 1989/03/15 ed1989. p. 1196-204.PMID: 2563669. **KQ2E6, KQ3E6**
36. Berker D, Aydin Y, Ustun I, Gul K, Tutuncu Y, Isik S, Delibasi T and Guler S. The value of fine-needle aspiration biopsy in subcentimeter thyroid nodules. Thyroid2008. p. 603-8.PMID: 18578608. **KQ3e3a**
37. Berthe E, Henry-Amar M, Michels JJ, Rame JP, Berthet P, Babin E, Icard P, Samama G, Galateau-Sallé F, Mahoudeau J and Bardet S. Risk of second primary cancer following differentiated thyroid cancer. European journal of nuclear medicine and molecular imaging2004. p. 685-91.PMID: CN-00488978. **KQ5e6g**
38. Besic N, Zgajnar J, Hocevar M and Petric R. Extent of thyroidectomy and lymphadenectomy in 254 patients with papillary thyroid microcarcinoma: a single-institution experience. Ann Surg Oncol. 2009/02/04 ed2009. p. 920-8.PMID: 19189188. **KQ1E2B, KQ4E2B, KQ5E6H**
39. Bhatkar SV, Rajan MG and Samuel AM. Screening for microalbuminuria by RIA in 131I-treated thyroid cancer patients. Nuclear Medicine Communications1996. p. 536-9.PMID: 8822754. **KQ5E5**
40. BK R, Judhan R, Chong B, Ubert A, AbuRahma Z, Mangano W and Thompson S. False-negative results with the Bethesda System of reporting thyroid cytopathology: predictors of malignancy in thyroid nodules classified as benign by cytopathologic evaluation. American surgeon2014. p. 811-6.PMID: 25105404. **KQ3e4d, KQ5e4d**
41. Bogdanova TI, Zurnadzhy LY, Greenebaum E, McConnell RJ, Robbins J, Epstein OV, Olijnyk VA, Hatch M, Zablotska LB and Tronko MD. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: pathology analysis of thyroid cancer cases in Ukraine detected during the first screening (1998-2000). Cancer2006. p. 2559-66.PMID: 17083123. **KQ2e3a, KQ3e3a**

42. Bohacek L, Milas M, Mitchell J, Siperstein A and Berber E. Diagnostic accuracy of surgeon-performed ultrasound-guided fine-needle aspiration of thyroid nodules. Annals of surgical oncology2012. p. 45-51.PMID: 21633868. **KQ3e6**
43. Boice JD, Jr., Berg G, Bjelkengren G, Ericsson UB, Hallquist A, Lidberg M, Lundell G, Mattsson A and Tennvall J. Leukaemia incidence after iodine-131 exposure. Lancet1992. p. 1-4.PMID: 1351599. **KQ4E2B, KQ5E6G**
44. Bononi M, Amore Bonapasta S, Vari A, Scarpini M, Cesare A, Miccini M, Meucci M and Tocchi A. Incidence and circumstances of cervical hematoma complicating thyroidectomy and its relationship to postoperative vomiting. Head & neck2010. p. 1173-7.PMID: CN-00772056. **kq5e5**
45. Bononi M, Tocchi A, Cangemi V, Vecchione A, Giovagnoli MR, De Cesare A, Fiori E, Volpino P, Brozzetti S, Meucci M, Scozzafava S and Cavallaro A. Lymph node dissection in papillary or follicular thyroid carcinoma. Anticancer Research2004. p. 2439-42.PMID: 15330196. **KQ5e6h**
46. Bozec A, Dassonville O, Chamorey E, Poissonnet G, Sudaka A, Peyrottes I, Ettore F, Haudebourg J, Bussiere F, Benisvy D, Marcy PY, Sadoul JL, Hofman P, Lassale S, Vallicioni J, Demard F and Santini J. Clinical impact of cervical lymph node involvement and central neck dissection in patients with papillary thyroid carcinoma: a retrospective analysis of 368 cases. European archives of oto-rhino-laryngology2011. p. 1205-12.PMID: 21607578. **KQ5E10**
47. Brandao CD, Miranda AE, Correa ND, Sieiro Netto L, Corbo R and Vaisman M. Radioiodine therapy and subsequent pregnancy. Arquivos Brasileiros de Endocrinologia e Metabologia2007. p. 534-40.PMID: 17684613. **KQ5e3a**
48. Brander A, Viikinkoski P, Tuuhea J, Voutilainen L and Kivisaari L. Clinical versus ultrasound examination of the thyroid gland in common clinical practice. Journal of Clinical Ultrasound1992. p. 37-42.PMID: 1309541. **KQ2E4A**
49. Brander A, Viikinkoski P, Tuuhea J, Voutilainen L and Kivisaari L. Clinical versus ultrasound examination of the thyroid gland in common clinical practice. J Clin Ultrasound. 1992/01/01 ed1992. p. 37-42.PMID: 1309541. **KQ2E4a**
50. Brignardello E, Corrias A, Isolato G, Palestini N, Cordero di Montezemolo L, Fagioli F and Boccuzzi G. Ultrasound screening for thyroid carcinoma in childhood cancer survivors: a case series. Journal of Clinical Endocrinology & Metabolism2008. p. 4840-3.PMID: 18812481. **KQ3e4**
51. Brito JP, Gionfriddo MR, Al Nofal A, Boehmer KR, Leppin AL, Reading C, Callstrom M, Elraiyah TA, Prokop LJ, Stan MN, Murad MH, Morris JC and Montori VM. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. Journal of Clinical Endocrinology & Metabolism2014. p. 1253-63.PMID: 24276450. **KQ2e2c**
52. Brito JP, Singh-Ospina N, Gionfriddo MR, Maraka S, Espinosa De Ycaza A, Rodriguez-Gutierrez R, Morris JC, Montori VM and Tuttle RM. Restricting ultrasound thyroid fine needle aspiration biopsy by nodule size: which tumors are we missing? A population-based study. Endocrine. 2015/08/10 ed2015.PMID: 26254791. **KQ3E5**
53. Brophy C, Stewart J, O'Donovan N, McCarthy J, Murphy M and Sheahan P. Impact of Microcalcifications on Risk of Malignancy in Thyroid Nodules with Indeterminate or Benign Cytology. Otolaryngology - Head & Neck Surgery2016. p. 46-51.PMID: 26392026. **KQ2E5**
54. Brownlie BE, Elliot JR, Ayling EM and Turner JG. Bone mineral density in patients receiving suppressive doses of thyroxine for thyroid carcinoma. New Zealand Medical Journal1993. p. 443-4.PMID: 8233173. **KQ2E2**
55. Bucci A, Shore-Freedman E, Gierlowski T, Mihailescu D, Ron E and Schneider AB. Behavior of small thyroid cancers found by screening radiation-exposed individuals. Journal of Clinical Endocrinology & Metabolism2001. p. 3711-6.PMID: 11502800. **KQ1E6A**
56. Burgess JR. Temporal trends for thyroid carcinoma in Australia: an increasing incidence of papillary thyroid carcinoma (1982-1997). Thyroid. 2002/03/28 ed2002. p. 141-9.PMID: 11916283. **KQALLE1**
57. Burgess JR and Tucker P. Incidence trends for papillary thyroid carcinoma and their correlation with thyroid surgery and thyroid fine-needle aspirate cytology. Thyroid2006. p. 47-53.PMID: 16487013. **KQ3E5, KQ5e5**

58. Caglar M, Tuncel M and Alpar R. Scintigraphic evaluation of salivary gland dysfunction in patients with thyroid cancer after radioiodine treatment. Clinical nuclear medicine2002. p. 767-71.PMID: CN-00410741. **KQ5E3A, KQ2E3A**
59. Calo PG, Medas F, Loi G, Erdas E, Pisano G and Nicolosi A. Differentiated thyroid cancer in the elderly: our experience. International Journal Of Surgery2014. p. S140-3.PMID: 25183640. **KQ5E5**
60. Calo PG, Medas F, Santa Cruz R, Podda F, Erdas E, Pisano G and Nicolosi A. Follicular nodules (Thy3) of the thyroid: is total thyroidectomy the best option? BMC Surgery2014. p. 12.PMID: 24597765. **KQ3E1**
61. Campos Z, Gooding GA and Higgins CB. MRI and ultrasound detection of asymptomatic thyroid nodules in hyperparathyroidism. Journal of Computer Assisted Tomography1992. p. 615-9.PMID: 1629423. **KQ3E4D**
62. Canchola AJ, Horn-Ross PL and Purdie DM. Risk of second primary malignancies in women with papillary thyroid cancer. American Journal of Epidemiology. 2006/01/20 ed2006. p. 521-7.PMID: 16421240. **KQ5E4**
63. Cannon CR and Replogle WH. Hypocalcemia following hemithyroidectomy. Journal of the Mississippi State Medical Association2008. p. 265-9.PMID: 19297915. **KQ4e2b, KQ5e6h**
64. Cappelli C, Castellano M, Pirola I, Gandossi E, De Martino E, Cumetti D, Agosti B and Rosei EA. Thyroid nodule shape suggests malignancy. European Journal of Endocrinology2006. p. 27-31.PMID: 16793946. **KQ2e2c, KQ3e4**
65. Carpi A, Sagripanti A, Nicolini A, Santini S, Ferrari E, Romani R and Di Coscio G. Large needle aspiration biopsy for reducing the rate of inadequate cytology on fine needle aspiration specimens from palpable thyroid nodules. Biomedicine & Pharmacotherapy1998. p. 303-7.PMID: 9809173. **KQ3E5**
66. Ceccarelli C, Bencivelli W, Morciano D, Pinchera A and Pacini F. 131I therapy for differentiated thyroid cancer leads to an earlier onset of menopause: results of a retrospective study. Journal of Clinical Endocrinology & Metabolism2001. p. 3512-5.PMID: 11502772. **KQ4E2B, KQ5E5**
67. Ceccarelli C, Caglieresi C, Moscatelli A, Gavioli S, Santini P, Elisei R and Vitti P. Effects of radioiodine treatment for differentiated thyroid cancer on testis function. Clinical endocrinology2015. p. 295-9.PMID: 25138547. **KQ5e2**
68. Cerbone G, Spiezia S, Colao A, Di Sarno A, Assanti AP, Lucci R, Siciliani M, Lombardi G and Fenzi G. Power Doppler improves the diagnostic accuracy of color Doppler ultrasonography in cold thyroid nodules: follow-up results. Hormone Research1999. p. 19-24.PMID: 10640895. **KQ2E2C, KQ3E5**
69. Cerci C, Cerci SS, Eroglu E, Dede M, Kapucuoglu N, Yildiz M and Bulbul M. Thyroid cancer in toxic and non-toxic multinodular goiter. Journal of Postgraduate Medicine2007. p. 157-60.PMID: 17699987. **KQ2e3a, KQ3e3a**
70. Chagas JF, Aquino JL, Pascoal MB, Teixeira AS, Ferro MM, Gambaro MC and Dedivitis RA. Multicentricity in the thyroid differentiated carcinoma. Revista Brasileira de Otorrinolaringologia2009. p. 97-100.PMID: 19488567. **KQ4e3a, KQ5e3a**
71. Chaikhoutdinov I, Mitzner R and Goldenberg D. Incidental Thyroid Nodules: Incidence, Evaluation, and Outcome. Otolaryngology - Head & Neck Surgery. 2014/03/13 ed2014. p. 939-942.PMID: 24618501. **KQ3E5**
72. Chammas MC, Gerhard R, de Oliveira IR, Widman A, de Barros N, Durazzo M, Ferraz A and Cerri GG. Thyroid nodules: evaluation with power Doppler and duplex Doppler ultrasound. Otolaryngology - Head & Neck Surgery2005. p. 874-82.PMID: 15944558. **KQ2e3a, KQ3e3a**
73. Chang TC, Hsiao YL and Kuo MS. Ultrasonographic findings of papillary thyroid carcinoma and their relation to pathologic changes. Journal of the Formosan Medical Association1994. p. 933-8.PMID: 7633197. **KQ2E2, KQ3E2**
74. Chao TC, Lin JD and Chen MF. Surgical treatment of Hurthle cell tumors of the thyroid. World journal of surgery2005. p. 164-8.PMID: 15650796. **KQ4e2b, KQ5e3a**
75. Chen AY, Jemal A and Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer. 2009/07/15 ed2009. p. 3801-7.PMID: 19598221. **KQALLE2**
76. Chiang FY, Lu IC, Tsai CJ, Hsiao PJ, Hsu CC and Wu CW. Does extensive dissection of recurrent laryngeal nerve during thyroid operation increase the risk of nerve injury? Evidence from the application of intraoperative neuromonitoring. American journal of otolaryngology2011. p. 499-503.PMID: CN-00972797. **KQ5e4d**

77. Chiang FY, Wang LF, Huang YF, Lee KW and Kuo WR. Recurrent laryngeal nerve palsy after thyroidectomy with routine identification of the recurrent laryngeal nerve. Surgery. 2005/03/05 ed2005. p. 342-7.PMID: 15746790. **KQ5E4D**
78. Chisholm EJ, Kulinskaya E and Tolley NS. Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. Laryngoscope2009. p. 1135-9.PMID: 19358241. **KQ4e2b, KQ5e8**
79. Chiu CG, Yao R, Chan SK, Strugnell SS, Bugis S, Irvine R, Anderson D, Walker B, Jones SJ and Wiseman SM. Hemithyroidectomy is the preferred initial operative approach for an indeterminate fine needle aspiration biopsy diagnosis. Canadian Journal of Surgery2012. p. 191-8.PMID: 22630062. **KQ3e2b**
80. Chiu WY, Chia NH, Wan SK, Yuen CH and Cheung MT. The investigation and management of thyroid nodules--a retrospective review of 183 cases. Annals of the Academy of Medicine, Singapore1998. p. 196-9.PMID: 9663309. **KQ3E2C**
81. Choi SH, Kim EK, Kwak JY, Kim MJ and Son EJ. Interobserver and intraobserver variations in ultrasound assessment of thyroid nodules. Thyroid2010. p. 167-72.PMID: 19725777. **KQ2e2c**
82. Choi SY, Woo SH, Shin JH, Choi N, Son YI, Jeong HS, Baek CH and Chung MK. Prevalence and prediction for malignancy of additional thyroid nodules coexisting with proven papillary thyroid microcarcinoma. Otolaryngology - Head & Neck Surgery2013. p. 53-9.PMID: 23525852. **KQ2e2c**
83. Choi WJ, Baek JH, Ha EJ, Choi YJ, Hong MJ, Song DE, Sung JY, Yoo H, Jung SL, Lee HY and Lee JH. The ultrasonography features of hyalinizing trabecular tumor of the thyroid gland and the role of fine needle aspiration cytology and core needle biopsy in its diagnosis. Acta Radiologica. 2014/09/19 ed2014.PMID: 25232186. **KQ3E1, KQ5E1**
84. Choi WJ, Park JS, Kim KG, Kim SY, Koo HR and Lee YJ. Computerized analysis of calcification of thyroid nodules as visualized by ultrasonography. European journal of radiology2015. p. 1949-53.PMID: 26137902. **KQ2E2C**
85. Choi YJ, Baek JH, Baek SH, Shim WH, Lee KD, Lee HS, Shong YK, Ha EJ and Lee JH. Web-Based Malignancy Risk Estimation for Thyroid Nodules Using Ultrasonography Characteristics: Development and Validation of a Predictive Model. Thyroid2015. p. 1306-12.PMID: 26437963. **KQ2E2C**
86. Choi YS, Hong SW, Kwak JY, Moon HJ and Kim EK. Clinical and ultrasonographic findings affecting nondiagnostic results upon the second fine needle aspiration for thyroid nodules. Annals of surgical oncology2012. p. 2304-9.PMID: 22395996. **KQ1E4, KQ2E4, KQ3E4**
87. Christensen SB, Bondeson L, Ericsson UB and Lindholm K. Prediction of malignancy in the solitary thyroid nodule by physical examination, thyroid scan, fine-needle biopsy and serum thyroglobulin. A prospective study of 100 surgically treated patients. Acta Chirurgica Scandinavica1984. p. 433-9.PMID: 6495973. **KQ1E1, KQ2E2C, KQ3E5, KQ4E2B, KQ5E5**
88. Christensen SB, Ljungberg O and Tibblin S. Surgical treatment of thyroid carcinoma in a defined population: 1960 to 1977. Evaluation of the results after a conservative surgical approach. American journal of surgery1983. p. 349-54.PMID: 6614326. **KQ5E6G**
89. Christensen SB, Ljungberg O and Tibblin S. A clinical epidemiologic study of thyroid carcinoma in Malmo, Sweden. Current Problems in Cancer1984. p. 1-49.PMID: 6488867. **KQ3E2**
90. Christensen SB and Tibblin S. The reliability of the clinical examination of the thyroid gland. A prospective study of 100 consecutive patients surgically treated for hyperparathyroidism. Annales Chirurgiae et Gynaecologiae1985. p. 151-4.PMID: 4083775. **KQ2E4D**
91. Chuang SC, Hashibe M, Yu GP, Le AD, Cao W, Hurwitz EL, Rao JY, Neugut AI and Zhang ZF. Radiotherapy for primary thyroid cancer as a risk factor for second primary cancers. Cancer Letters2006. p. 42-52.PMID: 16039041. **KQ5E6E**
92. Chukudebelu O, Dias A and Timon C. Changing trends in thyroidectomy. Irish Medical Journal2012. p. 167-9.PMID: 22973651. **KQ5e6h**
93. Chung J, Youk JH, Kim JA, Kwak JY, Kim EK, Ryu YH and Son EJ. Initially non-diagnostic ultrasound-guided fine needle aspiration cytology of thyroid nodules: value and management. Acta Radiologica2012. p. 168-73.PMID: 21969700. **KQ2e2c**

94. Ciatti S, Bartolozzi C, Cicchi P and Lucarelli E. The role of ultrasonography and ultrasound guided biopsy in the management of patients with cold nodules of the thyroid. Ultrasound in medicine & biology1983. p. 387-91.PMID: 6400254. **KQ2E2**
95. Clark OH and Duh QY. Thyroid cancer. Medical Clinics of North America. 1991/01/01 ed1991. p. 211-34.PMID: 1987444. **KQALLE2**
96. Cohen JP and Cho HT. The role of needle aspiration biopsy in the selection of patients for thyroidectomy. Laryngoscope1988. p. 35-9.PMID: 3336259. **KQ3E5, KQ5E5**
97. Colombo-Benkmann M, Raff J, Raue F, Klar E and Herfarth C. [Effect of primary surgical therapy on the course of C-cell carcinoma of the thyroid gland]. Langenbecks Archiv für Chirurgie. Supplement. Kongressband. Deutsche Gesellschaft für Chirurgie. Kongress1998. p. 1041-3.PMID: CN-00335562. **KQ4E9**
98. Colonna M, Grosclaude P, Remontet L, Schvartz C, Mace-Lesech J, Velten M, Guizard A, Tretarre B, Buemi AV, Arveux P and Esteve J. Incidence of thyroid cancer in adults recorded by French cancer registries (1978-1997). European journal of cancer2002. p. 1762-8.PMID: 12175693. **KQ3e2**
99. Conzo G, Calo PG, Gambardella C, Tartaglia E, Mauriello C, Della Pietra C, Medas F, Santa Cruz R, Podda F, Santini L and Troncone G. Controversies in the surgical management of thyroid follicular neoplasms. Retrospective analysis of 721 patients. International Journal Of Surgery2014. p. S29-34.PMID: 24859409. **KQ5E4**
100. Cordón C, Fajardo R, Ramírez J and Herrera M. A randomized, prospective, parallel group study comparing the Harmonic Scalpel to electrocautery in thyroidectomy. Surgery2005. p. 337-41.PMID: CN-00502492. **KQ5E6H**
101. Corso C, Gomez X, Sanabria A, Vega V, Dominguez LC and Osorio C. Total thyroidectomy versus hemithyroidectomy for patients with follicular neoplasm. A cost-utility analysis. International Journal Of Surgery2014. p. 837-42.PMID: 25017947. **KQ5E3A**
102. Creach KM, Siegel BA, Nussenbaum B and Grigsby PW. Radioactive iodine therapy decreases recurrence in thyroid papillary microcarcinoma. Isrn Endocrinology Print2012. p. 816386.PMID: 22462017. **KQ4e2b, KQ5e6h**
103. Dal Maso L, Lise M, Zambon P, Falcini F, Crocetti E, Serraino D, Cirilli C, Zanetti R, Vercelli M, Ferretti S, Stracci F, De Lisi V, Busco S, Tagliabue G, Budroni M, Tumino R, Giacomin A, Franceschi S and Group AW. Incidence of thyroid cancer in Italy, 1991-2005: time trends and age-period-cohort effects. Annals of oncology2011. p. 957-63.PMID: 20952599. **KQALLE6**
104. Davies L, Morris LGT, Haymart M, Chen AY, Goldenberg D, Morris J, Ogilvie JB, Terris DJ, Netterville J, Wong RJ, Randolph G and Committee obotAESS. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY DISEASE STATE CLINICAL REVIEW: THE INCREASING INCIDENCE OF THYROID CANCER. Endocrine practice2015. p. 686-696.PMID: 26135963. **KQ3E5**
105. Davies L, Ouellette M, Hunter M and Welch HG. The increasing incidence of small thyroid cancers: where are the cases coming from? Laryngoscope2010. p. 2446-51.PMID: 21108428. **KQ3e5**
106. Davies L and Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. Jama2006. p. 2164-7.PMID: 16684987. **KQ3E2**
107. Davis S. Screening For Thyroid Cancer after the Fukushima Disaster: What Do We Learn From Such An Effort? Epidemiology. 2015/10/07 ed2015.PMID: 26441344. **KQ1E5**
108. De Pasquale L, Bastagli A, Moro GP and Ghilardi G. Thyroid microcarcinoma approach: a ten year experience. Annali Italiani di Chirurgia2013. p. 533-9.PMID: 24140756. **KQ5E5**
109. de Vathaire F, Schlumberger M, Delisle MJ, Francese C, Challeton C, de la Genardiere E, Meunier F, Parmentier C, Hill C and Sancho-Garnier H. Leukaemias and cancers following iodine-131 administration for thyroid cancer. British Journal of Cancer1997. p. 734-9.PMID: 9043033. **KQ5E6G**
110. Debry C, Schmitt E, Senechal G, Siliste CD, Quevauvilliers J and Renou G. [Analysis of complications of thyroid surgery: recurrent paralysis et hypoparathyroidism. On a series of 588 cases]. Ann Otolaryngol Chir Cervicofac. 1995/01/01 ed1995. p. 211-7.PMID: 7503500. **KQ5E9**
111. Del Rio P, Arcuri MF, Ferreri G, Sommaruga L and Sianesi M. The utility of serum PTH assessment 24 hours after total thyroidectomy. Otolaryngology - Head & Neck Surgery2005. p. 584-6.PMID: 15806050. **KQ5e5**

112. Demeter JG, De Jong SA, Lawrence AM and Paloyan E. Anaplastic thyroid carcinoma: risk factors and outcome. Surgery. 1991/12/01 ed1991. p. 956-61; discussion 961-3.PMID: 1745983. **KQALLE5**
113. Demeter JG, Lawrence AM and Paloyan E. Necessity and safety of completion thyroidectomy for differentiated thyroid carcinoma. Surgery1992. p. 734-7; discussion 737-9.PMID: 1411945. **KQ5E2**
114. Demirel K, Kapucu O, Yucel C, Ozdemir H, Ayvaz G and Taneri F. A comparison of radionuclide thyroid angiography, (99m)Tc-MIBI scintigraphy and power Doppler ultrasonography in the differential diagnosis of solitary cold thyroid nodules. European Journal of Nuclear Medicine & Molecular Imaging2003. p. 642-50.PMID: 12612810. **KQ2e3a**
115. Di Filippo B, Schiazzano A, Cappabianca A, Barrella G, Ferraiuolo G and Mastrorilli G. The role or lymphnodal dissection in the treatment of differentiated thyroid cancers. Journal of experimental & clinical cancer research1998. p. 343-7.PMID: 9894773. **KQ4E5, KQ5E5**
116. Dincer N, Balci S, Yazgan A, Guney G, Ersoy R, Cakir B and Guler G. Follow-up of atypia and follicular lesions of undetermined significance in thyroid fine needle aspiration cytology. Cytopathology2013. p. 385-90.PMID: 23078633. **KQ3e3a**
117. Dingle IF, Mishoe AE, Nguyen SA, Overton LJ and Gillespie MB. Salivary morbidity and quality of life following radioactive iodine for well-differentiated thyroid cancer. Otolaryngology - Head & Neck Surgery2013. p. 746-52.PMID: 23462656. **KQ4e5, KQ5e7**
118. Dixon E, McKinnon JG and Pasieka JL. Feasibility of sentinel lymph node biopsy and lymphatic mapping in nodular thyroid neoplasms. World journal of surgery2000. p. 1396-401.PMID: 11038213. **KQ5E5**
119. Doci R, Pilotti S, Greco M and Cascinelli N. Long term results of surgical treatment of thyroid cancer. Annales de Radiologie1977. p. 775-8.PMID: 610548. **KQ5E6G**
120. Doddi S, Chohda E, Maghsoudi S, Sheehan L, Sinha A, Chandak P and Sinha P. The final outcome of indeterminate cytology of thyroid nodules in a District General Hospital. Giornale di Chirurgia2015. p. 122-7.PMID: 26188757. **KQ3E1**
121. Dodds P. Carcinoma of the thyroid gland in Auckland, New Zealand. Surgery, Gynecology & Obstetrics1990. p. 27-32.PMID: 2360146. **KQ4E5, KQ5E5**
122. Dottorini ME, Lomuscio G, Mazzucchelli L, Vignati A and Colombo L. Assessment of female fertility and carcinogenesis after iodine-131 therapy for differentiated thyroid carcinoma. J Nucl Med. 1995/01/01 ed1995. p. 21-7.PMID: 7799075. **KQ5E6**
123. du Cret RP and Mariash CN. Local reactions to radioiodine in the treatment of thyroid cancer. American Journal of Medicine1991. p. 217-22.PMID: 1996591. **KQ4E2B, KQ5E6G**
124. Duncan TD and McCord D. Thyroid carcinoma: criteria in selection of patients for total and subtotal thyroidectomy. Journal of the National Medical Association1983. p. 401-4.PMID: 6864818. **KQ4E2B**
125. Durante C, Attard M, Torlontano M, Ronga G, Monzani F, Costante G, Ferdeghini M, Tumino S, Meringolo D, Bruno R, De Toma G, Crocetti U, Montesano T, Dardano A, Lamartina L, Maniglia A, Giacomelli L, Filetti S and Papillary Thyroid Cancer Study G. Identification and optimal postsurgical follow-up of patients with very low-risk papillary thyroid microcarcinomas. Journal of Clinical Endocrinology & Metabolism2010. p. 4882-8.PMID: 20660054. **KQ4e2b**
126. Durante C, Costante G, Lucisano G, Bruno R, Meringolo D, Paciaroni A, Puxeddu E, Torlontano M, Tumino S, Attard M, Lamartina L, Nicolucci A and Filetti S. The natural history of benign thyroid nodules. Jama2015. p. 926-35.PMID: 25734734. **KQ3e2**
127. Ebina A, Sugitani I, Fujimoto Y and Yamada K. Risk-adapted management of papillary thyroid carcinoma according to our own risk group classification system: is thyroid lobectomy the treatment of choice for low-risk patients? Surgery2014. p. 1579-88; discussion 1588-9.PMID: 25262223. **KQ4e2b, KQ5e6h**
128. Eden K, Mahon S and Helfand M. Screening high-risk populations for thyroid cancer. Medical & Pediatric Oncology2001. p. 583-91.PMID: 11340616. **KQ2E8**
129. Edmonds CJ and Smith T. The long-term hazards of the treatment of thyroid cancer with radioiodine. British Journal of Radiology1986. p. 45-51.PMID: 3947807. **KQ5E6G**
130. Elliott MS, Gao K, Gupta R, Chua EL, Gargya A and Clark J. Management of incidental and non-incidental papillary thyroid microcarcinoma. Journal of Laryngology & Otology2013. p. S17-23.PMID: 23544739. **KQ3e4, KQ4e2b, KQ5e5**

131. Elsayed NM and Elkhatib YA. Diagnostic Criteria and Accuracy of Malignant Thyroid Nodules by Ultrasonography and Ultrasound Elastography with Pathologic Correlation. Ultrason Imaging. 2015/05/03 ed2015.PMID: 25933616. **KQ2E2C**
132. Erbil Y, Barbaros U, Salmaslio?lu A, Yanik BT, Bozbora A and Ozarma?an S. The advantage of near-total thyroidectomy to avoid postoperative hypoparathyroidism in benign multinodular goiter. Langenbeck's archives of surgery / Deutsche Gesellschaft für Chirurgie2006. p. 567-73.PMID: CN-00617490. **KQALLE3B**
133. Erdem E, Gülçelik M, Kuru B and Alagöl H. Comparison of completion thyroidectomy and primary surgery for differentiated thyroid carcinoma. European Journal of Surgical Oncology (EJSO)2003. p. 747-749**KQ5E3A**
134. Eroglu A, Unal M and Kocaoglu H. Total thyroidectomy for differentiated thyroid carcinoma: primary and secondary operations. European journal of surgical oncology1998. p. 283-7.PMID: 9724994. **KQ5E3A**
135. F IW, Fawad Khan S, Ur Rehman H and Ahmad Khan I. Role of fine needle aspiration cytology in diagnosis of solitary thyroid nodules. Iranian journal of otorhinolaryngology2011. p. 111-8.PMID: 24303370. **KQ3e3a**
136. F P, Jaconi M, Delitala A, Garancini M, Maternini M, Bono F, Giani A, Smith A and San Gerardo Hospital collaborators g. Incidental papillary thyroid carcinoma: diagnostic findings in a series of 287 carcinomas. Endocrine pathology2014. p. 288-96.PMID: 24997780. **KQ3E4**
137. Fahey TJ, 3rd, Reeve TS and Delbridge L. Increasing incidence and changing presentation of thyroid cancer over a 30-year period. British journal of surgery1995. p. 518-20.PMID: 7613899. **KQ3E5, KQ5E5**
138. Fallahi B, Adabi K, Majidi M, Fard-Esfahani A, Heshmat R, Larijani B and Haghpanah V. Incidence of second primary malignancies during a long-term surveillance of patients with differentiated thyroid carcinoma in relation to radioiodine treatment. Clinical nuclear medicine2011. p. 277-82.PMID: 21368600. **KQ5e3a**
139. Farkas EA, King TA, Bolton JS and Fuhrman GM. A comparison of total thyroidectomy and lobectomy in the treatment of dominant thyroid nodules. American surgeon2002. p. 678-82; discussion 682-3.PMID: 12206601. **KQ4E10**
140. Farrar WB, Cooperman M and James AG. Surgical management of papillary and follicular carcinoma of the thyroid. Annals of surgery1980. p. 701-4.PMID: 7447520. **KQ4E2B, KQ5E6G**
141. Favus MJ, Schneider AB, Stachura ME, Arnold JE, Ryo UY, Pinsky SM, Colman M, Arnold MJ and Frohman LA. Thyroid cancer occurring as a late consequence of head-and-neck irradiation. Evaluation of 1056 patients. New England journal of medicine1976. p. 1019-25.PMID: 1256510. **KQ2E4D, KQ3E5**
142. Fayek IS, Kamel AA and Sidhom NF. Safety and Prognostic Impact of Prophylactic Level VII Lymph Node Dissection for Papillary Thyroid Carcinoma. Asian Pacific Journal of Cancer Prevention: Apjcp2015. p. 8425-30.PMID: 26745096. **KQ5E3A**
143. Filho JG and Kowalski LP. Postoperative complications of thyroidectomy for differentiated thyroid carcinoma. American journal of otolaryngology2004. p. 225-30.PMID: 15239027. **KQ5e3a**
144. Fink A, Tomlinson G, Freeman JL, Rosen IB and Asa SL. Occult micropapillary carcinoma associated with benign follicular thyroid disease and unrelated thyroid neoplasms. Modern Pathology1996. p. 816-20.PMID: 8871922. **KQ5E5**
145. Florentine BD, Staymates B, Rabadi M, Barstis J, Black A and Cancer Committee of the Henry Mayo Newhall Memorial H. The reliability of fine-needle aspiration biopsy as the initial diagnostic procedure for palpable masses: a 4-year experience of 730 patients from a community hospital-based outpatient aspiration biopsy clinic. Cancer2006. p. 406-16.PMID: 16773630. **KQ3e4**
146. Foley CS, Agcaoglu O, Siperstein AE and Berber E. Robotic transaxillary endocrine surgery: a comparison with conventional open technique. Surg Endosc. 2012/02/09 ed2012. p. 2259-66.PMID: 22311302. **KQ4E5**
147. Fon LJ, Deans GT, Lioe TF, Lawson JT, Briggs K and Spence RA. An audit of thyroid surgery in a general surgical unit. Annals of the Royal College of Surgeons of England1996. p. 192-6.PMID: 8779503. **KQ4E2B, KQ5E4**
148. Franceschi S and Vaccarella S. Thyroid cancer: An epidemic of disease or an epidemic of diagnosis? International Journal of Cancer. 2014/11/05 ed2014.PMID: 25365909. **KQ3E2**

149. Frates MC, Benson CB, Doubilet PM, Cibas ES and Marqusee E. Can color Doppler sonography aid in the prediction of malignancy of thyroid nodules? Journal of ultrasound in medicine2003. p. 127-31; quiz 132-4.PMID: 12562117. **KQ2e2c**
150. Fukunari N, Nagahama M, Sugino K, Mimura T, Ito K and Ito K. Clinical evaluation of color Doppler imaging for the differential diagnosis of thyroid follicular lesions. World journal of surgery2004. p. 1261-5.PMID: 15517496. **KQ2e2c**
151. Gasperi M, Fugazzola L, Ceccarelli C, Lippi F, Centoni R, Martino E and Pinchera A. Testicular function in patients with differentiated thyroid carcinoma treated with radioiodine. Journal of nuclear medicine1994. p. 1418-22.PMID: 8071685. **KQ5E6G**
152. Gazdag A, Nagy EV, Erdei A, Bodor M, Berta E, Szabo Z and Jenei Z. Aortic stiffness and left ventricular function in patients with differentiated thyroid cancer. J Endocrinol Invest. 2014/09/10 ed2014.PMID: 25194423. **KQ5E6**
153. Gemsenjager E, Perren A, Seifert B, Schuler G, Schweizer I and Heitz PU. Lymph node surgery in papillary thyroid carcinoma. Journal of the American College of Surgeons2003. p. 182-90.PMID: 12892795. **KQ5e6h**
154. Gharib H, Suman VJ and Goellner JR. "Suspicious" thyroid cytologic findings: outcome in patients without immediate surgical treatment. Mayo Clinic proceedings1993. p. 343-8.PMID: 8455392. **KQ3E4**
155. Ghori FY, Gutterman-Litofsky DR, Jamal A, Yeung SC, Arem R and Sherman SI. Socioeconomic factors and the presentation, management, and outcome of patients with differentiated thyroid carcinoma. Thyroid2002. p. 1009-16.PMID: 12490079. **KQ3e1**
156. Ghossein R, Ganly I, Biagini A, Robenshtok E, Rivera M and Tuttle RM. Prognostic factors in papillary microcarcinoma with emphasis on histologic subtyping: a clinicopathologic study of 148 cases. Thyroid2014. p. 245-53.PMID: 23745671. **KQ5e5**
157. Giani C, Fierabracci P, Bonacci R, Gigliotti A, Campani D, De Negri F, Cecchetti D, Martino E and Pinchera A. Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy. Journal of Clinical Endocrinology & Metabolism1996. p. 990-4.PMID: 8772562. **KQ2E5, KQ3E5**
158. Giddings AE. Solitary thyroid nodule: audit shows improved care requires cytological diagnosis. Annals of the Royal College of Surgeons of England1989. p. 316-9.PMID: 2802479. **KQ5E4D**
159. Gimm O and Dralle H. Surgical strategies in papillary thyroid carcinoma. Current Topics in Pathology1997. p. 51-64.PMID: 9018916. **KQ5E5**
160. Goffredo P, Cheung K, Roman SA and Sosa JA. Can minimally invasive follicular thyroid cancer be approached as a benign lesion?: a population-level analysis of survival among 1,200 patients. Annals of surgical oncology2013. p. 767-72.PMID: 23111705. **KQ4E5, KQ5e6**
161. Goffredo P, Thomas SM, Dinan MA, Perkins JM, Roman SA and Sosa JA. Patterns of Use and Cost for Inappropriate Radioactive Iodine Treatment for Thyroid Cancer in the United States: Use and Misuse. JAMA Internal Medicine. 2015/02/17 ed2015.PMID: 25686394. **KQ5E5**
162. Goldfarb M, Gondek S, Solorzano C and Lew JI. Surgeon-performed ultrasound can predict benignity in thyroid nodules. Surgery2011. p. 436-41.PMID: 21878228. **KQ2e2c**
163. Golia F, Bruno-Bossio G, Vignali E and Pinchera A. Carefully monitored levothyroxine suppressive therapy is not associated with bone loss in premenopausal women. Journal of Clinical Endocrinology & Metabolism1994. p. 818-23.PMID: 8157704. **KQ5E4**
164. Goncalves Filho J and Kowalski LP. Surgical complications after thyroid surgery performed in a cancer hospital. Otolaryngology - Head & Neck Surgery2005. p. 490-4.PMID: 15746868. **KQ5e3a**
165. Gourin CG, Tufano RP, Forastiere AA, Koch WM, Pawlik TM and Bristow RE. Volume-based trends in thyroid surgery. Archives of Otolaryngology–Head & Neck Surgery2010. p. 1191-1198**KQ5E4D**
166. Govednik C, Snyder S, Quinn C, Saxena S and Jupiter D. Minimally invasive, nonendoscopic thyroidectomy: A cosmetic alternative to robotic-assisted thyroidectomy. Surgery (United States)2014. p. 1030-8.PMID: CN-01079446. **KQ5E6H**
167. Grant CS, van Heerden JA, Goellner JR, Ebersold JR and Bergstralh EJ. Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. Surgery1992. p. 1139-46; discussion 1146-7.PMID: 1455316. **KQ5E2**

168. Grauer A, Raue F and Gagel RF. Changing concepts in the management of hereditary and sporadic medullary thyroid carcinoma. Endocrinol Metab Clin North Am. 1990/09/01 ed1990. p. 613-35.PMID: 1979773. **KQALLE1**
169. Grover G, Sadler GP and Mihai R. Morbidity after thyroid surgery: patient perspective. Laryngoscope2013. p. 2319-23.PMID: 23824630. **KQ5e2**
170. Guasti L, Marino F, Cosentino M, Cimpanelli M, Rasini E, Piantanida E, Vanoli P, De Palma D, Crespi C, Klersy C, Maroni L, Loraschi A, Colombo C, Simoni C, Bartalena L, Lecchini S, Grandi AM and Venco A. Pain perception, blood pressure levels, and peripheral benzodiazepine receptors in patients followed for differentiated thyroid carcinoma: a longitudinal study in hypothyroidism and during hormone treatment. Clinical Journal of Pain2007. p. 518-23.PMID: 17575492. **KQ4e6, KQ5e6**
171. Gul K, Ersoy R, Dirikoc A, Korukluoglu B, Ersoy PE, Aydin R, Ugras SN, Belenli OK and Cakir B. Ultrasonographic evaluation of thyroid nodules: comparison of ultrasonographic, cytological, and histopathological findings. Endocrine2009. p. 464-72.PMID: 19859839. **KQ2e2c, KQ3e2c**
172. Gulcelik MA, Kuru B, Dincer H, Camlibel M, Yuksel UM, Yenidogan E and Reis E. Complications of completion versus total thyroidectomy. Asian Pacific Journal of Cancer Prevention: Apjcp2012. p. 5225-8.PMID: 23244139. **KQ4e3a, KQ5e3a**
173. Guo Z, Hu Y and Liu Q. [Clinical analysis of hoarseness after thyroidectomy]. Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2001/03/27 ed1998. p. 362-3, 373.PMID: 11263159. **KQ5E9**
174. Gutierrez S, Carbonell E, Galofrea P, Xamena N, Creus A and Marcos R. A cytogenetic follow-up study of thyroid cancer patients treated with 131I. Cancer Letters1995. p. 199-204.PMID: 7767910. **KQ5E5**
175. Gyory F, Lukacs G, Balazs G, Szakall S, Miltenyi L and Kiss A. Interdisciplinary treatment of the malignant lymphoma of the thyroid. Acta Chirurgica Hungarica1997. p. 110-2.PMID: 9408307. **KQ5E6G**
176. Gyory F, Lukacs G, Juhasz F, Mezosi E, Szakall S, Vegh T, Math J and Balazs G. Surgically treated Hashimoto's thyroiditis. Acta Chirurgica Hungarica1999. p. 243-7.PMID: 10935132. **KQ5E4**
177. Haber RS. Role of ultrasonography in the diagnosis and management of thyroid cancer. Endocrine practice2000. p. 396-400.PMID: 11141593. **KQ2E2C, KQ3E2C**
178. Hadjisavva IS, Dina R, Talias MA and Economides PA. Prevalence of Cancer in Patients with Thyroid Nodules in the Island of Cyprus: Predictive Value of Ultrasound Features and Thyroid Autoimmune Status. European Thyroid Journal2015. p. 123-8.PMID: 26279998. **KQ2E2C**
179. Haghpanah V, Abbas SI, Mahmoodzadeh H, Shojaei A, Soleimani A, Larijani B and Tavangar SM. Paraplegia as initial presentation of follicular thyroid carcinoma. Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan2006. p. 233-4.PMID: 16542610. **KQ3e2**
180. Hakala T, Kellokumpu-Lehtinen P, Kholova I, Holli K, Huhtala H and Sand J. Rising incidence of small size papillary thyroid cancers with no change in disease-specific survival in Finnish thyroid cancer patients. Scandinavian Journal of Surgery: SJS2012. p. 301-6.PMID: 23238509. **KQ3e2**
181. Hall P, Holm L, Lundell G, Bjelkengren G, Larsson L, Lindberg S, Tennvall J, Wicklund H and Boice Jr J. Cancer risks in thyroid cancer patients. British Journal of Cancer1991. p. 159**KQ5E6G**
182. Hall P, Holm LE and Lundell G. Second primary tumors following thyroid cancer. A Swedish record-linkage study. Acta Oncologica. 1990/01/01 ed1990. p. 869-73.PMID: 2261200. **KQ5E6**
183. Hamilton TE, van Belle G and LoGerfo JP. Thyroid neoplasia in Marshall Islanders exposed to nuclear fallout. Jama1987. p. 629-35.PMID: 3612986. **KQ2E3A, KQ3E3A**
184. Han MA, Choi KS, Lee HY, Kim Y, Jun JK and Park EC. Current status of thyroid cancer screening in Korea: results from a nationwide interview survey. Asian Pacific Journal of Cancer Prevention: Apjcp2011. p. 1657-63.PMID: 22126540. **KQ2E5**
185. Handelsman DJ and Turtle JR. Testicular damage after radioactive iodine (I-131) therapy for thyroid cancer. Clinical endocrinology1983. p. 465-72.PMID: 6409459. **KQ5E6G**
186. Harach HR, Franssila KO and Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. Cancer. 1985/08/01 ed1985. p. 531-8.PMID: 2408737. **KQALLE1**

187. Harada T, Fukunaga M, Furukawa J, Yamane Y, Yasuda K, Yanagimoto S, Tomomitsu T, Otsuka N and Morita R. New perspectives for diagnosis of nodular goiter by technetium-thallium subtraction scanning. Clinical nuclear medicine1989. p. 897-902.PMID: 2557998. **KQ2E2C, KQ3E5**
188. Hauch A, Al-Qurayshi Z, Randolph G and Kandil E. Total thyroidectomy is associated with increased risk of complications for low- and high-volume surgeons. Annals of surgical oncology2014. p. 3844-52.PMID: 24943236. **KQ5E4D**
189. Hay D. Local recurrence of papillary thyroid carcinoma after unilateral or bilateral thyroidectomy. Wiener klinische Wochenschrift1988. p. 342-6.PMID: 3407192. **KQ5E6G**
190. Hay ID, Goellner JR, Ryan JJ and McConahey WM. Mortality from papillary thyroid carcinoma. A case-control study of 56 lethal cases. Cancer1988. p. 1381-8.PMID: 3416277. **KQ5E6G**
191. Henry JF, Gramatica L, Denizot A, Kvachenyuk A, Puccini M and Defechereux T. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. Langenbecks Archives of Surgery1998. p. 167-9.PMID: 9641892. **KQ5E10**
192. Hesselink EN, Lefrandt JD, Schuurmans EP, Burgerhof JG, Groen B, Gansevoort RT, van der Horst-Schrivers AN, Dullaart RP, Van Gelder IC, Brouwers AH, Rienstra M and Links TP. Increased Risk of Atrial Fibrillation After Treatment for Differentiated Thyroid Carcinoma. Journal of Clinical Endocrinology & Metabolism2015. p. 4563-9.PMID: 26480284. **KQ5E5**
193. Hirsch D, Ginat M, Levy S, Benbassat C, Weinstein R, Tsvetov G, Singer J, Shraga-Slutzky I, Grozinski-Glasberg S, Mansiterski Y, Shimon I and Reicher-Atir R. Illness perception in patients with differentiated epithelial cell thyroid cancer. Thyroid2009. p. 459-65.PMID: 19415995. **KQ4e4**
194. Ho AS, Davies L, Nixon IJ, Palmer FL, Wang LY, Patel SG, Ganly I, Wong RJ, Tuttle RM and Morris LG. Increasing diagnosis of subclinical thyroid cancers leads to spurious improvements in survival rates. Cancer. 2015/02/26 ed2015.PMID: 25712809. **KQ3E2**
195. Hoelzer S, Steiner D, Bauer R, Reiners C, Farahati J, Hundahl SA and Dudeck J. Current practice of radioiodine treatment in the management of differentiated thyroid cancer in Germany. European journal of nuclear medicine2000. p. 1465-72.PMID: 11083534. **KQ4E2B, KQ5E5**
196. Holm LE. Cancer risks after diagnostic doses of 131I with special reference to thyroid cancer. Cancer Detect Prev1991. p. 27-30.PMID: 2044071. **KQ5E2**
197. Holm LE, Dahlqvist I, Israelsson A and Lundell G. Malignant thyroid tumors after iodine-131 therapy: a retrospective cohort study. New England journal of medicine1980. p. 188-91.PMID: 7383089. **KQ5E4D**
198. Howard JE, Vaswani A and Heotis P. Thyroid disease among the Rongelap and Utirik population--an update. Health Phys. 1997/07/01 ed1997. p. 190-8.PMID: 9199229. **KQALLE4**
199. Hrafnkelsson J, Tulinius H, Jonasson JG, Olafsdottir G and Sigvaldason H. Papillary thyroid carcinoma in Iceland. A study of the occurrence in families and the coexistence of other primary tumours. Acta Oncologica. 1989/01/01 ed1989. p. 785-8.PMID: 2611030. **KQ2E4C**
200. Hryhorczuk AL, Stephens T, Bude RO, Rubin JM, Bailey JE, Higgins EJ, Fox GA and Klein KA. Prevalence of malignancy in thyroid nodules with an initial nondiagnostic result after ultrasound guided fine needle aspiration. Ultrasound in medicine & biology2012. p. 561-7.PMID: 22341051. **KQ3e6**
201. Hsiao YL and Chang TC. Ultrasound evaluation of thyroid abnormalities and volume in Chinese adults without palpable thyroid glands. Journal of the Formosan Medical Association. 1994/02/01 ed1994. p. 140-4.PMID: 7912585. **KQALLE4**
202. Hu G, Zhu W, Yang W, Wang H, Shen L and Zhang H. The Effectiveness of Radioactive Iodine Remnant Ablation for Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-analysis. World journal of surgery2016. p. 100-9.PMID: 26578322. **KQ4E2B**
203. Huang X, Guo LH, Xu HX, Gong XH, Liu BJ, Xu JM, Zhang YF, Li XL, Li DD, Qu S and Fang L. Acoustic radiation force impulse induced strain elastography and point shear wave elastography for evaluation of thyroid nodules. International journal of clinical and experimental medicine2015. p. 10956-63.PMID: 26379890. **KQ2E2C**

204. Hughes DT, Haymart MR, Miller BS, Gauger PG and Doherty GM. The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. Thyroid. 2011/01/28 ed2011. p. 231-6.PMID: 21268762. **KQALLE1**
205. Hundahl SA, Fleming ID, Fremgen AM and Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see commetns]. Cancer1998. p. 2638-48.PMID: 9874472. **KQ4E2B**
206. Hussain F, Iqbal S, Mehmood A, Bazarbashi S, ElHassan T and Chaudhri N. Incidence of thyroid cancer in the Kingdom of Saudi Arabia, 2000-2010. Hematology/oncology & stem cell therapy2013. p. 58-64.PMID: 23756719. **KQ3e2**
207. Hwang S, Shin DY, Kim EK, Yang WI, Byun JW, Lee SJ, Kim G, Im SJ and Lee EJ. Focal Lymphocytic Thyroiditis Nodules Share the Features of Papillary Thyroid Cancer on Ultrasound. Yonsei medical journal2015. p. 1338-44.PMID: 26256977. **KQ2E2C**
208. Hyer S, Vini L, O'Connell M, Pratt B and Harmer C. Testicular dose and fertility in men following I(131) therapy for thyroid cancer. Clinical endocrinology2002. p. 755-8.PMID: 12072044. **KQ5e6g**
209. Hyer SL, Dandekar P, Newbold K, Haq M, Wechalakar K, Thway K and Harmer C. Thyroid cancer causing obstruction of the great veins in the neck.[Erratum appears in World J Surg Oncol. 2008;6:40 Note: Thway, Khin [added]]. World journal of surgical oncology2008. p. 36.PMID: 18387194. **KQ4e1, KQ5e1**
210. Ikeda Y, Takami H, Niimi M, Kan S, Sasaki Y and Takayama J. Endoscopic thyroidectomy and parathyroidectomy by the axillary approach. A preliminary report. Surgical endoscopy2002. p. 92-5.PMID: 11961613. **KQ5E6**
211. Illouz F, Rodien P, Saint-Andre JP, Triau S, Laboureau-Soares S, Dubois S, Vielle B, Hamy A and Rohmer V. Usefulness of repeated fine-needle cytology in the follow-up of non-operated thyroid nodules.[Erratum appears in Eur J Endocrinol. 2007 Jun;156(6):705 Note: Antoine, Hamy [corrected to Hamy, Antoine]]. European Journal of Endocrinology2007. p. 303-8.PMID: 17322489. **KQ3e5**
212. Imaizumi M, Usa T, Tominaga T, Akahoshi M, Ashizawa K, Ichimaru S, Nakashima E, Ishii R, Ejima E, Hida A, Soda M, Maeda R, Nagataki S and Eguchi K. Long-term prognosis of thyroid nodule cases compared with nodule-free controls in atomic bomb survivors. Journal of Clinical Endocrinology & Metabolism2005. p. 5009-14.PMID: 15941865. **KQ2e3b**
213. Isaac A, Jeffery CC, Seikaly H, Al-Marzouki H, Harris JR and DA OC. Predictors of non-diagnostic cytology in surgeon-performed ultrasound guided fine needle aspiration of thyroid nodules. Journal of Otolaryngology: Head and Neck Surgery. 2014/12/04 ed2014. p. 48.PMID: 25466726. **KQ3E5**
214. Ishigaki S, Shimamoto K, Satake H, Sawaki A, Itoh S, Ikeda M, Ishigaki T and Imai T. Multi-slice CT of thyroid nodules: comparison with ultrasonography. Radiation Medicine2004. p. 346-53.PMID: 15553016. **KQ2e2c**
215. Ishihara T, Yamazaki S, Kobayashi K, Inoue H, Fukai S, Ito K and Mimura T. Resection of the trachea infiltrated by thyroid carcinoma. Annals of surgery1982. p. 496-500.PMID: 7065753. **KQ4E4B, KQ5E4B**
216. Ishikawa K, Noguchi S, Tanaka K, Fukuda A and Hirohata T. Second primary neoplasms in thyroid cancer patients. Japanese Journal of Cancer Research. 1996/03/01 ed1996. p. 232-9.PMID: 8613424. **KQ5E6G**
217. Ito Y, Amino N, Yokozawa T, Ota H, Ohshita M, Murata N, Morita S, Kobayashi K and Miyauchi A. Ultrasonographic evaluation of thyroid nodules in 900 patients: comparison among ultrasonographic, cytological, and histological findings. Thyroid2007. p. 1269-76.PMID: 17988196. **KQ2E2C**
218. Ito Y, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K and Miyauchi A. Long-term follow-up for patients with papillary thyroid carcinoma treated as benign nodules. Anticancer Research2007. p. 1039-43.PMID: 17465240. **KQ4e2b, KQ5e5**
219. Ivanac G, Brkljacic B, Ivanac K, Huzjan R, Skreb F and Cikara I. Vascularisation of benign and malignant thyroid nodules: CD US evaluation. Ultraschall in der Medizin2007. p. 502-6.PMID: 17492574. **KQ2e2c, KQ3e5**
220. J R, B L, LL Z, HY L, F Z, S L and LR Z. A taller-than-wide shape is a good predictor of papillary thyroid carcinoma in small solid nodules. Journal of ultrasound in medicine2015. p. 19-26.PMID: 25542935. **KQ3E1A**

221. J T, Goldberg AS, Jones J, Zhang J, Lowe J, Ezzat S, Gilbert J, Zahedi A, Segal P and Sawka AM. A systematic review of randomized controlled trials for management of persistent post-treatment fatigue in thyroid cancer survivors. Thyroid2015. p. 198-210.PMID: 25382050. **KQ4e4, KQ5e6**
222. Jacob P, Kenigsberg Y, Goulko G, Buglova E, Gering F, Golovneva A, Kruk J and Demidchik EP. Thyroid cancer risk in Belarus after the Chernobyl accident: comparison with external exposures. Radiation & Environmental Biophysics2000. p. 25-31.PMID: 10789892. **KQ1,2,3,4,5E3B**
223. Jamski J, Jamska A, Graca M, Barczynski M and Wlodyka J. [Recurrent laryngeal nerve injury following thyroid surgery]. Przegl Lek. 2004/07/03 ed2004. p. 13-6.PMID: 15230099. **KQ5E9**
224. Jatzko GR, Lisborg PH, Muller MG and Wette VM. Recurrent nerve palsy after thyroid operations--principal nerve identification and a literature review. Surgery1994. p. 139-44.PMID: 8310401. **KQALLE2**
225. Jeannon JP, Orabi AA, Bruch GA, Abdalsalam HA and Simo R. Diagnosis of recurrent laryngeal nerve palsy after thyroidectomy: a systematic review. International journal of clinical practice2009. p. 624-9.PMID: 19335706. **KQ4e2b, KQ5e8**
226. Jeong HS, Baek CH, Son YI, Choi JY, Kim HJ, Ko YH, Chung JH and Baek HJ. Integrated 18F-FDG PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: comparison with ultrasound and contrast-enhanced CT. Clinical endocrinology2006. p. 402-7.PMID: 16918964. **KQ2e5**
227. Jeong SP, Ki KO, Kim EK, Chang HS and Soon WH. Sonographic screening for thyroid cancer in females undergoing breast sonography. AJR. American Journal of Roentgenology2006. p. 1025-8.PMID: CN-00735838. **KQ3E2B**
228. Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer.[Erratum appears in Am J Med 1995 Feb;98(2):215]. American Journal of Medicine1994. p. 418-28.PMID: 7977430. **KQ4E6G**
229. Jog VB, Baluja CA and Damle SR. Risk of hypoparathyroidism after surgery for carcinoma of the thyroid. Head & neck1990. p. 321-5.PMID: 2361862. **KQ5E3**
230. Johns ME, Shikhani AH, Kashima HK and Matanoski GM. Multiple primary neoplasms in patients with salivary gland or thyroid gland tumors. Laryngoscope. 1986/07/01 ed1986. p. 718-21.PMID: 3724320. **KQALLE4**
231. Jonklaas J. Nasal symptoms after radioiodine therapy: a rarely described side effect with similar frequency to lacrimal dysfunction. Thyroid2014. p. 1806-14.PMID: 25090584. **KQ5E7**
232. Joseph KR, Edirimanne S and Eslick GD. The association between breast cancer and thyroid cancer: a meta-analysis. Breast Cancer Research & Treatment2015. p. 173-81.PMID: 26058757. **KQ5E1**
233. JR B, HF S, DC B and JN P. Surgical therapy for thyroid carcinoma: a review of 1249 solitary thyroid nodules. Surgery1988. p. 940-6.PMID: 3194845. **KQ5E6G**
234. Jung H and Schlager B. [Recurrent laryngeal nerve paralysis after thyroidectomy]. Laryngorhinootologie. 2000/07/27 ed2000. p. 297-303.PMID: 10911606. **KQ5E9**
235. Kacar Guveli T, Ozkan S, Oner Tamam M, Uyanik E, Ediz N, Mulazimoglu M and Ozpacaci T. The Effect of High Dose Radioiodine Therapy on Formation of Radiation Retinopathy During Thyroid Cancer Treatment. Molecular Imaging and Radionuclide Therapy. 2014/12/30 ed2014. p. 84-88.PMID: 25541931. **KQ5E3A**
236. Kahn C, Simonella L, Sywak M, Boyages S, Ung O and O'Connell D. Post-surgical pathology reporting of thyroid cancer in New South Wales, Australia. Thyroid. 2012/02/16 ed2012.PMID: 22332763. **KQ4E5**
237. Kandil E, Noureldine SI and Tufano RP. Thyroidectomy vs Active Surveillance for Subcentimeter Papillary Thyroid Cancers-The Cost Conundrum. JAMA Otolaryngology--Head & Neck Surgery. 2015/12/15 ed2015. p. 1-2.PMID: 26661274. **KQ5E5**
238. Kang SW, Lee SH, Park JH, Jeong JS, Park S, Lee CR, Jeong JJ, Nam KH, Chung WY and Park CS. A comparative study of the surgical outcomes of robotic and conventional open modified radical neck dissection for papillary thyroid carcinoma with lateral neck node metastasis. Surgical endoscopy2012. p. 3251-7.PMID: 22648105. **KQ4e2b, KQ5e4**
239. Kaplan EL, McCormick M and Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. Journal of Clinical Endocrinology & Metabolism1990. p. 414-24.PMID: 2380337. **KQ5E6**

240. Kaplan EL, Straus FH and Shukla MS. Does the method of management of papillary thyroid carcinoma make a difference in outcome? World journal of surgery1994. p. 123-30.PMID: 8197768. **KQ4E2, KQ5E2**
241. Karapanou O, Papadopoulos A, Vlassopoulou B, Vassilopoulos C, Pappa E, Tsagarakis S and Niakas D. Health status of Greek thyroid cancer patients after radioiodine administration compared to a demographically matched general population sample. Hellenic journal of nuclear medicine2012. p. 98-102.PMID: 22741146. **KQ4e2b, KQ5e2**
242. Kawai T, Nishihara E, Kudo T, Ota H, Morita S, Kobayashi K, Ito M, Kubota S, Amino N and Miyauchi A. Histopathological diagnoses of "accessory" thyroid nodules diagnosed as benign by fine-needle aspiration cytology and ultrasonography. Thyroid2012. p. 299-303.PMID: 22300250. **KQ2e2c**
243. Kazaure HS, Roman SA and Sosa JA. Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. Annals of surgical oncology2012. p. 1874-80.PMID: 22065195. **KQ4e6**
244. Kerber RA, Till JE, Simon SL, Lyon JL, Thomas DC, Preston-Martin S, Rallison ML, Lloyd RD and Stevens W. A cohort study of thyroid disease in relation to fallout from nuclear weapons testing. Jama. 1993/11/03 ed1993. p. 2076-82.PMID: 8411574. **KQALLE4**
245. Kern KA. Comparative analysis of complications from I-131 radioablation for well-differentiated thyroid cancer. Surgery1994. p. 1024-30.PMID: 7985082. **KQ5E2**
246. Kessler A, Gavriel H, Zahav S, Vaiman M, Shlamkovitch N, Segal S and Eviatar E. Accuracy and consistency of fine-needle aspiration biopsy in the diagnosis and management of solitary thyroid nodules. Israel Medical Association Journal: Imaj2005. p. 371-3.PMID: 15984379. **KQ3e6**
247. Keyhani-Rofagha S, Cunningham JJ and Mazzaferri EL. Cystic thyroid nodules. The dilemma of malignant lesions. Archives of Internal Medicine1990. p. 1422-7.PMID: 2196027. **KQ2E2C, KQ3E5**
248. Khang AR, Cho SW, Choi HS, Ahn HY, Yoo WS, Kim KW, Kang KW, Yi KH, Park do J, Lee DS, Chung JK, Cho BY and Park YJ. The risk of second primary malignancy is increased in differentiated thyroid cancer patients with a cumulative I dose over 37 GBq. Clin Endocrinol (Oxf). 2014/08/15 ed2014.PMID: 25115234. **KQ5E5**
249. Kiernan CM, Parikh AA, Parks LL and Solorzano CC. Use of Radioiodine after Thyroid Lobectomy in Patients with Differentiated Thyroid Cancer: Does It Change Outcomes? Journal of the American College of Surgeons. 2015/02/11 ed2014.PMID: 25667136. **KQ4E2B**
250. Kiernan CM, Parikh AA, Parks LL and Solorzano CC. Use of radioiodine after thyroid lobectomy in patients with differentiated thyroid cancer: does it change outcomes? Journal of the American College of Surgeons2015. p. 617-25.PMID: 25667136. **KQ5E2B**
251. Kikuchi S, Perrier ND, Cheah WK, Siperstein AE, Duh QY and Clark OH. Complication of thyroidectomy in patients with radiation-induced thyroid neoplasms. Archives of Surgery2004. p. 1185-8.PMID: 15545564. **KQ5e5**
252. Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, Zhang Y, Bai Y, Zhu C, Guo GL, Rothman N and Zhang Y. International patterns and trends in thyroid cancer incidence, 1973-2002. Cancer Causes & Control. 2008/11/20 ed2009. p. 525-31.PMID: 19016336. **KQALLE2**
253. Kim BM, Kim MJ, Kim EK, Kwak JY, Hong SW, Son EJ and Kim KH. Sonographic differentiation of thyroid nodules with eggshell calcifications. Journal of ultrasound in medicine2008. p. 1425-30.PMID: 18809952. **KQ2e5**
254. Kim C, Bi X, Pan D, Chen Y, Carling T, Ma S, Udelsman R and Zhang Y. The risk of second cancers after diagnosis of primary thyroid cancer is elevated in thyroid microcarcinomas. Thyroid2013. p. 575-82.PMID: 23237308. **KQ5e6h**
255. Kim DL, Song KH and Kim SK. High prevalence of carcinoma in ultrasonography-guided fine needle aspiration cytology of thyroid nodules. Endocrine journal2008. p. 135-42.PMID: 18219180. **KQ3E1**
256. Kim DW. Ultrasonographic Features of the Major Salivary Glands after Radioactive Iodine Ablation in Patients with Papillary Thyroid Carcinoma. Ultrasound in medicine & biology2015. p. 2640-5.PMID: 26215493. **KQ5E5**
257. Kim DW, Lee EJ, In HS and Kim SJ. Sonographic differentiation of partially cystic thyroid nodules: a prospective study. Ajnr: American Journal of Neuroradiology2010. p. 1961-6.PMID: 20634308. **KQ2e2c**

258. Kim DW, Lee EJ, Kim SH, Kim TH, Lee SH, Kim DH and Rho MH. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules: comparison in efficacy according to nodule size. Thyroid2009. p. 27-31.PMID: 19021460. **KQ2e4a**
259. Kim DW, Lee EJ and Lee JH. Role of ultrasound diagnosis in assessing and managing thyroid nodules with inadequate cytology. AJR. American Journal of Roentgenology2011. p. 1213-9.PMID: 22021517. **KQ2e2c**
260. Kim HJ, Kim NK, Choi JH, Kim SW, Jin SM, Suh S, Bae JC, Min YK, Chung JH and Kim SW. Radioactive iodine ablation does not prevent recurrences in patients with papillary thyroid microcarcinoma. Clinical endocrinology2013. p. 614-20.PMID: 22957654. **KQ4e2b, KQ5e5**
261. Kim JA, Kim JS, Chang MS, Yoo YK and Kim DK. Influence of carbon dioxide insufflation of the neck on intraocular pressure during robot-assisted endoscopic thyroidectomy: a comparison with open thyroidectomy. Surg Endosc. 2012/10/18 ed2013. p. 1587-93.PMID: 23073689. **KQ5E5**
262. Kim KM, Park JB, Kang SJ and Bae KS. Ultrasonographic guideline for thyroid nodules cytology: single institute experience. Journal of The Korean Surgical Society2013. p. 73-9.PMID: 23396617. **KQ2e2c**
263. Kim SK, Kang SY, Youn HJ and Jung SH. Comparison of conventional thyroidectomy and endoscopic thyroidectomy via axillo-bilateral breast approach in papillary thyroid carcinoma patients. Surg Endosc. 2015/10/30 ed2015.PMID: 26511120. **KQ5E6H**
264. Kita T, Yokoyama K, Higuchi T, Kinuya S, Taki J, Nakajima K, Michigishi T and Tonami N. Multifactorial analysis on the short-term side effects occurring within 96 hours after radioiodine-131 therapy for differentiated thyroid carcinoma. Annals of nuclear medicine2004. p. 345-9.PMID: 15359929. **KQ5e5**
265. Knudsen N, Perrild H, Christiansen E, Rasmussen S, Dige-Petersen H and Jorgensen T. Thyroid structure and size and two-year follow-up of solitary cold thyroid nodules in an unselected population with borderline iodine deficiency. European Journal of Endocrinology2000. p. 224-30.PMID: 10700715. **KQ2E5, KQ3E5**
266. Ko KY, Kao CH, Lin CL, Huang WS and Yen RF. (131)I treatment for thyroid cancer and the risk of developing salivary and lacrimal gland dysfunction and a second primary malignancy: a nationwide population-based cohort study. European Journal of Nuclear Medicine & Molecular Imaging2015. p. 1172-8.PMID: 25900274. **KQ5E3B**
267. Ko SY, Kim EK, Moon HJ, Yoon JH, Kim HY and Kwak JY. Application of Thyroid Imaging Reporting and Data System in the Ultrasound Assessment of Thyroid Nodules According to Physician Experience. Ultrasound Quarterly. 2015/08/19 ed2015.PMID: 26280583. **KQ2E2C**
268. Koh J, Moon HJ, Park JS, Kim SJ, Kim HY, Kim EK and Kwak JY. Variability in Interpretation of Ultrasound Elastography and Gray-Scale Ultrasound in Assessing Thyroid Nodules. Ultrasound in medicine & biology2016. p. 51-9.PMID: 26386478. **KQ2E2C**
269. Koike E, Noguchi S, Yamashita H, Murakami T, Ohshima A, Kawamoto H and Yamashita H. Ultrasonographic characteristics of thyroid nodules: prediction of malignancy. Archives of Surgery2001. p. 334-7.PMID: 11231857. **KQ2E2C**
270. Koike E, Yamashita H, Noguchi S, Murakami T, Ohshima A, Maruta J, Kawamoto H and Yamashita H. Effect of combining ultrasonography and ultrasound-guided fine-needle aspiration biopsy findings for the diagnosis of thyroid nodules. European Journal of Surgery2001. p. 656-61.PMID: 11759733. **KQ2E2C**
271. Kountakis SE, Skoulas IG and Maillard AAJ. The radiologic work-up in thyroid surgery: fine-needle biopsy versus scintigraphy and ultrasound. Ear, Nose, & Throat Journal2002. p. 151-4.PMID: 11913059. **kq2e2c**
272. Kouvaraki MA, Lee JE, Shapiro SE, Sherman SI and Evans DB. Preventable reoperations for persistent and recurrent papillary thyroid carcinoma. Surgery2004. p. 1183-91.PMID: 15657574. **KQ5e6**
273. Kovacevic DO and Skurla MS. Sonographic diagnosis of thyroid nodules: correlation with the results of sonographically guided fine-needle aspiration biopsy.[Erratum appears in J Clin Ultrasound. 2007 Jun;35(5):293 Note: Kovacevic, Obad [corrected to Kovacevic, Dragica Obad]]. Journal of Clinical Ultrasound2007. p. 63-7.PMID: 17206727. **KQ2E2**

274. Krishnamurthy GT and Blahd WH. Radioiodine I-31 therapy in the management of thyroid cancer. A prospective study. Cancer1977. p. 195-202.PMID: 880551. **KQ4E2B, KQ5E6G**
275. Kube R, Horschig P, Marusch F, Horntrich J and Gastinger I. [Postoperative recurrent nerve paralysis after initial interventions for benign goiter]. Zentralbl Chir. 1998/05/23 ed1998. p. 11-6.PMID: 9542022. **KQ5E9**
276. Kucuk NO, Tari P, Tokmak E and Aras G. Treatment for microcarcinoma of the thyroid--clinical experience. Clinical nuclear medicine2007. p. 279-81.PMID: 17413573. **KQ5E3A**
277. Kuhn MA, Bloom G and Myssiorek D. Patient perspectives on dysphonia after thyroidectomy for thyroid cancer. Journal of Voice2013. p. 111-4.PMID: 22925427. **KQ5e2**
278. Kuo JH, Chabot JA and Lee JA. Breast cancer in thyroid cancer survivors: An analysis of the Surveillance, Epidemiology, and End Results-9 database. Surgery2016. p. 23-30.PMID: 26522696. **KQ5E2**
279. Kupferman ME, Patterson DM, Mandel SJ, LiVolsi V and Weber RS. Safety of modified radical neck dissection for differentiated thyroid carcinoma. Laryngoscope2004. p. 403-6.PMID: 15091209. **KQ5E6H**
280. Kupferman ME, Patterson M, Mandel SJ, LiVolsi V and Weber RS. Patterns of lateral neck metastasis in papillary thyroid carcinoma. Archives of Otolaryngology -- Head & Neck Surgery2004. p. 857-60.PMID: 15262763. **KQ5e5**
281. Kurukahvecioglu O, Taneri F, Yuksel O, Aydin A, Tezel E and Onuk E. Total thyroidectomy for the treatment of Hashimoto's thyroiditis coexisting with papillary thyroid carcinoma. Advances in Therapy2007. p. 510-6.PMID: 17660159. **KQ5e3a**
282. Kwak H, Kim H, Lee H, Jung S, Son G, Lee J and Bae J. Assessment of vocal function with intraoperative neuromonitoring (IONM) during robotic thyroidectomy: A randomized clinical trial. Thyroid2014. p. A57.PMID: CN-01077843. **KQALLE7 (only abstract available)**
283. Kwak JY, Kim EK, Kim MJ and Son EJ. Significance of sonographic characterization for managing subcentimeter thyroid nodules. Acta Radiologica2009. p. 917-23.PMID: 19636989. **kq3e2c**
284. Kwon JH, Kim EK, Lee HS, Moon HJ and Kwak JY. Neck ultrasonography as preoperative localization of primary hyperparathyroidism with an additional role of detecting thyroid malignancy. European journal of radiology2013. p. e17-21.PMID: 22921682. **KQ2e2**
285. La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F and Negri E. Thyroid cancer mortality and incidence: a global overview. International Journal of Cancer. 2014/10/07 ed2015. p. 2187-95.PMID: 25284703. **KQALLE1**
286. Lang BH, Ng SH, Lau LL, Cowling BJ, Wong KP and Wan KY. A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. Thyroid2013. p. 1087-98.PMID: 23402640. **KQ5e2**
287. Lang BH, Wong CK, Tsang JS and Wong KP. A systematic review and meta-analysis comparing outcomes between robotic-assisted thyroidectomy and non-robotic endoscopic thyroidectomy. Journal of surgical research2014. p. 389-98.PMID: 24814766. **KQ4e2b, KQ5e8**
288. Lasithiotakis K, Grisbolaki E, Koutsomanolis D, Venianaki M, Petrakis I, Vrachassotakis N, Chrysos E, Zoras O and Chalkiadakis G. Indications for surgery and significance of unrecognized cancer in endemic multinodular goiter. World journal of surgery2012. p. 1286-92.PMID: 22395348. **KQ2e4d, KQ3e4d, KQ5e4d**
289. Leblanc BJ, Ryan S, Martin E, Milligan E and Nathan CA. Thyroid Nodules in a Veterans Affairs Population. Otolaryngology - Head & Neck Surgery. 2012/08/01 ed2012. p. P184-P185.PMID: 25718654. **KQ4E5**
290. Lee D, Oh K, Cho J-G, Kwon S-Y, Woo J-S, Baek S-K and Jung K-Y. The Benefits and Risks of Prophylactic Central Neck Dissection for Papillary Thyroid Carcinoma: Prospective Cohort Study. International journal of endocrinology2015.PMID: CN-01103105. **KQ5E6H**
291. Lee HN, An JY, Lee KM, Kim EJ, Choi WS and Kim DY. Salivary gland dysfunction after radioactive iodine (I-131) therapy in patients following total thyroidectomy: emphasis on radioactive iodine therapy dose. Clinical imaging2015. p. 396-400.PMID: 25630229. **KQ5E7**

292. Lee HS, Park HS, Kim SW, Choi G, Park HS, Hong JC, Lee SG, Baek SM and Lee KD. Clinical characteristics of papillary thyroid microcarcinoma less than or equal to 5 mm on ultrasonography. European archives of oto-rhino-laryngology2013. p. 2969-74.PMID: 23873032. **KQ5E2**
293. Lee J, Kwon IS, Bae EH and Chung WY. Comparative analysis of oncological outcomes and quality of life after robotic versus conventional open thyroidectomy with modified radical neck dissection in patients with papillary thyroid carcinoma and lateral neck node metastases. Journal of clinical endocrinology and metabolism2013. p. 2701-8.PMID: CN-00867252. **KQ5E6**
294. Lee J, Nah KY, Kim RM, Ahn YH, Soh EY and Chung WY. Differences in postoperative outcomes, function, and cosmesis: open versus robotic thyroidectomy. Surg Endosc. 2010/05/22 ed2010. p. 3186-94.PMID: 20490558. **KQ5E6H**
295. Lee JC and Siow JK. Thyroid surgery--the Tan Tock Seng Hospital otolaryngology experience. Annals of the Academy of Medicine, Singapore2002. p. 158-64.PMID: 11957551. **KQ4E10, KQ5E10**
296. Lee KE, Koo do H, Im HJ, Park SK, Choi JY, Paeng JC, Chung JK, Oh SK and Youn YK. Surgical completeness of bilateral axillo-breast approach robotic thyroidectomy: comparison with conventional open thyroidectomy after propensity score matching. Surgery2011. p. 1266-74.PMID: 22136850. **KQ5E5**
297. Lee MJ, Hong SW, Chung WY, Kwak JY, Kim MJ and Kim EK. Cytological results of ultrasound-guided fine-needle aspiration cytology for thyroid nodules: emphasis on correlation with sonographic findings. Yonsei medical journal2011. p. 838-44.PMID: 21786450. **KQ2e2c**
298. Lee NJ, Blakey JD, Bhuta S and Calcaterra TC. Unintentional parathyroidectomy during thyroidectomy. Laryngoscope1999. p. 1238-40.PMID: 10443826. **KQ4E2B, KQ5E4**
299. Lee S, Lee YY, Yoon HJ, Choi E, Suh M, Park B, Jun JK, Kim Y and Choi KS. Responses to Overdiagnosis in Thyroid Cancer Screening Among Korean Women. Cancer Res Treat. 2016/01/05 ed2015.PMID: 26727718. **KQ3E5**
300. Lee S, Ryu HR, Park JH, Kim KH, Kang SW, Jeong JJ, Nam KH, Chung WY and Park CS. Early surgical outcomes comparison between robotic and conventional open thyroid surgery for papillary thyroid microcarcinoma. Surgery2012. p. 724-30.PMID: 22284763. **KQ5E6h**
301. Lee YH, Kim DW, In HS, Park JS, Kim SH, Eom JW, Kim B, Lee EJ and Rho MH. Differentiation between benign and malignant solid thyroid nodules using an US classification system. Korean Journal of Radiology2011. p. 559-67.PMID: 21927557. **KQ2e2c**
302. Leenhardt L, Grosclaude P, Cherie-Challine L and Thyroid Cancer C. Increased incidence of thyroid carcinoma in france: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. Thyroid. 2005/01/15 ed2004. p. 1056-60.PMID: 15650358. **KQALLE1**
303. Leenhardt L, Menegaux F, Franc B, Delbot T, Mansour G, Hoang C, Guillausseau C, Aurengo H, Le Guillouzic D, Turpin G, Aurengo A, Chigot JP and Hejblum G. Selection of patients with solitary thyroid nodules for operation. European Journal of Surgery2002. p. 236-41.PMID: 12440762. **KQ2e2c**
304. Levine RA. Value of Doppler ultrasonography in management of patients with follicular thyroid biopsy specimens. Endocrine practice2006. p. 270-4.PMID: 16772198. **KQ2E2, KQ3E2**
305. Li C, Tao Z, Qu J, Zhou T and Xia F. A voice acoustic analysis of thyroid adenoma patients after a unilateral thyroid lobectomy. Journal of Voice2012. p. e23-6.PMID: 21530164. **KQ5e4d**
306. Li F, Zhang J, Wang Y and Liu L. Clinical value of elasticity imaging and contrast-enhanced ultrasound in the diagnosis of papillary thyroid microcarcinoma. Oncol Lett. 2015/12/02 ed2015. p. 1371-1377.PMID: 26622676. **KQ3E3A**
307. Li Y, Jian WH, Guo ZM, Li QL, Lin SJ and Huang HY. A Meta-analysis of Carbon Nanoparticles for Identifying Lymph Nodes and Protecting Parathyroid Glands during Surgery. Otolaryngology - Head & Neck Surgery2015. p. 1007-16.PMID: 25897006. **KQ5E3A**
308. Li YJ, Wang YZ, Yi ZB, Chen LL and Zhou XD. Comparison of Completion Thyroidectomy and Primary Total Surgery for Differentiated Thyroid Cancer: A Meta-Analysis. Oncology Research and Treatment2015. p. 528-31.PMID: 26451702. **KQ5E3A**

309. Liehn JC, Maes B and Delisle MJ. Multivariate analysis in solitary cold thyroid nodules for the diagnosis of malignancy. European Journal of Cancer & Clinical Oncology1988. p. 881-8.PMID: 3169093. **KQ2E2C**
310. Lin JD, Chao TC, Huang BY, Chen ST, Chang HY and Hsueh C. Thyroid cancer in the thyroid nodules evaluated by ultrasonography and fine-needle aspiration cytology. Thyroid2005. p. 708-17.PMID: 16053388. **KQ2e2c, KQ2e2**
311. Lin JD, Chao TC, Sun JH, Ho C and Weng HF. Trends in the clinical characteristics of patients with papillary thyroid carcinoma in Taiwan. Oncology2000. p. 280-5.PMID: 10838492. **KQ4E2B**
312. Lin JD, Hsueh C and Chao TC. Long-Term Follow-Up of the Therapeutic Outcomes for Papillary Thyroid Carcinoma With Distant Metastasis. Medicine2015. p. e1063.PMID: 26131826. **KQ4E2B**
313. Lin JD, Hsueh C, Chao TC, Weng HF and Huang BY. Thyroid follicular neoplasms diagnosed by high-resolution ultrasonography with fine needle aspiration cytology. Acta cytologica1997. p. 687-91.PMID: 9167684. **KQ2E2C, KQ3E4**
314. Lin JK, Lee CH, Lui WY and P'Eng FK. The result of the treatment of thyroid cancer. A retrospective study. Taiwan i Hsueh Hui Tsa Chih - Journal of the Formosan Medical Association1985. p. 482-93.PMID: 3860620. **KQ5E6G**
315. Lin WY, Shen YY and Wang SJ. Short-term hazards of low-dose radioiodine ablation therapy in postsurgical thyroid cancer patients. Clinical nuclear medicine1996. p. 780-2.PMID: 8896926. **KQ5E5**
316. Lindahl F. Papillary thyroid carcinoma in Denmark 1943-68. II. Treatment and survival. Acta Chirurgica Scandinavica1975. p. 504-13.PMID: 52963. **KQ5E6G**
317. Lindahl F. Papillary thyroid carcinoma in Denmark, 1943--1968. Cancer1975. p. 540-52.PMID: 1157017. **KQ5E6G**
318. Lips CJ, Landsvater RM, Hoppener JW, Geerdink RA, Blijham G, van Veen JM, van Gils AP, de Wit MJ, Zewald RA, Berends MJ and et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. N Engl J Med. 1994/09/29 ed1994. p. 828-35.PMID: 7915822. **KQALLE5**
319. Liu Q, Djuricin G and Prinz RA. Total thyroidectomy for benign thyroid disease. Surgery1998. p. 2-7.PMID: 9457216. **KQ5E4D**
320. Liu S, Semenciw R, Ugnat AM and Mao Y. Increasing thyroid cancer incidence in Canada, 1970-1996: time trends and age-period-cohort effects. British Journal of Cancer. 2001/11/27 ed2001. p. 1335-9.PMID: 11720471. **KQALLE1**
321. Lo CY, Kwok KF and Yuen PW. A prospective evaluation of recurrent laryngeal nerve paralysis during thyroidectomy. Archives of Surgery. 2000/02/11 ed2000. p. 204-7.PMID: 10668882. **KQ5E4D**
322. Lodewijk L, Vriens MR, Vorselaars WM, van der Meij NT, Kist JW, Barentsz MW, Verkooijen HM, Rinkes IH and Valk GD. SAME-DAY FINE NEEDLE ASPIRATION CYTOLOGY DIAGNOSIS FOR THYROID NODULES ACHIEVES RAPID ANXIETY DECREASE AND HIGH DIAGNOSTIC ACCURACY. Endocr Pract. 2016/01/01 ed2015.PMID: 26720251. **KQ3E4**
323. Lombardi CP, Raffaelli M, D'Alatri L, Crea C, Marchese MR, Maccora D, Paludetti G and Bellantone R. Video-assisted thyroidectomy significantly reduces the risk of early postthyroidectomy voice and swallowing symptoms. World journal of surgery2008. p. 693-700.PMID: CN-00647649. **KQ5e5**
324. Lombardi CP, Raffaelli M, de Crea C, Princi P, Castaldi P, Spaventa A, Salvatori M and Bellantone R. Report on 8 years of experience with video-assisted thyroidectomy for papillary thyroid carcinoma. Surgery2007. p. 944-51; discussion 944-51.PMID: 18063080. **KQ5e6**
325. Lombardi CP, Raffaelli M, De Crea C, Sessa L and Bellantone R. Morbidity of central neck dissection: primary surgery vs reoperation. Results of a case-control study. Langenbecks Archives of Surgery2014. p. 747-53.PMID: 24781962. **KQ5E7**
326. Londero SC, Krogdahl A, Bastholt L, Overgaard J, Pedersen HB, Frisch T, Bentzen J, Pedersen PU, Christiansen P and Godballe C. Papillary thyroid carcinoma in Denmark 1996-2008: an investigation of changes in incidence. Cancer Epidemiology2013. p. e1-6.PMID: 23182499. **KQ3E5, KQ4E5**
327. Lopez-Bru D, Palazon-Bru A, Folgado-de la Rosa DM and Gil-Guillen VF. Scoring System for Mortality in Patients Diagnosed with and Treated Surgically for Differentiated Thyroid Carcinoma with a 20-Year Follow-Up. PLoS ONE [Electronic Resource]2015. p. e0128620.PMID: 26115328. **KQ5E5**

328. Lorente-Poch L, Sancho JJ, Ruiz S and Sitges-Serra A. Importance of in situ preservation of parathyroid glands during total thyroidectomy. British journal of surgery2015. p. 359-67.PMID: 25605285. **KQ5E4**
329. Loyo M, Tufano RP and Gourin CG. National trends in thyroid surgery and the effect of volume on short-term outcomes. The Laryngoscope2013. p. 2056-2063**KQ5E4D**
330. Lu CH, Lee KD, Chen PT, Chen CC, Kuan FC, Huang CE, Chen MF and Chen MC. Second primary malignancies following thyroid cancer: a population-based study in Taiwan. Eur J Endocrinol. 2013/08/14 ed2013. p. 577-85.PMID: 23939917. **KQ5E2**
331. Lu X, Huang XM, Sun W, Liang WW and Cai Q. [Comparison of the surgical stress between endoscopic thyroidectomy via anterior chest approach and conventional thyroidectomy]. Zhonghua er bi yan hou tou jing wai ke za zhi [Chinese journal of otorhinolaryngology head and neck surgery]2010. p. 895-8.PMID: CN-00802001. **KQ5e2**
332. Lundgren CI, Stalberg P, Grodski S, Sidhu S, Sywak M and Delbridge L. Minimally invasive thyroid surgery for diagnostic excision of solitary thyroid nodules. Asian Journal of Surgery2007. p. 250-4.PMID: 17962127. **KQ5e4d**
333. Lushbaugh CC and Casarett GW. The effects of gonadal irradiation in clinical radiation therapy: a review. Cancer. 1976/02/01 ed1976. p. 1111-25.PMID: 766956. **KQ5E6G**
334. LY W, IJ N, FL P, D T, RM T, AR S, SG P, JP S and I G. Comparable outcomes for patients with pT1a and pT1b differentiated thyroid cancer: Is there a need for change in the AJCC classification system? Surgery2014. p. 1484-9; discussion 1489-90.PMID: 25456937. **KQ5e5**
335. Lyle MA and Dean DS. Ultrasound-Guided Fine-Needle Aspiration Biopsy of Thyroid Nodules in Patients Taking Novel Oral Anticoagulants. Thyroid. 2015/01/15 ed2015.PMID: 25584817. **KQ3E5**
336. Lyons KJ, Tarter JW and Ragsdale TL. Local complications after surgical resection for thyroid carcinoma. American journal of surgery1994. p. 404-7.PMID: 7977960. **KQ5E6G**
337. M B, JA S, RC N, HA H, NM W and JK H. Thyroid cancers incidentally detected at imaging in a 10-year period: how many cancers would be missed with use of the recommendations from the Society of Radiologists in Ultrasound? Radiology2014. p. 888-94.PMID: 24475865. **KQ3e4**
338. Ma SH, Liu QJ, Zhang YC and Yang R. Alternative surgical strategies in patients with sporadic medullary thyroid carcinoma: Long-term follow-up. Oncol Lett. 2012/08/07 ed2011. p. 975-980.PMID: 22866159. **KQ4E5, KQ5E5**
339. Ma X, Zhang B, Ling W, Liu R, Jia H, Zhu F, Wang M, Liu H, Huang J and Liu L. Contrast-enhanced sonography for the identification of benign and malignant thyroid nodules: Systematic review and meta-analysis. Journal of Clinical Ultrasound. 2015/09/25 ed2015.PMID: 26402325. **KQ2E6**
340. Machens A, Hinze R, Thomusch O and Dralle H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World journal of surgery2002. p. 22-8.PMID: 11898029. **KQ4E5, KQ5E5**
341. Mäenpää HO, Heikkonen J, Vaalavirta L, Tenhunen M and Joensuu H. Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. PloS one2008. p. e1885.PMID: CN-00638670. **KQ5E2B**
342. Magri F, Chytiris S, Zerbini F, Capelli V, Gaiti M, Carbone A, Fonte R, Malovini A, Rotondi M, Bellazzi R and Chiovato L. Maximal stiffness evaluation by real-time ultrasound elastography, an improved tool for the differential diagnosis of thyroid nodules. Endocrine practice2015. p. 474-81.PMID: 25667375. **KQ2E2C**
343. Maier TM, Schober O, Gers J, Gorlich D, Wenning C, Schaefers M, Riemann B and Vrachimis A. Differentiated thyroid cancer patients more than 60 years old paradoxically show an increased life expectancy. Journal of nuclear medicine2015. p. 190-5.PMID: 25613533. **KQ4E5, KQ5E5**
344. Makay O, Unalp O, Icoz G, Akyildiz M and Yetkin E. Completion thyroidectomy for thyroid cancer. Acta Chirurgica Belgica2006. p. 528-31.PMID: 17168263. **KQ5e6**
345. Mallick U, Harmer C, Hackshaw A and Moss L. Iodine or Not (IoN) for Low-risk Differentiated Thyroid Cancer: The Next UK National Cancer Research Network Randomised Trial following HiLo. Clinical oncology2012. p. 159-61.PMID: CN-00897194. **KQ4e2**
346. Marchegiani C, Lucci S, De Antoni E, Catania A, Grilli P, Pierro A and Di Matteo G. Thyroid cancer: surgical experience with 322 cases. International surgery1985. p. 121-4.PMID: 4055275. **KQ5E6G**

347. Marchetta FC and Sako K. The diagnosis of thyroid carcinoma during the postoperative period after less than total thyroidectomy. American journal of surgery1978. p. 455-6.PMID: 707724. **KQ4E2B, KQ5E6G**
348. Marti JL, Jain KS and Morris LG. Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer. Thyroid2015. p. 681-7.PMID: 25851829. **KQ5E4**
349. Martins AS, Melo GM, Valerio JB, Langner E, Lage HT and Tincani AJ. Treatment of locally aggressive well-differentiated thyroid cancer. International surgery2001. p. 213-9.PMID: 12056464. **KQ5E6H**
350. Martins RG, Caplan RH, Lambert PJ, Rooney B and Kisken WA. Management of thyroid cancer of follicular cell origin: Gundersen/Lutheran Medical Center, 1969-1995. Journal of the American College of Surgeons1997. p. 388-97.PMID: 9328388. **KQ5E6G**
351. Matesa N, Tabain I, Dabelic N, Petric V and Kusic Z. Diagnostic relevance of fine needle aspiration cytology for follicular lesions of the thyroid: retrospective study. Croatian Medical Journal2002. p. 606-9.PMID: 12402405. **KQ3E5**
352. Matsuyama H, Sugitani I, Fujimoto Y and Kawabata K. Indications for thyroid cancer surgery in elderly patients. Surgery today2009. p. 652-7.PMID: 19639430. **KQ4e7**
353. Matsuzu K, Sugino K, Masudo K, Nagahama M, Kitagawa W, Shibuya H, Ohkuwa K, Uruno T, Suzuki A, Magoshi S, Akaishi J, Masaki C, Kawano M, Suganuma N, Rino Y, Masuda M, Kameyama K, Takami H and Ito K. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. World journal of surgery2014. p. 68-79.PMID: 24081532. **KQ4e2b, KQ5e5**
354. Matsuzuka F, Kobayashi A, Hirai K, Morita S, Miyauchi A, Katayama S and Sugawara M. Outcome of long standing solitary thyroid nodules. World journal of surgery1992. p. 583-7; discussion 587-8.PMID: 1413828. **KQ3E2**
355. Matsuzuka F, Yokozawa T, Miyauchi A and Sugawara M. Fate of untreated benign thyroid nodules: results of long-term follow-up. World journal of surgery1994. p. 495-8; discussion 499.PMID: 7725734. **kq2e2, KQ3E5, KQ5E5**
356. McConnell RJ, Brenner AV, Oliynyk VA, Robbins J, Terekhova GM, Fink DJ, Epshtein OV, Hatch M, Shpak VM, Brill AB, Shelkovoy YA, Zablotska LB, Masnyk IJ, Howe GR and Tronko MD. Factors associated with elevated serum concentrations of anti-TPO antibodies in subjects with and without diffuse goitre. Results from the Ukrainian-American Cohort Study of thyroid cancer and other thyroid diseases following the Chornobyl accident. Clinical endocrinology2007. p. 879-90.PMID: 18052943. **KQ2e3b, KQ5e5**
357. McGuire ST and English JC, 3rd. Papillary thyroid cancer: an indication for thyroid palpation by the dermatologist. Archives of Dermatology2010. p. 1056-7.PMID: 20855721. **KQ2e2a**
358. Mehrvarz S, Mohebbi HA, Kalantar Motamedi MH, Khatami SM, Rezaie R and Rasouli HR. Parathyroid hormone measurement in prediction of hypocalcaemia following thyroidectomy. Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan2014. p. 82-7.PMID: 24490999. **KQ5e3a**
359. Meijer JA, Bakker LE, Valk GD, Herder WW, Wilt JH, Netea-Maier RT, Schaper N, Fliers E, Lips P, Plukker JT, Links TP and Smit JA. Radioactive iodine in the treatment of medullary thyroid carcinoma: a controlled multicenter study. European journal of endocrinology / European Federation of Endocrine Societies2013. p. 779-86.PMID: CN-00965040. **KQ4E2B**
360. Merchant WJ, Thomas SM, Coppen MJ and Prentice MG. The role of thyroid fine needle aspiration (FNA) cytology in a District General Hospital setting. Cytopathology. 1995/12/01 ed1995. p. 409-18.PMID: 8770542. **KQALLE1**
361. Merchavy S, Marom T, Forest V-I, Hier M, Mlynarek A, McHugh T and Payne R. Comparison of the incidence of postoperative hypocalcemia following total thyroidectomy vs completion thyroidectomy. Otolaryngology--head and neck surgery2014. p. 0194599814556250**KQ5E6H**
362. Mettler FA, Jr., Williamson MR, Royal HD, Hurley JR, Khafagi F, Sheppard MC, Beral V, Reeves G, Saenger EL, Yokoyama N and et al. Thyroid nodules in the population living around Chernobyl. Jama. 1992/08/15 ed1992. p. 616-9.PMID: 1629989. **KQALLE4**

363. Miccoli P, Minuto MN, Galleri D, D'Agostino J, Basolo F, Antonangeli L, Aghini-Lombardi F and Berti P. Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. ANZ Journal of Surgery2006. p. 123-6.PMID: 16626346. **KQ3e4d**
364. Mihailescu DV and Schneider AB. Size, number, and distribution of thyroid nodules and the risk of malignancy in radiation-exposed patients who underwent surgery. Journal of Clinical Endocrinology & Metabolism2008. p. 2188-93.PMID: 18381575. **KQ3e4d**
365. Miki H, Oshimo K, Inoue H, Kawano M, Tanaka K, Komaki K, Uyama T, Morimoto T and Monden Y. Incidence of ultrasonographically-detected thyroid nodules in healthy adults. Tokushima J Exp Med. 1993/06/01 ed1993. p. 43-6.PMID: 8211979. **KQALLE2**
366. Mikosch P, Wartner U, Kresnik E, Gallowitsch HJ, Heinisch M, Dinges HP and Lind P. Results of preoperative ultrasound guided fine needle aspiration biopsy of solitary thyroid nodules as compared with the histology. A retrospective analysis of 538 patients. Nuclear-Medizin2001. p. 148-54.PMID: 11727627. **KQ2E2C, KQ3E2C**
367. Miller W, Butters M, Leibl B and Bittner R. [Quality assurance in goiter surgery by rate of recurrent nerve paralysis]. Chirurg. 1995/12/01 ed1995. p. 1210-4.PMID: 8582164. **KQ5E9**
368. Mishra A and Mishra SK. Total thyroidectomy for differentiated thyroid cancer: primary compared with completion thyroidectomy. European Journal of Surgery. 2002/10/12 ed2002. p. 283-7.PMID: 12375610. **KQ5E3A**
369. Misiakos EP, Liakakos T, Macheras A, Zachaki A, Kakaviatos N and Karatzas G. Total thyroidectomy for the treatment of thyroid diseases in an endemic area. Southern Medical Journal2006. p. 1224-9.PMID: 17195417. **KQ5e4d**
370. Misiolek M, Waler J, Namyslowski G, Kucharzewski M, Podwinski A and Czecior E. Recurrent laryngeal nerve palsy after thyroid cancer surgery: a laryngological and surgical problem. Eur Arch Otorhinolaryngol. 2002/01/05 ed2001. p. 460-2.PMID: 11769992. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**
371. Mitov F, Dimov R, Outchikov P, Manchev I, Mourdjev K and Todorov A. A comparative analysis of the postoperative complications of thyroid cancer surgery related to surgical approach. Folia Medica (Plovdiv)1999. p. 34-9.PMID: 10658364. **KQ5E6H**
372. Mitra I, Nichani JR, Yap B and Homer JJ. Effect of central compartment neck dissection on hypocalcaemia incidence after total thyroidectomy for carcinoma. Journal of Laryngology & Otology2011. p. 497-501.PMID: 21106140. **KQ5e6h**
373. Miyauchi A. Clinical Trials of Active Surveillance of Papillary Microcarcinoma of the Thyroid. World J Surg. 2016/01/09 ed2016**KQ4E1, KQ5E1**
374. M'Kacher R, Legal JD, Schlumberger M, Aubert B, Beron-Gaillard N, Gaussen A and Parmentier C. Sequential biological dosimetry after a single treatment with iodine-131 for differentiated thyroid carcinoma. Journal of nuclear medicine1997. p. 377-80.PMID: 9074522. **KQ5E5**
375. Monsieurs M, Thierens H, Dierckx RA, Casier K, De Baere E, De Ridder L, De Saedeleer C, De Winter H, Lippens M, van Imschoot S, Wulfrank D and Simons M. Real-life radiation burden to relatives of patients treated with iodine-131: a study in eight centres in Flanders (Belgium). European journal of nuclear medicine1998. p. 1368-76.PMID: 9818275. **KQ5E5**
376. Monzen S, Mariya Y, Wojcik A, Kawamura C, Nakamura A, Chiba M, Hosoda M and Takai Y. Predictive factors of cytotoxic damage in radioactive iodine treatment of differentiated thyroid cancer patients. Mol Clin Oncol. 2015/07/03 ed2015. p. 692-698.PMID: 26137289. **KQ5E2B**
377. Moon HJ, Lee HS, Kim EK, Ko SY, Seo JY, Park WJ, Park HY and Kwak JY. Thyroid nodules < 5 mm on ultrasonography: are they "leave me alone" lesions? Endocrine2015. p. 735-44.PMID: 25600483. **KQ1E2, KQ2E2C, KQ3E2, KQ4E7, KQ5E5**
378. Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, Kim J, Kim HS, Byun JS, Lee DH, Thyroid Study Group KSoN, Head and Neck R. Benign and malignant thyroid nodules: US differentiation--multicenter retrospective study. Radiology. 2008/04/12 ed2008. p. 762-70.PMID: 18403624. **KQ2E2C**
379. Mori I, Miyauchi A, Kuma S, Tang W and Kakudo K. Thyroid nodular lesion: analysis of cancer risk based on Kuma Hospital experience. Pathology International2003. p. 579-83.PMID: 14507313. **KQ3e5**
380. Moritani S. Impact of lymph node metastases with recurrent laryngeal nerve invasion on patients with papillary thyroid carcinoma. Thyroid2015. p. 107-11.PMID: 25317601. **KQ5E4**

381. Morris LF, Ragavendra N and Yeh MW. Evidence-based assessment of the role of ultrasonography in the management of benign thyroid nodules. World journal of surgery2008. p. 1253-63.PMID: 18311500. **KQ2e8**
382. Morris LG and Myssiorek D. Improved detection does not fully explain the rising incidence of well-differentiated thyroid cancer: a population-based analysis. Am J Surg. 2010/06/22 ed2010. p. 454-61.PMID: 20561605. **KQ2E5, KQ3E5, KQ4E5**
383. Morris LG, Sikora AG, Tosteson TD and Davies L. The increasing incidence of thyroid cancer: the influence of access to care. Thyroid2013. p. 885-91.PMID: 23517343. **KQ3e5**
384. Morrissey AT, Chau J, Yunker WK, Mechor B, Seikaly H and Harris JR. Comparison of drain versus no drain thyroidectomy: randomized prospective clinical trial. Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale [Journal of otolaryngology - head & neck surgery]2008. p. 43-7.PMID: CN-00639625. **KQ5e6**
385. Mortensen JD, Woolner LB and Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol Metab. 1955/10/01 ed1955. p. 1270-80.PMID: 13263417. **KQ2E2**
386. Moulton-Barrett R, Crumley R, Jalilie S, Segina D, Allison G, Marshak D and Chan E. Complications of thyroid surgery. Int Surg. 1997/01/01 ed1997. p. 63-6.PMID: 9189806. **KQ5E10**
387. Mulaudzi TV, Ramdial PK, Madiba TE and Callaghan RA. Thyroid carcinoma at King Edward VIII Hospital, Durban, South Africa. East African Medical Journal2001. p. 242-5.PMID: 12002083. **KQ5E6H**
388. Muruganandham K, Sistla SC, Elangovan S and Verma SK. Routine ultrasound-guided aspiration cytology for evaluation of palpable thyroid nodules in an endemic area: is it justified? Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale [Journal of otolaryngology - head & neck surgery]2009. p. 222-6.PMID: CN-00721469. **KQ2e3A**
389. Musacchio MJ, Kim AW, Vijungco JD and Prinz RA. Greater local recurrence occurs with "berry picking" than neck dissection in thyroid cancer. American surgeon2003. p. 191-6; discussion 196-7.PMID: 12678473. **KQ5E2**
390. Musella M, Innaro N, Castaldo P, Carrano A, Cimmino G and Musella S. 10-year experience of total thyroidectomy with special reference to 85 thyroid cancers in one Italian centre. European journal of surgical oncology1997. p. 211-4.PMID: 9236893. **KQ5E6H**
391. Nagataki S, Shibata Y, Inoue S, Yokoyama N, Izumi M and Shimaoka K. Thyroid diseases among atomic bomb survivors in Nagasaki. JAMA. 1994/08/03 ed1994. p. 364-70.PMID: 8028167. **KQALLE5**
392. Nam KH, Yoon JH, Chang HS and Park CS. Optimal timing of surgery in well-differentiated thyroid carcinoma detected during pregnancy. Journal of surgical oncology2005. p. 199-203.PMID: 16118775. **KQ5E7**
393. Nam-Goong IS, Kim HY, Gong G, Lee HK, Hong SJ, Kim WB and Shong YK. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with pathological findings. Clinical endocrinology2004. p. 21-8.PMID: 14678283. **KQ3e2**
394. Narendra H and Vamsi R. Prophylactic central node dissection in well differentiated thyroid cancers: Does this increase morbidity? European journal of cancer2014. p. e13.PMID: CN-01059262. **KQ5E3a**
395. Negro R, Gharib H, Savoldi L, Barbieri V and Valcavi R. A longitudinal study of thyroidectomized patients in a region of northern Italy: benign versus malignant disease. Endocrine practice2013. p. 259-62.PMID: 23512384. **KQ5e5**
396. Nielsen TR, Andreassen UK, Brown CL, Balle VH and Thomsen J. Microsurgical technique in thyroid surgery--a 10-year experience. Journal of Laryngology & Otology1998. p. 556-60.PMID: 9764296. **KQ4E2B, KQ5E4**
397. Nilubol N and Kebebew E. Should small papillary thyroid cancer be observed? A population-based study. Cancer2015. p. 1017-24.PMID: 25425528. **KQ5E5**
398. Nishiyama RLG, Thompson NW. The prevalence of small papillary thyroid carcinomas in 100 consecutive necropsies in an American population. In: L. DeGroot, editor. New York: Grune & Stratton; 1977. p. 123-125**KQ2E5**
399. Nixon IJ, Ganly I, Patel S, Palmer FL, Whitcher MM, Tuttle RM, Shaha AR and Shah JP. The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. Surgery2011. p. 1242-9.PMID: 22136847. **KQ4e2b, KQ5e5**

400. Nixon IJ, Wang LY, Ganly I, Patel SG, Morris LG, Migliacci JC, Tuttle RM, Shah JP and Shaha AR. Outcomes for patients with papillary thyroid cancer who do not undergo prophylactic central neck dissection. Br J Surg. 2015/10/30 ed2015.PMID: 26511531. **KQ4E2B, KQ5E4**
401. Njolstad PR, Akslen LA, Albrektsen G, Viste A, Soreide O and Varhaug JE. Thyroid carcinoma: results from surgical treatment in 211 consecutive patients. European Journal of Surgery1991. p. 521-6.PMID: 1683575. **KQ5E6G**
402. Noguchi S, Yamashita H, Murakami N, Nakayama I, Toda M and Kawamoto H. Small carcinomas of the thyroid. A long-term follow-up of 867 patients. Archives of Surgery1996. p. 187-91.PMID: 8611077. **KQ5E6G**
403. Noguchi S, Yamashita H, Uchino S and Watanabe S. Papillary microcarcinoma. World journal of surgery2008. p. 747-53.PMID: 18264828. **KQ3e5**
404. Nolan NG, Koppikar MM and Kotlyarov EV. Thyroid scanning of the patient with history of childhood irradiation. Annals of Clinical & Laboratory Science1981. p. 31-6.PMID: 7212627. **KQALLE2**
405. Noureldine SI, Abbas A, Tufano RP, Srivastav S, Slakey DP, Friedlander P and Kandil E. The impact of surgical volume on racial disparity in thyroid and parathyroid surgery. Annals of surgical oncology2014. p. 2733-9.PMID: 24633666. **KQ5E4**
406. Noureldine SI, Genther DJ, Lopez M, Agrawal N and Tufano RP. Early predictors of hypocalcemia after total thyroidectomy: an analysis of 304 patients using a short-stay monitoring protocol. JAMA Otolaryngology--Head & Neck Surgery2014. p. 1006-13.PMID: 25321339. **KQ4e2b, KQ5e5**
407. Nygard B, Hegedus L, Karstrup S and Hansen JM. Observer variation in ultrasound assessment of the thyroid gland. British Journal of Radiology1993. p. 625-7.PMID: 8374729. **KQ1E2B, KQ2E2, KQ3E5**
408. Oeda T, Terano T, Omura M, Tahara K, Nishikawa T, Tamura Y and Yoshida S. Comparative studies on fine-needle aspiration cytology with ultrasound scanning in the assessment of thyroid nodule. Japanese Journal of Medicine1990. p. 478-80.PMID: 1708432. **KQ2E2C, KQ3E5**
409. Olbricht T, Emrich D, Benker G and Reinwein D. Long-term follow-up in patients with autonomous thyroid adenoma. Acta Endocrinologica1993. p. 51-5.PMID: 8447194. **KQ4E5**
410. Ontai S and Straehley CJ. The surgical treatment of well-differentiated carcinoma of the thyroid. American surgeon1985. p. 653-7.PMID: 4062059. **KQ5E6G**
411. Orloff LA, Weymuller EA and Flaherty MJ. Papillary thyroid carcinoma mistaken for malignant melanoma: pitfalls in diagnosis. Head & neck1995. p. 157-60.PMID: 7558815. **KQ2E2, KQ3E2**
412. Orsenigo E, Beretta E, Veronesi P, Mari G, Gini P and Di Carlo V. Total thyroidectomy in the treatment of thyroid cancer. European journal of surgical oncology1995. p. 478-81.PMID: 7589589. **KQ4E5, KQ5E6G**
413. Otto RA and Cochran CS. Sensitivity and specificity of intraoperative recurrent laryngeal nerve stimulation in predicting postoperative nerve paralysis. Annals of Otology, Rhinology & Laryngology. 2002/11/27 ed2002. p. 1005-7.PMID: 12450175. **KQ5E5**
414. Ozel A, Erturk SM, Ercan A, Yilmaz B, Basak T, Cantisani V, Basak M and Karpat Z. The diagnostic efficiency of ultrasound in characterization for thyroid nodules: how many criteria are required to predict malignancy? Medical Ultrasonography2012. p. 24-8.PMID: 22396935. **KQ2e2c**
415. Pacini F, Vorontsova T, Molinaro E, Shavrova E, Agate L, Kuchinskaya E, Elisei R, Demidchik EP and Pinchera A. Thyroid consequences of the Chernobyl nuclear accident. Acta Paediatrica Supplement1999. p. 23-7.PMID: 10626541. **KQALLE3B**
416. Paek SH, Lee YM, Min SY, Kim SW, Chung KW and Youn YK. Risk factors of hypoparathyroidism following total thyroidectomy for thyroid cancer. World journal of surgery2013. p. 94-101.PMID: 23052805. **KQ5e6h**
417. Panzarella T, Carruthers JS, Gospodarowicz MK and Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. International Journal of Radiation Oncology, Biology, Physics1988. p. 1063-75.PMID: 2454902. **KQ4E2B, KQ5E6G**
418. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, Panunzi C, Rinaldi R, Toscano V and Pacella CM. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. Journal of Clinical Endocrinology & Metabolism2002. p. 1941-6.PMID: 11994321. **KQ2e4, KQ3e4**

419. Park CS, Kim SH, Jung SL, Kang BJ, Kim JY, Choi JJ, Sung MS, Yim HW and Jeong SH. Observer variability in the sonographic evaluation of thyroid nodules. Journal of Clinical Ultrasound2010. p. 287-93.PMID: 20544863. **KQ2e2c, KQ3e4**
420. Park KN, Jung CH, Mok JO, Kwak JJ and Lee SW. Prospective comparative study of endoscopic via unilateral axillobreast approach versus open conventional total thyroidectomy in patients with papillary thyroid carcinoma. Surg Endosc. 2015/12/15 ed2015.PMID: 26659230. **KQ5E7**
421. Paschke R, Lincke T, Muller SP, Kreissl MC, Dralle H and Fassnacht M. The Treatment of Well-Differentiated Thyroid Carcinoma. Deutsches Arzteblatt International2015. p. 452-8.PMID: 26205749. **KQ5E2**
422. Passler C, Avanessian R, Kaczirek K, Prager G, Scheuba C and Niederle B. Thyroid surgery in the geriatric patient. Archives of Surgery2002. p. 1243-8.PMID: 12413310. **KQ5e5**
423. Pathak KA, Leslie WD, Klonisch TC and Nason RW. The changing face of thyroid cancer in a population-based cohort. Cancer Medicine2013. p. 537-44.PMID: 24156026. **KQ4e2b**
424. Peccin S, de Castsro JA, Furlanetto TW, Furtado AP, Brasil BA and Czepielewski MA. Ultrasonography: is it useful in the diagnosis of cancer in thyroid nodules? Journal of endocrinological investigation2002. p. 39-43.PMID: 11885575. **KQ2E3A**
425. Peiling Yang S, Bach AM, Michael Tuttle R and Fish SA. Frequent screening with serial neck ultrasound is more likely to identify false positive abnormalities than clinically significant disease in the surveillance of intermediate risk papillary thyroid cancer patients without suspicious findings on follow-up ultrasound evaluation. Journal of Clinical Endocrinology & Metabolism. 2015/01/31 ed2015. p. jc20143651.PMID: 25632970. **KQ2E5, KQ3E5**
426. Pelizzo MR, Boschin IM, Toniato A, Piotto A, Bernante P, Pagetta C, Rampin L and Rubello D. Papillary thyroid microcarcinoma (PTMC): prognostic factors, management and outcome in 403 patients. European journal of surgical oncology2006. p. 1144-8.PMID: 16872798. **KQ5e6h**
427. Pellegriti G, Frasca F, Regalbuto C, Squatrito S and Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013/06/06 ed2013. p. 965212.PMID: 23737785. **KQALLE1**
428. Pellegriti G, Scollo C, Lumera G, Regalbuto C, Vigneri R and Belfiore A. Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: study of 299 cases. Journal of Clinical Endocrinology & Metabolism2004. p. 3713-20.PMID: 15292295. **kQ3e4**
429. Pereira JA, Jimeno J, Miquel J, Iglesias M, Munne A, Sancho JJ and Sitges-Serra A. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Surgery2005. p. 1095-100, discussion 1100-1.PMID: 16360396. **KQ5e6h**
430. Perrino M, Vannucchi G, Vicentini L, Cantoni G, Dazzi D, Colombo C, Rodari M, Chiti A, Beck-Peccoz P and Fugazzola L. Outcome predictors and impact of central node dissection and radiometabolic treatments in papillary thyroid cancers < or =2 cm. Endocrine-related cancer2009. p. 201-10.PMID: 19106146. **KQ5e2a**
431. Pezzullo L, Delrio P, Losito NS, Caraco C and Mozzillo N. Post-operative complications after completion thyroidectomy for differentiated thyroid cancer. European journal of surgical oncology1997. p. 215-8.PMID: 9236894. **KQ5E6**
432. Podnos YD, Smith D, Wagman LD and Ellenhorn JD. Radioactive iodine offers survival improvement in patients with follicular carcinoma of the thyroid. Surgery2005. p. 1072-6; discussion 1076-7.PMID: 16360393. **KQ4e2b**
433. Polistena A, Monacelli M, Lucchini R, Triola R, Conti C, Avenia S, Barillaro I, Sanguinetti A and Avenia N. Surgical morbidity of cervical lymphadenectomy for thyroid cancer: A retrospective cohort study over 25 years. International Journal Of Surgery2015. p. 128-34.PMID: 26253851. **KQ5E6H**
434. Polyzos SA, Kita M, Efstathiadou Z, Goulis DG, Benos A, Flaris N, Leontsini M and Avramidis A. The use of demographic, ultrasonographic and scintigraphic data in the diagnostic approach of thyroid nodules. Experimental & Clinical Endocrinology & Diabetes2009. p. 159-64.PMID: 19085697. **KQ2e2a**
435. Porterfield JR, Jr., Grant CS, Dean DS, Thompson GB, Farley DR, Richards ML, Reading CC, Charboneau JW, Vollrath BK and Sebo TJ. Reliability of benign fine needle aspiration cytology of large thyroid nodules. Surgery2008. p. 963-8; discussion 968-9.PMID: 19041004. **KQ2E1, KQ3E5**

436. Pottern LM, Kaplan MM, Larsen PR, Silva JE, Koenig RJ, Lubin JH, Stovall M and Boice JD, Jr. Thyroid nodularity after childhood irradiation for lymphoid hyperplasia: a comparison of questionnaire and clinical findings. J Clin Epidemiol. 1990/01/01 ed1990. p. 449-60.PMID: 2324785. **KQALLE5**
437. Qiu ZL, Shen CT and Luo QY. Clinical management and outcomes in patients with hyperfunctioning distant metastases from differentiated thyroid cancer after total thyroidectomy and radioactive iodine therapy. Thyroid2015. p. 229-37.PMID: 25331724. **KQ5E3A**
438. Quan ML, Pasieka JL and Rorstad O. Bone mineral density in well-differentiated thyroid cancer patients treated with suppressive thyroxine: a systematic overview of the literature. Journal of surgical oncology2002. p. 62-9; discussion 69-70.PMID: 11754378. **KQ5E8**
439. Rafferty MA, Goldstein DP, Rotstein L, Asa SL, Panzarella T, Gullane P, Gilbert RW, Brown DH and Irish JC. Completion thyroidectomy versus total thyroidectomy: is there a difference in complication rates? An analysis of 350 patients. Journal of the American College of Surgeons2007. p. 602-7.PMID: 17903736. **KQ5E4D**
440. Rapoport A, Curioni OA, Amar A and Dedivitis RA. Review of survival rates 20-years after conservative surgery for papillary thyroid carcinoma. Revista Brasileira de Otorrinolaringologia2015. p. 389-93.PMID: 26120098. **KQ5E3B**
441. Rassael H, Thompson LD and Heffess CS. A rationale for conservative management of microscopic papillary carcinoma of the thyroid gland: a clinicopathologic correlation of 90 cases. European archives of oto-rhino-laryngology1998. p. 462-7.PMID: 9833215. **KQ5E6G**
442. Reeve TS, Delbridge L, Sloan D and Crummer P. The impact of fine-needle aspiration biopsy on surgery for single thyroid nodules. Medical Journal of Australia1986. p. 308-11.PMID: 3531785. **KQ2E2, KQ3E2**
443. Renshaw A. An estimate of risk of malignancy for a benign diagnosis in thyroid fine-needle aspirates.[Erratum appears in Cancer Cytopathol. 2010 Oct 25;118(5):303]. Cancer Cytopathology2010. p. 190-5.PMID: 20586117. **KQ3e5**
444. Renshaw AA. Focal features of papillary carcinoma of the thyroid in fine-needle aspiration material are strongly associated with papillary carcinoma at resection. American Journal of Clinical Pathology2002. p. 208-10.PMID: 12162679. **KQ3e2a**
445. Roberts JW, Symmonds RE, Jr., Hendricks JC, Snyder SK, Frazee RC, Smith RW, McKenney JF and Brindley GV, Jr. Safety and efficacy of total thyroidectomy for differentiated thyroid carcinoma: a 20-year review. American surgeon1993. p. 110-4.PMID: 8476139. **KQ5E2**
446. Robie DK, Dinauer CW, Tuttle RM, Ward DT, Parry R, McClellan D, Svec R, Adair C and Francis G. The impact of initial surgical management on outcome in young patients with differentiated thyroid cancer. Journal of Pediatric Surgery1998. p. 1134-8; discussion 1139-40.PMID: 9694109. **KQ5E4E**
447. Roh JL, Park JY and Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Annals of surgery2007. p. 604-10.PMID: 17414610. **KQ5E5**
448. Roher HD, Goretzki PE, Hellmann P and Witte J. [Complications in thyroid surgery. Incidence and therapy]. Chirurg. 1999/09/29 ed1999. p. 999-1010.PMID: 10501664. **KQ5E9**
449. Ron E, Modan B, Preston D, Alfandary E, Stovall M and Boice JD, Jr. Thyroid neoplasia following low-dose radiation in childhood. Radiat Res. 1989/12/01 ed1989. p. 516-31.PMID: 2594972. **KQ2e2**
450. Rosario PW, Barroso AL, Rezende LL, Padrao EL, Borges MA, Guimaraes VC and Purisch S. Testicular function after radioiodine therapy in patients with thyroid cancer. Thyroid. 2006/08/08 ed2006. p. 667-70.PMID: 16889490. **KQALLE3A**
451. Rosário PW, Pereira LF, Padrão EL, Rezende LL, Barroso ÁL and Purisch S. Comparison of completion thyroidectomy and primary surgery for thyroid carcinoma. ANZ Journal of Surgery2007. p. 305-305**KQ5E3A**
452. Rosario PW, Vasconcelos FP, Cardoso LD, Lauria MW, Rezende LL, Padrao EL, Barroso AL, Guimaraes VC and Purisch S. Managing thyroid cancer without thyroxine withdrawal. Arquivos Brasileiros de Endocrinologia e Metabologia2006. p. 91-6.PMID: 16628280. **KQ5e3a**

453. Rosato L, Carlevato MT, De Toma G and Avenia N. Recurrent laryngeal nerve damage and phonetic modifications after total thyroidectomy: surgical malpractice only or predictable sequence? World J Surg. 2005/05/17 ed2005. p. 780-4.PMID: 15895296. **KQ5E6H**
454. Rosen IB, Wallace C, Strawbridge HG and Walfish PG. Reevaluation of needle aspiration cytology in detection of thyroid cancer. Surgery1981. p. 747-56.PMID: 7281013. **KQ5E6G**
455. Rosenbaum MA and McHenry CR. Central neck dissection for papillary thyroid cancer. Archives of Otolaryngology -- Head & Neck Surgery2009. p. 1092-7.PMID: 19917920. **KQ5E6H**
456. Rosenbluth BD, Serrano V, Happersett L, Shaha AR, Tuttle RM, Narayana A, Wolden SL, Rosenzweig KE, Chong LM and Lee NY. Intensity-modulated radiation therapy for the treatment of nonanaplastic thyroid cancer. International Journal of Radiation Oncology, Biology, Physics2005. p. 1419-26.PMID: 16154712. **KQ5e6**
457. Rossi R, Roti E, Trasforini G, Pansini G, Cavazzini L, Zatelli MC, Pearce EN, Braverman LE and Uberti EC. Differentiated thyroid cancers 11-20 mm in diameter have clinical and histopathologic characteristics suggesting higher aggressiveness than those < or =10 mm. Thyroid2008. p. 309-15.PMID: 18341377. **KQ5e5**
458. Rossing M, Nygaard B, Nielsen FC and Bennedbaek FN. High prevalence of papillary thyroid microcarcinoma in danish patients: a prospective study of 854 consecutive patients with a cold thyroid nodule undergoing fine-needle aspiration. European Thyroid Journal2012. p. 110-7.PMID: 24783005. **KQ2e5**
459. Royce PC, MacKay BR and DiSabella PM. Value of postirradiation screening for thyroid nodules. A controlled study of recalled patients. Jama. 1979/12/14 ed1979. p. 2675-8.PMID: 501862. **KQ2E4D**
460. Rubino C, de Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, Dondon MG, Abbas MT, Langlois C and Schlumberger M. Second primary malignancies in thyroid cancer patients. British Journal of Cancer2003. p. 1638-44.PMID: 14583762. **KQ5e6g**
461. Ruel E, Thomas S, Dinan M, Perkins JM, Roman SA and Sosa JA. Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer. Journal of Clinical Endocrinology & Metabolism2015. p. 1529-36.PMID: 25642591. **KQ5E2B**
462. Ryu HR, Lee J, Park JH, Kang SW, Jeong JJ, Hong JY and Chung WY. A comparison of postoperative pain after conventional open thyroidectomy and transaxillary single-incision robotic thyroidectomy: a prospective study. Annals of surgical oncology2013. p. 2279-84.PMID: CN-00964673. **KQ5E6h**
463. Ryu J, Ryu YM, Jung YS, Kim SJ, Lee YJ, Lee EK, Kim SK, Kim TS, Kim TH, Lee CY, Park SY and Chung KW. Extent of thyroidectomy affects vocal and throat functions: a prospective observational study of lobectomy versus total thyroidectomy. Surgery2013. p. 611-20.PMID: 23932596. **KQ5E5**
464. S C, Zanocco K, Sturgeon C, Yeh MW and Harari A. Risk-based ultrasound screening for thyroid cancer in obese patients is cost-effective. Thyroid2014. p. 975-86.PMID: 24512476. **KQ1E2**
465. Saad MF, Guido JJ and Samaan NA. Radioactive iodine in the treatment of medullary carcinoma of the thyroid. Journal of Clinical Endocrinology & Metabolism1983. p. 124-8.PMID: 6853671. **KQ4E6G**
466. Sabel MS, Haque D, Velasco JM and Staren ED. Use of ultrasound-guided fine needle aspiration biopsy in the management of thyroid disease. American surgeon1998. p. 738-41; discussion 741-2.PMID: 9697903. **KQ3E5**
467. Sadetzki S, Calderon-Margalit R, Peretz C, Novikov I, Barchana M and Papa MZ. Second primary breast and thyroid cancers (Israel). Cancer Causes & Control. 2003/07/09 ed2003. p. 367-75.PMID: 12846369. **KQ5E5**
468. Sahin SB, Ogullar S, Ural UM, Ilkkilic K, Metin Y and Ayaz T. Alterations of thyroid volume and nodular size during and after pregnancy in a severe iodine-deficient area. Clinical endocrinology2014. p. 762-8.PMID: 24811142. **KQ2E3A**
469. Saint-Vil D, Emran MA, Lambert R, Alos N, Turpin S and Huot C. Cumulative doses of adjunct 131I treatment depend on location of residual thyroid tissue after total thyroidectomy in differentiated thyroid cancer. Journal of Pediatric Surgery2007. p. 853-6.PMID: 17502198. **KQ5e6**
470. Samaan NA, Maheshwari YK, Nader S, Hill CS, Jr., Schultz PN, Haynie TP, Hickey RC, Clark RL, Goepfert H, Ibanez ML and Litton CE. Impact of therapy for differentiated carcinoma of the thyroid: an analysis of 706 cases. Journal of Clinical Endocrinology & Metabolism1983. p. 1131-8.PMID: 6841555. **KQ4E2B, KQ5E6G**

471. Sampson RJ, Woolner LB, Bahn RC and Kurland LT. Occult thyroid carcinoma in Olmsted County, Minnesota: prevalence at autopsy compared with that in Hiroshima and Nagasaki, Japan. Cancer. 1974/12/01 ed1974. p. 2072-6.PMID: 4474057. **KQ2E5**
472. Sancho JJ, Lennard TW, Paunovic I, Triponez F and Sitges-Serra A. Prophylactic central neck disection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbecks Archives of Surgery2014. p. 155-63.PMID: 24352594. **KQ5E2**
473. Sand J, Palkola K and Salmi J. Surgical complications after total thyroidectomy and resections for differentiated thyroid carcinoma. Annales Chirurgiae et Gynaecologiae1996. p. 305-8.PMID: 9014059. **KQ4E2B, KQ5E6G**
474. Sandeep TC, Strachan MW, Reynolds RM, Brewster DH, Scelo G, Pukkala E, Hemminki K, Anderson A, Tracey E, Friis S, McBride ML, Kee-Seng C, Pompe-Kirn V, Kliewer EV, Tonita JM, Jonasson JG, Martos C, Boffetta P and Brennan P. Second primary cancers in thyroid cancer patients: a multinational record linkage study. Journal of Clinical Endocrinology & Metabolism2006. p. 1819-25.PMID: 16478820. **KQ5e5**
475. Sarkar SD, Beierwaltes WH, Gill SP and Cowley BJ. Subsequent fertility and birth histories of children and adolescents treated with 131I for thyroid cancer. Journal of nuclear medicine1976. p. 460-4.PMID: 944243. **KQ5E6G**
476. Sarlis NJ and Gourgiotis L. Unresolved issues, dilemmas and points of interest in thyroid cancer: a current perspective. Hormones2004. p. 149-70.PMID: 16982589. **KQALLE2**
477. Sarlis NJ, Gourgiotis L and Filie AC. Misclassification of cytologic diagnoses in patients with follicular lesions or follicular neoplasms of the thyroid gland: implications for patient care and clinical research. Cancer2002. p. 323-4.PMID: 12478678. **KQ3e2**
478. Sasson AR, Pingpank JF, Jr., Wetherington RW, Hanlon AL and Ridge JA. Incidental parathyroidectomy during thyroid surgery does not cause transient symptomatic hypocalcemia. Archives of Otolaryngology -- Head & Neck Surgery2001. p. 304-8.PMID: 11255476. **KQ2E5, KQ5E6H**
479. Sawka AM, Brierley JD, Tsang RW, Thabane L, Rotstein L, Gafni A, Straus S and Goldstein DP. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinology & Metabolism Clinics of North America2008. p. 457-80, x.PMID: 18502337. **KQ4e2b**
480. Sawka AM, Lakra DC, Lea J, Alshehri B, Tsang RW, Brierley JD, Straus S, Thabane L, Gafni A, Ezzat S, George SR and Goldstein DP. A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors. Clinical endocrinology2008. p. 479-90.PMID: 18284643. **KQ5e2**
481. Sawka AM, Lea J, Alshehri B, Straus S, Tsang RW, Brierley JD, Thabane L, Rotstein L, Gafni A, Ezzat S and Goldstein DP. A systematic review of the gonadal effects of therapeutic radioactive iodine in male thyroid cancer survivors. Clinical endocrinology2008. p. 610-7.PMID: 17973944. **KQ5E8**
482. Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, Straus S, Ezzat S and Goldstein DP. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid2009. p. 451-7.PMID: 19281429. **KQ5e8**
483. Scerrino G, Attard A, Melfa GI, Raspanti C, Di Giovanni S, Attard M, Inviati A, Mazzola S, Modica G, Gulotta G and Bonventre S. Role of Prophylactic Central Neck Dissection in CN0-Papillary Thyroid Carcinoma: Results from a High-Prevalence Area. Minerva Chirurgica. 2015/06/06 ed2015.PMID: 26046958. **KQ4E4 KQ5E4**
484. Scheuller MC and Ellison D. Laryngeal mask anesthesia with intraoperative laryngoscopy for identification of the recurrent laryngeal nerve during thyroidectomy. Laryngoscope. 2002/09/28 ed2002. p. 1594-7.PMID: 12352669. **KQ5E2A**
485. Schleder S, Janke M, Agha A, Schacherer D, Hornung M, Schlitt HJ, Stroszczynski C, Schreyer AG and Jung EM. Preoperative differentiation of thyroid adenomas and thyroid carcinomas using high resolution contrast-enhanced ultrasound (CEUS). Clinical Hemorheology & Microcirculation. 2014/06/06 ed2014.PMID: 24898562. **KQ2E5, KQ3E5**

486. Schleder S, Janke M, Agha A, Schacherer D, Hornung M, Schlitt HJ, Stroszczynski C, Schreyer AG and Jung EM. Preoperative differentiation of thyroid adenomas and thyroid carcinomas using high resolution contrast-enhanced ultrasound (CEUS). Clinical Hemorheology & Microcirculation2015. p. 13-22.PMID: 24898562. **KQ2E2C**
487. Schlumberger M, Berg G, Cohen O, Duntas L, Jamar F, Jarzab B, Limbert E, Lind P, Pacini F, Reiners C, Sanchez Franco F, Toft A and Wiersinga WM. Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. European Journal of Endocrinology2004. p. 105-12.PMID: 14763906. **KQ5e1**
488. Schneider AB, Bekerman C, Leland J, Rosengarten J, Hyun H, Collins B, Shore-Freedman E and Gierlowski TC. Thyroid nodules in the follow-up of irradiated individuals: comparison of thyroid ultrasound with scanning and palpation. Journal of Clinical Endocrinology & Metabolism1997. p. 4020-7.PMID: 9398706. **KQ2E5, KQ3E5**
489. Schneider DF, Mazeh H, Oltmann SC, Chen H and Sippel RS. Novel thyroidectomy difficulty scale correlates with operative times. World journal of surgery2014. p. 1984-9.PMID: 24615607. **KQ5E4D**
490. Schroder DM, Chambors A and France CJ. Operative strategy for thyroid cancer. Is total thyroidectomy worth the price? Cancer1986. p. 2320-8.PMID: 3756777. **KQ5E6G**
491. Schultz PN, Hickey RC, Goepfert H, Haynie TP, Johnston DA and Ordonez NG. The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. Journal of Clinical Endocrinology & Metabolism1992. p. 714-20.PMID: 1517360. **KQ5E5**
492. Schvartz C, Bonnetain F, Dabakuyo S, Gauthier M, Cueff A, Fieffe S, Pochart JM, Cochet I, Crevisy E, Dalac A, Papathanassiou D and Toubeau M. Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. Journal of Clinical Endocrinology & Metabolism2012. p. 1526-35.PMID: 22344193. **KQ4E6G, KQ5E6G**
493. Schwerk WB, Grun R and Wahl R. Ultrasound diagnosis of C-cell carcinoma of the thyroid. Cancer1985. p. 624-30.PMID: 2856898. **KQ2E4C, KQ3E4C**
494. Scopa CD, Gatopoulou C, Chalmoukis A, Androulakis J and Vagenakis A. Diagnosis of thyroid cancer in southwestern Greece. Bulletin du Cancer1991. p. 953-9.PMID: 1768941. **KQ2E2, KQ3E2**
495. Sdano MT, Falciglia M, Welge JA and Steward DL. Efficacy of thyroid hormone suppression for benign thyroid nodules: meta-analysis of randomized trials. Otolaryngology - Head & Neck Surgery2005. p. 391-6.PMID: 16143188. **KQ4e6, KQ5e6**
496. Seiberling KA, Dutra JC and Gunn J. Ultrasound-guided fine needle aspiration biopsy of thyroid nodules performed in the office. Laryngoscope2008. p. 228-31.PMID: 17989576. **KQ1E2B, KQ2E2C, KQ3E5**
497. Selberherr A, Scheuba C, Riss P and Niederle B. Postoperative hypoparathyroidism after thyroidectomy: efficient and cost-effective diagnosis and treatment. Surgery2015. p. 349-53.PMID: 25532435. **KQ5E4D**
498. Seo H, Na DG, Kim JH, Kim KW and Yoon JW. Ultrasound-Based Risk Stratification for Malignancy in Thyroid Nodules: A Four-Tier Categorization System. Eur Radiol. 2015/02/15 ed2015.PMID: 25680723. **KQ2E2C**
499. Sevim T. Risk factors for permanent laryngeal nerve paralysis in patients with thyroid carcinoma. Clinical Otolaryngology2007. p. 378-83.PMID: 17883559. **KQ5e3a**
500. Shan CX, Zhang W, Jiang DZ, Zheng XM, Liu S and Qiu M. Routine central neck dissection in differentiated thyroid carcinoma: a systematic review and meta-analysis. Laryngoscope2012. p. 797-804.PMID: 22294492. **KQ5e2**
501. Shao J, Shen Y, Lu J and Wang J. Ultrasound scoring in combination with ultrasound elastography for differentiating benign and malignant thyroid nodules. Clin Endocrinol (Oxf). 2014/08/21 ed2014.PMID: 25138622. **KQ2E3A, KQ3E3A**
502. Sharen G, Zhang B, Zhao R, Sun J, Gai X and Lou H. Retrospective epidemiological study of thyroid nodules by ultrasound in asymptomatic subjects. Chinese Medical Journal2014. p. 1661-5.PMID: 24791871. **KQ2E3A**
503. Shaub M and Wilson R. The ultrasonic evaluation of nonfunctioning thyroid nodules. Western Journal of Medicine1975. p. 265-8.PMID: 1199079. **KQ2E2C, KQ3E5**

504. Shen WT, Ogawa L, Ruan D, Suh I, Kebebew E, Duh QY and Clark OH. Central neck lymph node dissection for papillary thyroid cancer: comparison of complication and recurrence rates in 295 initial dissections and reoperations. Archives of Surgery2010. p. 272-5.PMID: 20231628. **KQ5E5**
505. Shore RE, Hildreth N, Dvoretsky P, Andresen E, Moseson M and Pasternack B. Thyroid cancer among persons given X-ray treatment in infancy for an enlarged thymus gland. American Journal of Epidemiology1993. p. 1068-80.PMID: 8317436. **KQ2E5**
506. Siebers G, Neumann C and Ritzl EK. Thyroid carcinoma: a follow-up study of 11 years. Radiation & Environmental Biophysics1987. p. 283-8.PMID: 3685251. **KQ5E2**
507. Silberstein EB. Reducing the incidence of 131I-induced sialadenitis: the role of pilocarpine. Journal of nuclear medicine2008. p. 546-9.PMID: CN-00638377. **KQ5e2b**
508. Sinnott B, Ron E and Schneider AB. Exposing the thyroid to radiation: a review of its current extent, risks, and implications. Endocr Rev. 2010/07/24 ed2010. p. 756-73.PMID: 20650861. **KQALLE2**
509. Slowinnska-Klencka D, Sporny S, Klencki M and Lewinnski A. Non-diagnostic cytological outcome of thyroid biopsy and the risk of thyroid malignancy. Endocrine pathology2004. p. 65-75.PMID: 15067178. **KQ3e5**
510. Slowinska-Klencka D, Popowicz B, Lewinski A, Sporny S and Klencki M. The fine-needle aspiration biopsy efficacy of small thyroid nodules in the area of recently normalized iodine supply. European Journal of Endocrinology2008. p. 747-54.PMID: 18794209. **KQ3e3**
511. Smith JA, Sharma N, Nankivell P and Watkinson JC. The presentation, natural history and outcome of T1 a/b thyroid cancer with regard to new grading systems. European archives of oto-rhino-laryngology2015. p. 439-44.PMID: 24643850. **KQ5E2**
512. Smith-Bindman R, Lebda P, Feldstein VA, Sellami D, Goldstein RB, Brasic N, Jin C and Kornak J. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. JAMA Internal Medicine2013. p. 1788-96.PMID: 23978950. **KQ2e2c, KQ3e5**
513. Solbiati L, Volterrani L, Rizzatto G, Bazzocchi M, Busilacci P, Candiani F, Ferrari F, Giuseppetti G, Maresca G, Mirk P and et al. The thyroid gland with low uptake lesions: evaluation by ultrasound. Radiology. 1985/04/01 ed1985. p. 187-91.PMID: 3883413. **KQ2E2C**
514. Solomon NP, Helou LB, Henry LR, Howard RS, Coppit G, Shaha AR and Stojadinovic A. Utility of the voice handicap index as an indicator of postthyroidectomy voice dysfunction. Journal of Voice2013. p. 348-54.PMID: 23294708. **KQ5e2**
515. Somerville HM, Steinbeck KS, Stevens G, Delbridge LW, Lam AH and Stevens MM. Thyroid neoplasia following irradiation in adolescent and young adult survivors of childhood cancer. Medical Journal of Australia2002. p. 584-7.PMID: 12064957. **KQ2e4e, KQ3e4e**
516. Son SK, Kim JH, Bae JS and Lee SH. Surgical Safety and Oncologic Effectiveness in Robotic versus Conventional Open Thyroidectomy in Thyroid Cancer: A Systematic Review and Meta-Analysis. Ann Surg Oncol. 2015/01/31 ed2015.PMID: 25634780. **KQ5E4**
517. Song HJ, Qiu ZL, Shen CT, Wei WJ and Luo QY. Pulmonary metastases in differentiated thyroid cancer: efficacy of radioiodine therapy and prognostic factors. European Journal of Endocrinology2015. p. 399-408.PMID: 26104753. **KQ5E3A**
518. Songun I, Kievit J and van de Velde CJ. Complications of thyroid surgery. Annals of surgical oncology1995. p. 56-60.PMID: 7834455. **KQ5E4D**
519. Songun I, Kievit J, Wobbes T, Peerdeman A and van de Velde CJ. Extent of thyroidectomy in nodular thyroid disease. European Journal of Surgery1999. p. 839-42.PMID: 10533757. **KQ5E4D**
520. Soreide O, Varhaug JE and Heimann P. Thyroid carcinoma: diagnosis and treatment in 106 patients. Acta Chirurgica Scandinavica1979. p. 137-41.PMID: 494958. **KQ1E1, KQ2E1, KQ3E1, KQ4E6G, KQ5E6G**
521. Souza MC, Momesso DP, Vaisman F, Vieira Neto L, Martins RA, Corbo R and Vaisman M. Is radioactive iodine- 131 treatment related to the occurrence of non-synchronous second primary malignancy in patients with differentiated thyroid cancer? Arch Endocrinol Metab. 2015/07/30 ed2015. p. 0.PMID: 26222230. **KQ5E3A**

522. Spencer R, Brown MC and Annis D. Ultrasonic scanning of the thyroid gland as a guide to the treatment of the clinically solitary nodule. British journal of surgery1977. p. 841-6.PMID: 588980. **KQ5E6G**
523. Stacul F, Bertolotto M, De Gobbis F, Calderan L, Cioffi V, Romano A, Zanconati F and Cova MA. US, colour-Doppler US and fine-needle aspiration biopsy in the diagnosis of thyroid nodules. Radiologia Medica2007. p. 751-62.PMID: 17657415. **KQ2e2c**
524. Stacul F, Bertolotto M, Zappetti R, Zanconati F and Cova MA. The radiologist and the cytologist in diagnosing thyroid nodules: results of cooperation. Radiologia Medica2007. p. 597-602.PMID: 17563853. **KQ2e5, KQ3e5**
525. Staren ED, D'Amore MJ, Kluskens LF, Martirano M and Economou SG. Importance of repeat fine-needle biopsy in the management of thyroid nodules. American journal of surgery1993. p. 350-2.PMID: 8214290. **KQ3E5**
526. Steinmuller T, Klupp J, Wenking S and Neuhaus P. Complications associated with different surgical approaches to differentiated thyroid carcinoma. Langenbecks Archives of Surgery. 1999/06/15 ed1999. p. 50-3.PMID: 10367630. **KQ5E6G**
527. Stockwell RM, Barry M and Davidoff F. Managing thyroid abnormalities in adults exposed to upper body irradiation in childhood: a decision analysis. Should patients without palpable nodules be scanned and those with scan defects be subjected to subtotal thyroidectomy? Journal of Clinical Endocrinology & Metabolism1984. p. 804-12.PMID: 6707185. **KQ2E5**
528. Stojadinovic A, Shaha AR, Orlikoff RF, Nissan A, Kornak MF, Singh B, Boyle JO, Shah JP, Brennan MF and Kraus DH. Prospective functional voice assessment in patients undergoing thyroid surgery. Annals of surgery2002. p. 823-32.PMID: 12454521. **KQ5e5**
529. Stokkel MP, Hoekstra A and van Rijk PP. The detection of small carcinoma with 18F-FDG using a dual head coincidence camera. European journal of radiology1999. p. 160-2.PMID: 10632552. **KQALLE2C**
530. Strong EW. Complications after total thyroidectomy. Otolaryngology - Head & Neck Surgery1989. p. 472-5.PMID: 2508025. **KQ5E4**
531. Sturniolo G, D'Alia C, Tonante A, Gagliano E, Taranto F and Lo Schiavo MG. The recurrent laryngeal nerve related to thyroid surgery. Am J Surg. 1999/07/22 ed1999. p. 485-8.PMID: 10414699. **KQ45E4D**
532. Subramanian S, Goldstein DP, Parlea L, Thabane L, Ezzat S, Ibrahim-Zada I, Straus S, Brierley JD, Tsang RW, Gafni A, Rotstein L and Sawka AM. Second primary malignancy risk in thyroid cancer survivors: a systematic review and meta-analysis. Thyroid2007. p. 1277-88.PMID: 18020916. **KQ5E8**
533. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M and Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World journal of surgery2010. p. 1222-31.PMID: 20066418. **KQ5e5**
534. Sugitani I, Toda K, Yamamoto N, Sakamoto A and Fujimoto Y. Re-evaluation of histopathological factors affecting prognosis of differentiated thyroid carcinoma in an iodine-sufficient country. World J Surg. 2009/12/03 ed2010. p. 1265-73.PMID: 19953247. **KQALLE5**
535. Suh CH, Baek JH, Lee JH, Choi YJ, Kim JK, Sung TY, Yoon JH and Shong YK. The Role of Core-Needle Biopsy as a First-Line Diagnostic Tool for Initially Detected Thyroid Nodules. Thyroid. 2015/12/15 ed2016.PMID: 26651390. **KQ3E6**
536. Sun GH, Peress L and Pynnonen MA. Systematic review and meta-analysis of robotic vs conventional thyroidectomy approaches for thyroid disease. Otolaryngology - Head & Neck Surgery2014. p. 520-32.PMID: 24500878. **KQ4e2b, KQ5e8**
537. Svendsen FM, Badsgard SE, Nielsen PH and Egeblad K. [Recurrent nerve injury after goiter surgery]. Ugeskr Laeger. 1990/04/30 ed1990. p. 1288-90.PMID: 2343481. **KQALLE4**
538. Tae HJ, Lim DJ, Baek KH, Park WC, Lee YS, Choi JE, Lee JM, Kang MI, Cha BY, Son HY, Lee KW and Kang SK. Diagnostic value of ultrasonography to distinguish between benign and malignant lesions in the management of thyroid nodules. Thyroid2007. p. 461-6.PMID: 17542676. **KQ2E2C**
539. Tae K, Song CM, Ji YB, Kim KR, Kim JY and Choi YY. Comparison of surgical completeness between robotic total thyroidectomy versus open thyroidectomy. Laryngoscope2014. p. 1042-7.PMID: 24338236. **KQ5E6H**
540. Takahashi T, Trott KR, Fujimori K, Simon SL, Ohtomo H, Nakashima N, Takaya K, Kimura N, Satomi S and Schoemaker MJ. An investigation into the prevalence of thyroid disease on Kwajalein Atoll, Marshall Islands. Health Phys. 1997/07/01 ed1997. p. 199-213.PMID: 9199230. **KQALLE4**

541. Takamura Y, Miyauchi A, Yabuta T, Kihara M, Ito Y and Miya A. Attenuation of postmenopausal bone loss in patients with transient hypoparathyroidism after total thyroidectomy. World journal of surgery2013. p. 2860-5.PMID: 24045966. **KQ5E2B**
542. Tan GH, Gharib H and Reading CC. Solitary thyroid nodule. Comparison between palpation and ultrasonography. Archives of Internal Medicine1995. p. 2418-23.PMID: 7503600. **KQ2E2C**
543. Tan Z, Gu J, Han Q, Wang W, Wang K, Ge M and Shang J. Comparison of Conventional Open Thyroidectomy and Endoscopic Thyroidectomy via Breast Approach for Papillary Thyroid Carcinoma. International Journal of Endocrinology Print2015. p. 239610.PMID: 26379706. **KQ5E6H**
544. Tanriover O, Comunoglu N, Eren B, Comunoglu C, Turkmen N, Dogan M and Gundogmus UN. Occult papillary thyroid carcinoma: prevalence at autopsy in Turkish people. European Journal of Cancer Prevention. 2011/04/06 ed2011. p. 308-12.PMID: 21464719. **KQ1E2, KQ2E2, KQ3E3A, KQ4E2, KQ5E2**
545. Tay SY, Chen CY and Chan WP. Sonographic criteria predictive of benign thyroid nodules useful in avoiding unnecessary ultrasound-guided fine needle aspiration. Journal of the Formosan Medical Association2015. p. 590-7.PMID: 24866975. **KQ2E2C**
546. Taylor T, Specker B, Robbins J, Sperling M, Ho M, Ain K, Bigos ST, Brierley J, Cooper D, Haugen B, Hay I, Hertzberg V, Klein I, Klein H, Ladenson P, Nishiyama R, Ross D, Sherman S and Maxon HR. Outcome after treatment of high-risk papillary and non-Hurthle-cell follicular thyroid carcinoma. Annals of internal medicine1998. p. 622-7.PMID: 9786809. **KQ4E2B, KQ5E5**
547. Teng CJ, Hu YW, Chen SC, Yeh CM, Chiang HL, Chen TJ and Liu CJ. Use of Radioactive Iodine for Thyroid Cancer and Risk of Second Primary Malignancy: A Nationwide Population-Based Study. Journal of the National Cancer Institute2016.PMID: 26538627. **KQ5E3B**
548. Terris DJ, Bonnett A, Gourin CG and Chin E. Minimally invasive thyroidectomy using the Sofferman technique. Laryngoscope2005. p. 1104-8.PMID: 15933531. **KQ4e2b, KQ5e6h**
549. Terris DJ, Gourin CG and Chin E. Minimally invasive thyroidectomy: basic and advanced techniques. Laryngoscope2006. p. 350-6.PMID: 16540887. **KQ5e6**
550. Testini M, Nacchiero M, Portincasa P, Miniello S, Piccinni G, Di Venere B, Campanile L, Lissidini G and Bonomo GM. Risk factors of morbidity in thyroid surgery: analysis of the last 5 years of experience in a general surgery unit. International surgery2004. p. 125-30.PMID: 15521247. **KQ4e2b, KQ5e4d**
551. Thachil J, Gatt A and Martlew V. Management of surgical patients receiving anticoagulation and antiplatelet agents. Br J Surg. 2008/11/11 ed2008. p. 1437-48.PMID: 18991253. **KQALLE1**
552. Thermann M, Feltkamp M, Elies W and Windhorst T. [Recurrent laryngeal nerve paralysis after thyroid gland operations. Etiology and consequences]. Chirurg. 1998/11/17 ed1998. p. 951-6.PMID: 9816453. **KQ5E9**
553. Thomson DB, Grammes CF, Starkey RH, Monsaert RP and Sunderlin FS. Thyroid abnormalities in patients previously treated with irradiation for acne vulgaris. Southern Medical Journal1984. p. 21-3.PMID: 6229881. **KQ2E7**
554. Tomoda C, Takamura Y, Ito Y, Miya A and Miyauchi A. Transient vocal cord paralysis after fine-needle aspiration biopsy of thyroid tumor. Thyroid2006. p. 697-9.PMID: 16889495. **KQ3e5**
555. Toniato A, Boschin IM, Piotto A, Pelizzo MR, Guolo A, Foletto M and Casalide E. Complications in thyroid surgery for carcinoma: one institution's surgical experience. World journal of surgery2008. p. 572-5.PMID: 18204947. **KQ4e5, KQ5e6h**
556. Trerotoli P, Ciampolillo A, Marinelli G, Giorgino R and Serio G. Prevalence of thyroid nodules in an occupationally radiation exposed group: a cross sectional study in an area with mild iodine deficiency. BMC Public Health2005. p. 73.PMID: 16000179. **KQ3e4**
557. Trimboli P, Nasrollah N, Amendola S, Rossi F, Ramacciato G, Romanelli F, Aurello P, Crescenzi A, Laurenti O, Condorelli E, Ventura C and Valabrega S. Should we use ultrasound features associated with papillary thyroid cancer in diagnosing medullary thyroid cancer? Endocr J. 2012/03/27 ed2012. p. 503-8.PMID: 22447142. **KQ1E2B, KQ2E2C, KQ3E4, KQ4E4, KQ5E4**
558. Trimboli P, Treglia G, Sadeghi R, Romanelli F and Giovanella L. Reliability of real-time elastography to diagnose thyroid nodules previously read at FNAC as indeterminate: a meta-analysis. Endocrine. 2014/12/24 ed2014.PMID: 25534701. **KQ2E2**

559. TS W, Goffredo P, Sosa JA and Roman SA. Papillary thyroid microcarcinoma: an over-treated malignancy? World journal of surgery2014. p. 2297-303.PMID: 24791670. **KQ4E5, KQ5E5**
560. Tseng LM, Lee CH, Wang HC, Shyr YM, Chiu JH, Wu CW, Lui WY and P'Eng F K. The surgical treatment and prognostic factors of well-differentiated thyroid cancers in Chinese patients: a 20-year experience. Chung Hua i Hsueh Tsa Chih - Chinese Medical Journal1996. p. 121-31.PMID: 8915115. **KQ4E2B, KQ5E6G**
561. Tseng YT and Chang TC. Multimodality treatment of anaplastic thyroid cancer with nearly resolved effect. Journal of the Formosan Medical Association. 2014/04/24 ed2014.PMID: 24755268. **KQ4E2A, KQ5E2A**
562. Tucker MA, Jones PH, Boice JD, Jr., Robison LL, Stone BJ, Stovall M, Jenkin RD, Lubin JH, Baum ES, Siegel SE and et al. Therapeutic radiation at a young age is linked to secondary thyroid cancer. The Late Effects Study Group. Cancer Res. 1991/06/11 ed1991. p. 2885-8.PMID: 1851664. **KQALLE5**
563. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T and Smith PA. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf). 1977/12/01 ed1977. p. 481-93.PMID: 598014. **KQALLE1**
564. Tunca F, Giles Y, Terzioglu T, Mudun A, Adalet I, Salmaslioglu A and Tezelman S. Does intraoperative radioguided surgery influence the complication rates and completeness of completion thyroidectomy? American journal of surgery2008. p. 40-6.PMID: CN-00638978. **KQ4e2b, KQ5e4**
565. Ukrainski MB, Pribitkin EA and Miller JL. Increasing Incidence of Thyroid Nodules and Thyroid Cancer: Does Increased Detection of a Subclinical Reservoir Justify the Associated Anxiety and Treatment? Clinical Therapeutics. 2015/10/06 ed2015.PMID: 26434793. **KQALLE5**
566. Uppal A, White MG, Nagar S, Aschebrook-Kilfoy B, Chang PJ, Angelos P, Kaplan EL and Grogan RH. Benign and Malignant Thyroid Incidentalomas Are Rare in Routine Clinical Practice: A Review of 97,908 Imaging Studies. Cancer Epidemiology, Biomarkers & Prevention2015. p. 1327-31.PMID: 26160694. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E5**
567. Uruno T, Miyauchi A, Shimizu K, Tomoda C, Takamura Y, Ito Y, Miya A, Kobayashi K, Matsuzuka F, Amino N and Kuma K. Favorable surgical results in 433 elderly patients with papillary thyroid cancer. World journal of surgery2005. p. 1497-501; discussion 1502-3.PMID: 16222446. **KQ4E7, KQ5E5**
568. Vaiman M, Nagibin A and Olevson J. Complications in primary and completed thyroidectomy. Surgery today2010. p. 114-8.PMID: 20107949. **KQ5e3a**
569. Valachis A and Nearchou A. High versus low radioiodine activity in patients with differentiated thyroid cancer: a meta-analysis. Acta Oncologica2013. p. 1055-61.PMID: 23193961. **KQ5e6**
570. Valerio L, Viola D, Materazzi G, Miccoli P, Basolo F, Sensi E, Faviana P, Molinaro E, Agate L and Elisei R. Prophylactic central compartment lymph node dissection (CCND) does not improve the outcome of papillary thyroid cancer (PTC) patients: Results from the first prospective cohort study. European Thyroid Journal2013. p. 94.PMID: CN-01100913. **KQALLE7 (ONLY ABSTRACT AVAILABLE)**
571. Valerio L, Viola D, Materazzi G, Miccoli P, Basolo F, Sensi E, Faviana P, Molinaro E, Agate L, Pinchera A and Elisei R. Pros and cons of prophylactic central compartment lymph node dissection in differentiated thyroid cancer patients. European Thyroid Journal2012. p. 181.PMID: CN-01088909. **KQALLE7 (ONLY ABLSTRACT AVAILABLE)**
572. Valle LA and Kloos RT. The prevalence of occult medullary thyroid carcinoma at autopsy. Journal of Clinical Endocrinology & Metabolism. 2010/10/15 ed2011. p. E109-13.PMID: 20943788. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E1**
573. Van de Velde CJ, Goslings BM, Schelfhout LJ, Fleuren GJ, Hermans J and Zwaveling A. Prognosis and morbidity after total thyroidectomy for papillary, follicular and medullary thyroid cancer. European Journal of Cancer & Clinical Oncology1989. p. 1317-23.PMID: 2806355. **KQ5E6G**
574. Van Fossen VL, Wilhelm SM, Eaton JL and McHenry CR. Association of thyroid, breast and renal cell cancer: a population-based study of the prevalence of second malignancies. Annals of surgical oncology2013. p. 1341-7.PMID: 23263698. **KQ5e6**
575. van Heerden JA, Groh MA and Grant CS. Early postoperative morbidity after surgical treatment of thyroid carcinoma. Surgery1987. p. 224-7.PMID: 3810493. **KQ5E6G**

576. Vanderpump MP, Alexander L, Scarpello JH and Clayton RN. An audit of the management of thyroid cancer in a district general hospital. Clinical endocrinology1998. p. 419-24.PMID: 9640408. **KQ4E5, KQ5E5**
577. Varverakis E and Neonakis E. Contribution of high-resolution ultrasonography in the differential diagnosis of benign from malignant thyroid nodules. Hormones2002. p. 51-6.PMID: 17018439. **KQ2E5**
578. Varverakis E, Neonakis E, Tzardi M and Chrysos E. Role of color Doppler ultrasonography in the preoperative management of cold thyroid nodules. Hormones2007. p. 44-51.PMID: 17324917. **KQ2e2c**
579. Vega-Vazquez MA, Gonzalez-Rodriguez L, Santiago-Rodriguez EJ, Garces-Dominguez A, Shum LM, Tirado-Gomez M and Ramirez-Vick M. Quality of life-in patients with differentiated thyroid cancer at the general endocrinology clinics of the University Hospital of Puerto Rico. Boletin - Asociacion Medica de Puerto Rico2015. p. 25-31.PMID: 26035981. **KQ2E2C**
580. Verbeek HH, Meijer JA, Zandee WT, Kramp KH, Sluiter WJ, Smit JW, Kievit J, Links TP and Plukker JT. Fewer cancer reoperations for medullary thyroid cancer after initial surgery according to ATA guidelines. Annals of surgical oncology2015. p. 1207-13.PMID: 25316487. **KQ5E4**
581. Verburg FA, Stokkel MP, Duren C, Verkooijen RB, Mader U, van Isselt JW, Marlowe RJ, Smit JW, Reiners C and Luster M. No survival difference after successful (131)I ablation between patients with initially low-risk and high-risk differentiated thyroid cancer. European Journal of Nuclear Medicine & Molecular Imaging2010. p. 276-83.PMID: 20091165. **KQ5e5**
582. Verkooijen RB, Smit JW, Romijn JA and Stokkel MP. The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer. European Journal of Endocrinology2006. p. 801-6.PMID: 17132748. **KQ5E2**
583. Vincent G. Thyroidectomy over a quarter of a century in the Belgian Ardennes: a retrospective study of 1207 patients. Acta Chirurgica Belgica2008. p. 542-7.PMID: 19051463. **KQ5e4**
584. Vini L, Hyer S, Al-Saadi A, Pratt B and Harmer C. Prognosis for fertility and ovarian function after treatment with radioiodine for thyroid cancer. Postgraduate Medical Journal2002. p. 92-3.PMID: 11807191. **KQ5E6**
585. Viola D, Valerio L, Faviana P, Molinaro E, Sensi E, Agate L, Materazzi G, Basolo F, Miccoli P, Vitti P and Elisei R. Advantages and disadvantages of prophylactic central compartment lymph node dissection for differentiated thyroid cancer: The first randomized controlled study from a single referral center. Endocrine reviews2013.PMID: CN-01049521. **KQALLE7 (only abstract available)**
586. Wada N, Hasegawa S, Masudo Y, Hirakawa S, Matsuzu K, Suganuma N, Nakayama H, Rino Y and Imada T. Clinical outcome by AMES risk definition in Japanese differentiated thyroid carcinoma patients. Asian Journal of Surgery2007. p. 102-7.PMID: 17475578. **KQ5E5**
587. Walker J, Findlay D, Amar SS, Small PG, Wastie ML and Pegg CA. A prospective study of thyroid ultrasound scan in the clinically solitary thyroid nodule. British Journal of Radiology1985. p. 617-9.PMID: 3893613. **KQ5E6G**
588. Walter MA, Turtschi CP, Schindler C, Minnig P, Muller-Brand J and Muller B. The dental safety profile of high-dose radioiodine therapy for thyroid cancer: long-term results of a longitudinal cohort study. Journal of nuclear medicine2007. p. 1620-5.PMID: 17873131. **KQ5e6H**
589. Wang LY, Roman BR, Palmer FL, Tuttle RM, Shaha AR, Shah JP, Patel SG and Ganly I. Effectiveness of routine ultrasonographic surveillance of patients with low-risk papillary carcinoma of the thyroid. Surgery. 2016/01/10 ed2015.PMID: 26747227. **KQ4E5, KQ5E5**
590. Wang Y and Wang W. Increasing Incidence of Thyroid Cancer in Shanghai, China, 1983-2007. Asia Pac J Public Health. 2012/02/22 ed2012.PMID: 22345304. **KQ3E2**
591. Wei X, Li Y, Zhang S and Gao M. A Meta-analysis of thyroid imaging reporting and data system in the ultrasonographic diagnosis of 10,437 thyroid nodules. Head Neck. 2014/09/23 ed2014.PMID: 25244250. **KQ2E2C**
592. Wei X, Li Y, Zhang S, Li X, Luo J and Ming G. WITHDRAWN:Evaluation of microcirculation of thyroid cancer in Chinese females with breast cancer using contrast-enhanced ultrasound (CEUS) combined with VEGF and microvessel density (MVD). Clinical Hemorheology & Microcirculation. 2013/03/13 ed2013.PMID: 23478226. **KQ2E2, KQ3E2**

593. Weinrib SL, Lane WS and Rappaport JM. Successful management of differentiated thyroid cancer in a community-based endocrine practice. Endocrine practice2012. p. 170-8.PMID: 21940280. **KQ3E5**
594. Welch K and McHenry CR. Selective lateral compartment neck dissection for thyroid cancer. Journal of surgical research2013. p. 193-9.PMID: 23816244. **KQ5e2b**
595. Weng HF, Huang MJ, Huang BY, Huang HS and Jeng LB. Thyroid cancer treated in Chang Gung Memorial Hospital (northern Taiwan) during the period 1979-1992: clinical presentation, pathological finding, analysis of prognostic variables, and results of treatment. Journal of surgical oncology1994. p. 252-9; discussion 259-60.PMID: 7990481. **KQ3E5, KQ5E6G**
596. Wichers M, Benz E, Palmedo H, Biersack HJ, Grunwald F and Klingmuller D. Testicular function after radioiodine therapy for thyroid carcinoma. European journal of nuclear medicine2000. p. 503-7.PMID: 10853804. **KQ5E5**
597. Widder S, Guggisberg K, Khalil M and Pasieka JL. A pathologic re-review of follicular thyroid neoplasms: the impact of changing the threshold for the diagnosis of the follicular variant of papillary thyroid carcinoma. Surgery2008. p. 80-5.PMID: 18571588. **KQ3e1**
598. Wienhold R, Scholz M, Adler JR, C GN and Paschke R. The management of thyroid nodules: a retrospective analysis of health insurance data. Deutsches Arzteblatt International2013. p. 827-34.PMID: 24355935. **KQ5e4d**
599. Wiest PW, Hartshorne MF, Inskip PD, Crooks LA, Vela BS, Telepak RJ, Williamson MR, Blumhardt R, Bauman JM and Tekkel M. Thyroid palpation versus high-resolution thyroid ultrasonography in the detection of nodules. Journal of ultrasound in medicine1998. p. 487-96.PMID: 9697951. **KQ2E2B**
600. Wilhelm SM, Robinson AV, Krishnamurthi SS and Reynolds HL. Evaluation and management of incidental thyroid nodules in patients with another primary malignancy. Surgery2007. p. 581-6; discussion 586-7.PMID: 17950351. **KQ2e5b**
601. Winchester DJ. Total lobectomy and total thyroidectomy in the management of thyroid lesions. Archives of Surgery1993. p. 1060-3; discussion 1064.PMID: 8368926. **KQ5E4D**
602. Wingo PA, Tong T and Bolden S. Cancer statistics, 1995. CA Cancer J Clin. 1995/01/01 ed1995. p. 8-30.PMID: 7528632. **KQALLE6**
603. Wiseman SM, Baliski C, Irvine R, Anderson D, Wilkins G, Filipenko D, Zhang H and Bugis S. Hemithyroidectomy: the optimal initial surgical approach for individuals undergoing surgery for a cytological diagnosis of follicular neoplasm. Annals of surgical oncology2006. p. 425-32.PMID: 16485160. **KQ5e5**
604. Witt RL and McNamara AM. Prognostic factors in mortality and morbidity in patients with differentiated thyroid cancer. Ear, Nose, & Throat Journal2002. p. 856-63.PMID: 12516384. **KQ5e5**
605. Wolinski K, Szkudlarek M, Szczepanek-Parulska E and Ruchala M. Usefulness of different ultrasound features of malignancy in predicting the type of thyroid lesions: a meta-analysis of prospective studies. Polskie Archiwum Medycyny Wewnetrznej2014. p. 97-104.PMID: 24473342. **KQ2e8**
606. Wu JQ, Feng HJ, Ouyang W, Sun YG, Chen P, Wang J, Xian JL and Huang LH. Systematic evaluation of salivary gland damage following I-131 therapy in differentiated thyroid cancer patients by quantitative scintigraphy and clinical follow-up. Nuclear Medicine Communications2015. p. 819-26.PMID: 25932534. **KQ5E3A**
607. Wu Q, Wang Y, Li Y, Hu B and He ZY. Diagnostic value of contrast-enhanced ultrasound in solid thyroid nodules with and without enhancement. Endocrine. 2016/01/07 ed2016.PMID: 26732040. **KQ2E3A**
608. Xia Q, Dong S, Bian PD, Wang J and Li CJ. Effects of endocrine therapy on the prognosis of elderly patients after surgery for papillary thyroid carcinoma. Eur Arch Otorhinolaryngol. 2015/03/07 ed2015.PMID: 25744048. **KQ5E5**
609. Xue H, Takahashi H, Cangir A and Andrassy RJ. Iodine 131 thyroid ablation in female children and adolescents: long-term risk of infertility and birth defects. Annals of surgical oncology1994. p. 128-31.PMID: 7834437. **KQ5E4**
610. Xue S, Wang P, Liu J, Li R, Zhang L and Chen G. Prophylactic central lymph node dissection in cN0 patients with papillary thyroid carcinoma: A retrospective study in China. Asian J Surg. 2015/06/29 ed2015.PMID: 26117203. **KQ5E3A**
611. Yamashita H, Noguchi S, Watanabe S, Uchino S, Kawamoto H, Toda M, Murakami N, Nakayama I and Yamashita H. Thyroid cancer associated with adenomatous goiter: an analysis of the incidence and clinical factors. Surgery today1997. p. 495-9.PMID: 9306541. **KQ2E4, KQ3E4**

612. Yang GC, LiVolsi VA and Baloch ZW. Thyroid microcarcinoma: fine-needle aspiration diagnosis and histologic follow-up. International Journal of Surgical Pathology2002. p. 133-9.PMID: 12075406. **KQ3e5**
613. Yi H, Long B, Ye X, Zhang L, Liu X and Zhang C. Autophagy: A potential target for thyroid cancer therapy (Review). Mol Clin Oncol. 2014/07/24 ed2014. p. 661-665.PMID: 25054028. **KQALLE4**
614. Yi O, Yoon JH, Lee YM, Sung TY, Chung KW, Kim TY, Kim WB, Shong YK, Ryu JS and Hong SJ. Technical and oncologic safety of robotic thyroid surgery. Annals of surgical oncology2013. p. 1927-33.PMID: 23306957. **kq5e6h**
615. Yokozawa T, Miyauchi A, Kuma K and Sugawara M. Accurate and simple method of diagnosing thyroid nodules the modified technique of ultrasound-guided fine needle aspiration biopsy. Thyroid1995. p. 141-5.PMID: 7647575. **KQ2E2, KQ3E2**
616. Yoo JY, Chae YJ, Cho HB, Park KH, Kim JS and Lee SY. Comparison of the incidence of postoperative nausea and vomiting between women undergoing open or robot-assisted thyroidectomy. Surg Endosc. 2012/12/15 ed2013. p. 1321-5.PMID: 23239293. **kq5e5**
617. Yoon JH, Kwak JY, Kim EK, Moon HJ, Kim MJ, Kim JY, Koo HR and Kim MH. How to approach thyroid nodules with indeterminate cytology. Annals of surgical oncology2010. p. 2147-55.PMID: 20217250. **KQ1E2C, KQ3E4**
618. Yoon JH, Lee HS, Kim EK, Moon HJ and Kwak JY. Malignancy Risk Stratification of Thyroid Nodules: Comparison between the Thyroid Imaging Reporting and Data System and the 2014 American Thyroid Association Management Guidelines. Radiology. 2015/09/09 ed2015. p. 150056.PMID: 26348102. **KQ2E2C**
619. Yoon JH, Shin HJ, Kim EK, Moon HJ, Roh YH and Kwak JY. Quantitative Evaluation of Vascularity Using 2-D Power Doppler Ultrasonography May Not Identify Malignancy of the Thyroid. Ultrasound in medicine & biology2015. p. 2873-83.PMID: 26298035. **KQ2E2C**
620. You YN and Wells SA, Jr. Role of surgeons in clinical trials for thyroid cancer. World journal of surgery2007. p. 987-95.PMID: 17426898. **KQ4e2, KQ5e2**
621. Younes J, Ghorra C, Abadjian G, Sidaoui J and Abboud B. Differentiated thyroid carcinoma in early adulthood patients. Acta Chirurgica Belgica2014. p. 388-92.PMID: 26021683. **KQ5E6H**
622. Young S, Harari A, Smooke-Praw S, Ituarte PH and Yeh MW. Effect of reoperation on outcomes in papillary thyroid cancer. Surgery2013. p. 1354-61; discussion 1361-2.PMID: 24238053. **KQ4e2b**
623. Yu XM, Wan Y, Sippel RS and Chen H. Should all papillary thyroid microcarcinomas be aggressively treated? An analysis of 18,445 cases. Annals of surgery2011. p. 653-60.PMID: 21876434. **KQ3e2, KQ4e2b**
624. Yuan WH, Chiou HJ, Chou YH, Hsu HC, Tiu CM, Cheng CY and Lee CH. Gray-scale and color Doppler ultrasonographic manifestations of papillary thyroid carcinoma: analysis of 51 cases. Clinical imaging2006. p. 394-401.PMID: 17101408. **KQ2e2c**
625. Ywata de Carvalho A, Chulam TC and Kowalski LP. Long-term Results of Observation vs Prophylactic Selective Level VI Neck Dissection for Papillary Thyroid Carcinoma at a Cancer Center. JAMA Otolaryngology-- Head & Neck Surgery2015. p. 599-606.PMID: 25997016. **KQ5E3A**
626. Zeppa P, Benincasa G, Lucariello A and Palombini L. Association of different pathologic processes of the thyroid gland in fine needle aspiration samples. Acta cytologica2001. p. 347-52.PMID: 11393065. **KQ3E5**
627. Zhang J, Chen Z and Anil G. Ultrasound-guided thyroid nodule biopsy: outcomes and correlation with imaging features. Clin Imaging. 2014/12/06 ed2014.PMID: 25475702. **KQ2E2C, KQ3E2C**
628. Zhang J, Liu BJ, Xu HX, Xu JM, Zhang YF, Liu C, Wu J, Sun LP, Guo LH, Liu LN, Xu XH and Qu S. Prospective validation of an ultrasound-based thyroid imaging reporting and data system (TI-RADS) on 3980 thyroid nodules. International journal of clinical and experimental medicine2015. p. 5911-7.PMID: 26131184. **KQ2E2C**
629. Zhang L, Liu Z, Liu Y, Gao W and Zheng C. The clinical prognosis of patients with cN0 papillary thyroid microcarcinoma by central neck dissection. World journal of surgical oncology2015. p. 138.PMID: 25889385. **KQ5E3A**
630. Zhang S, Zheng XQ, Wei X, Zhao J, Zhang Y and Gao M. Evaluation of ultrasound application in diagnosis and clinical staging of thyroid cancers. Indian Journal of Cancer. 2014/12/11 ed2014. p. 193-199.PMID: 25494104. **KQ3E3A, KQ2E3A**

631. Zhang Y, Liang J, Li H, Cong H and Lin Y. Risk of second primary breast cancer after radioactive iodine treatment in thyroid cancer: a systematic review and meta-analysis. Nuclear Medicine Communications2016. p. 110-5.PMID: 26513055. **KQ5E2**

632. Zhang YF, Xu HX, Xu JM, Liu C, Guo LH, Liu LN, Zhang J, Xu XH, Qu S and Xing M. Acoustic Radiation Force Impulse Elastography in the Diagnosis of Thyroid Nodules: Useful or Not Useful? Ultrasound in medicine & biology2015. p. 2581-93.PMID: 26119458. **KQ2E2C**

633. Zhang YF, Xu JM, Xu HX, Liu C, Bo XW, Li XL, Guo LH, Liu BJ, Liu LN and Xu XH. Acoustic Radiation Force Impulse Elastography: A Useful Tool for Differential Diagnosis of Thyroid Nodules and Recommending Fine-Needle Aspiration: A Diagnostic Accuracy Study. Medicine2015. p. e1834.PMID: 26496325. **KQ2E2C**

634. Zhao ZH, Li FQ, Han JK and Li XJ. Effect of I 'clear residual thyroid tissue' after surgery on the function of parathyroid gland in differentiated thyroid cancer. Exp Ther Med. 2015/12/17 ed2015. p. 2079-2082.PMID: 26668598. **KQ5E3A**

635. Zhu W, Zhong M and Ai Z. Systematic evaluation of prophylactic neck dissection for the treatment of papillary thyroid carcinoma. Japanese Journal of Clinical Oncology2013. p. 883-8.PMID: 23858039. **KQ5E2A**

636. Zuniga S and Sanabria A. Prophylactic central neck dissection in stage N0 papillary thyroid carcinoma. Archives of Otolaryngology -- Head & Neck Surgery2009. p. 1087-91.PMID: 19917919. **KQ4e2b, KQ5e3a**