實證醫學報告

R3 郭宜瑾

Clinical Scenario

- This 41-year-old female patient has underlying of hypertension.
- A thyroid nodule(left side 2.4*2cm,) was found accidently in 2009/11
  - FNA on 11/19:negative
  - Total thyroidectomy on 12/14 was done

Clinical Scenario

- Pathology report:

  Left lobe:

  - Histologic type: papillary carcinoma,
  - Vascular permeation: histologically negative.
  - Capsular invasion: histologically positive (Not penetrate the entire thickness of the capsule).
  - Extrathyroid extension: histologically negative.
  - An ill-circumscribed grayish nodule without capsule, which measures 2.0 cm in greatest diameter in left lobe.
- Staging:T1N0M0,stage I

Background

- Radioiodine therapy for thyroid cancer
  - Well- differentiated thyroid cancer still incorporates radioiodine, though less efficiently than normal thyroid follicular cell.
  - Postoperative thyroid ablation and radioiodine treatment of known residual PTC or FTC clearly reduces recurrence rates but has a smaller impact on mortality,particularly in patients at relatively low risk.(stage 1 with primary tumor s<1.5 cm)

17th Edition Harrison's Principles of Internal Medicine

Table 4. TNM Classification System for Differentiated Thyroid Carcinoma

	Definition	
T1	Tumor diameter 2 cm or smaller	
T2	Primary tumor diameter >2 to 4 cm	
T3	Primary tumor diameter >4 cm limited to the thyroid or with minimal extrathyroidal extension	
$T4_a$	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve	
$T4_b$	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels	
TX	Primary tumor size unknown, but without extrathyroidal invasion	
N0	No metastatic nodes	
$N1_a$	Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)	
$N1_b$	Metastasis to unilateral, bilateral, contralateral cervical or superior mediastinal nodes	
NX	Nodes not assessed at surgery	
M0	No distant metastases	
M1	Distant metastases	
MX	Distant metastases not assessed	
Stages		
	Patient age <45 years	*Patient age 45 years or older*
Stage I	Any T, any N, M0	T1, N0, M0
Stage II	Any T, any N, M1	T2, N0, M0
Stage III		T3, N0, M0
		T1, $N1_a$, M0
		T2, $N1_a$, M0
		T3, $N1_a$, M0
Stage IVA		$T4_a$, N0, M0
		$T4_a$, $N1_a$, M0
		T1, $N1_b$, M0
		T2, $N1_b$, M0
		T3, $N1_b$, N0
		$T4_a$, $N1_b$, M0
Stage IVB		$T4_b$, Any N, M0
Stage IVC		Any T, Any N, M1

實證醫學五大步驟

- Asking
  - 將病人的問題寫成PICO
- Acquire
  - 找資料來回答問題
- Appraisal
  - 嚴格評讀文獻
- Apply
  - 是否可應用到病人身上
- Audit
  - 自我評估

Clarifying the problem using PICO model

Patient	Patient with papillary cancer s/p total thyroidectomy
Intervention	Radioiodine therapy
Comparison	No radioiodine therapy
Outcome	Distant metastasis

Search Strategy ”The 5S” Levels

The "5S" levels of organisation of evidence from healthcare research

Brian Haynes, R Evid Based Med 2006;11:162-164

EBM ONLINE

UpToDate

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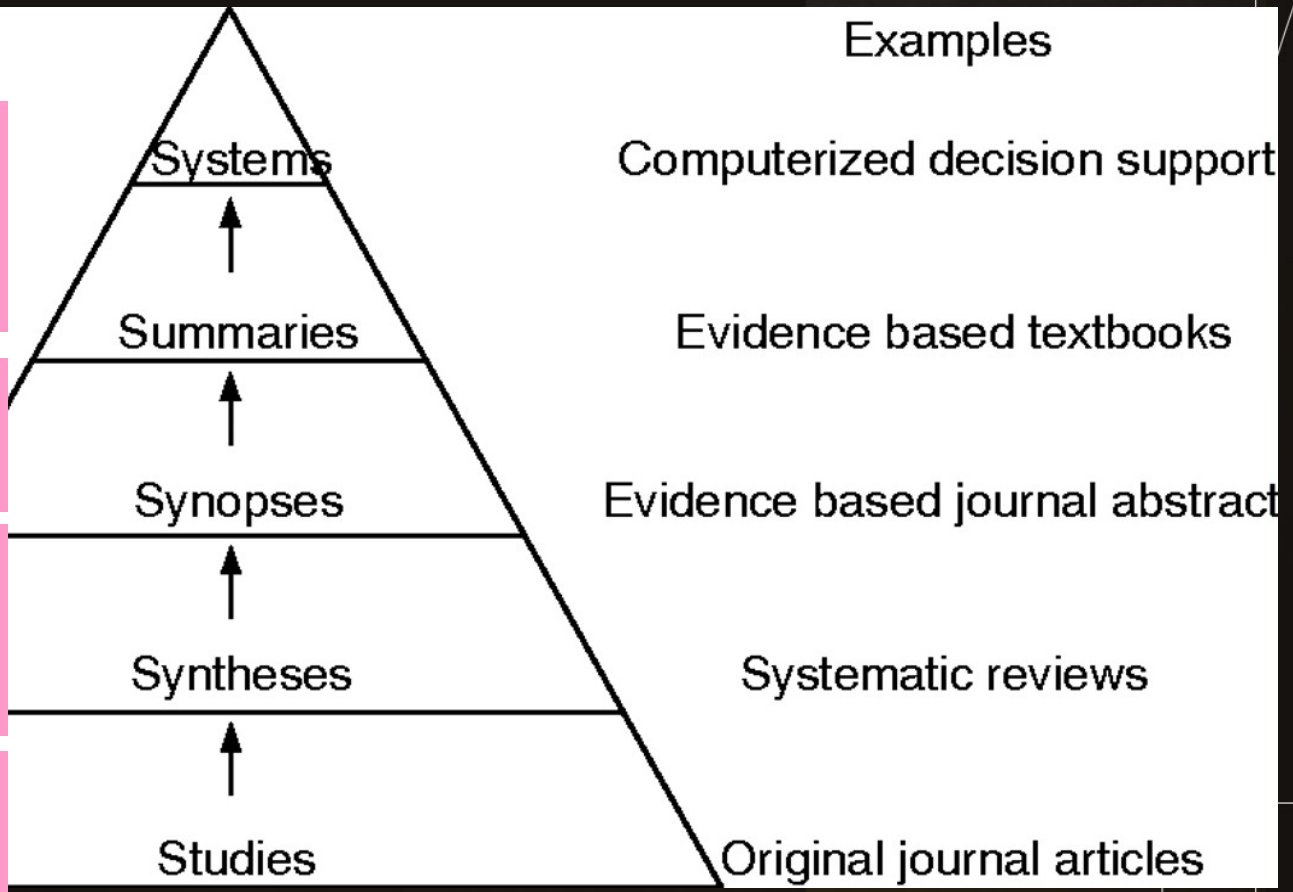


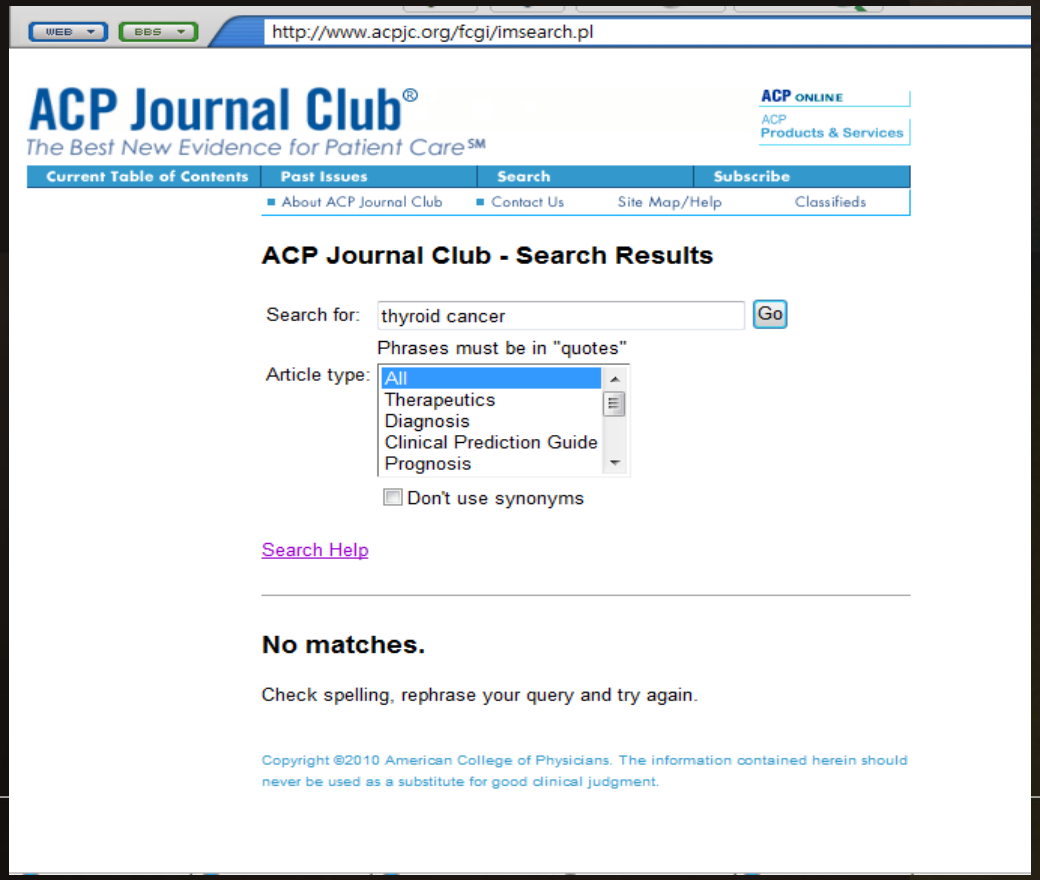
UpToDate

- Keyword: thyroid cancer，radioiodine
  - **Radioiodine treatment of differentiated thyroid cancer**

- Indications for I-131 administration in the post-thyroidectomy treatment of patients with differentiated thyroid cancer include adjuvant ablation of residual thyroid tissue, imaging for possible metastatic disease, and treatment of known residual or metastatic thyroid cancer.
- Available data, including the report from the National Thyroid Cancer Treatment Cooperative Study Group, suggests improved overall survival with postsurgical radioiodine (RAI) treatment in many patients
- We currently suggest postoperative radioiodine ablation for most patients with National Thyroid Cancer Treatment Cooperative Study Group Stage II, III, and IV disease (**Grade 1B**).
- In the absence of a proven benefit on either disease free survival or recurrence, we suggest against radioiodine ablation for patients with Stage 1 disease with tumors < 1 cm (**Grade 2B**).
- However, we do consider RAI in some Stage I patients with microscopic extrathyroidal extension or macroscopic multifocal disease depending upon the surgical findings, postoperative serum thyroglobulin (Tg), the desire of the patient, and to enhance the sensitivity of our follow up testing (serum Tg and RAI scanning).

ACP Journal Club

- Keyword: thyroid cancer,radioiodine



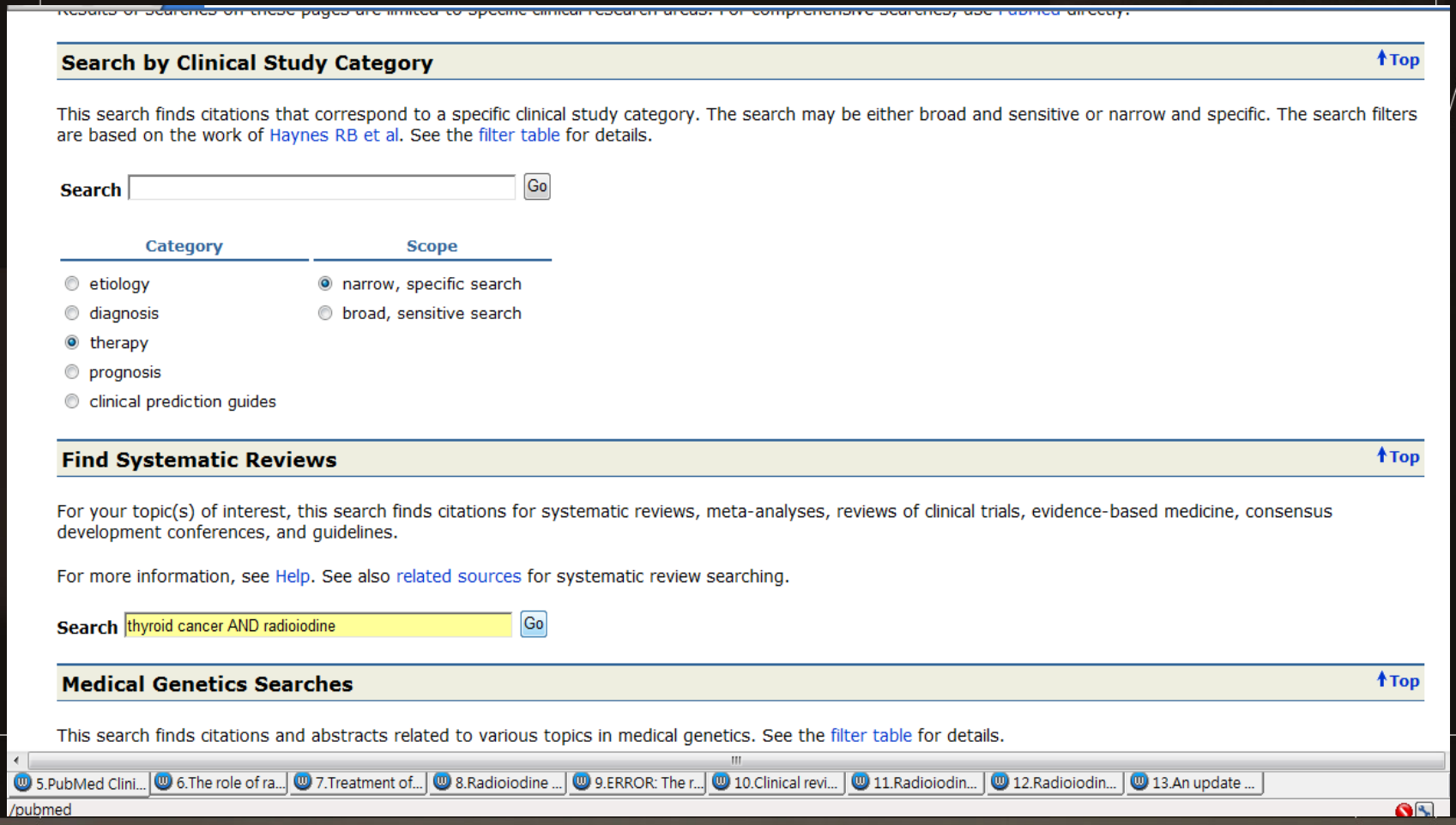
Cochrane Library

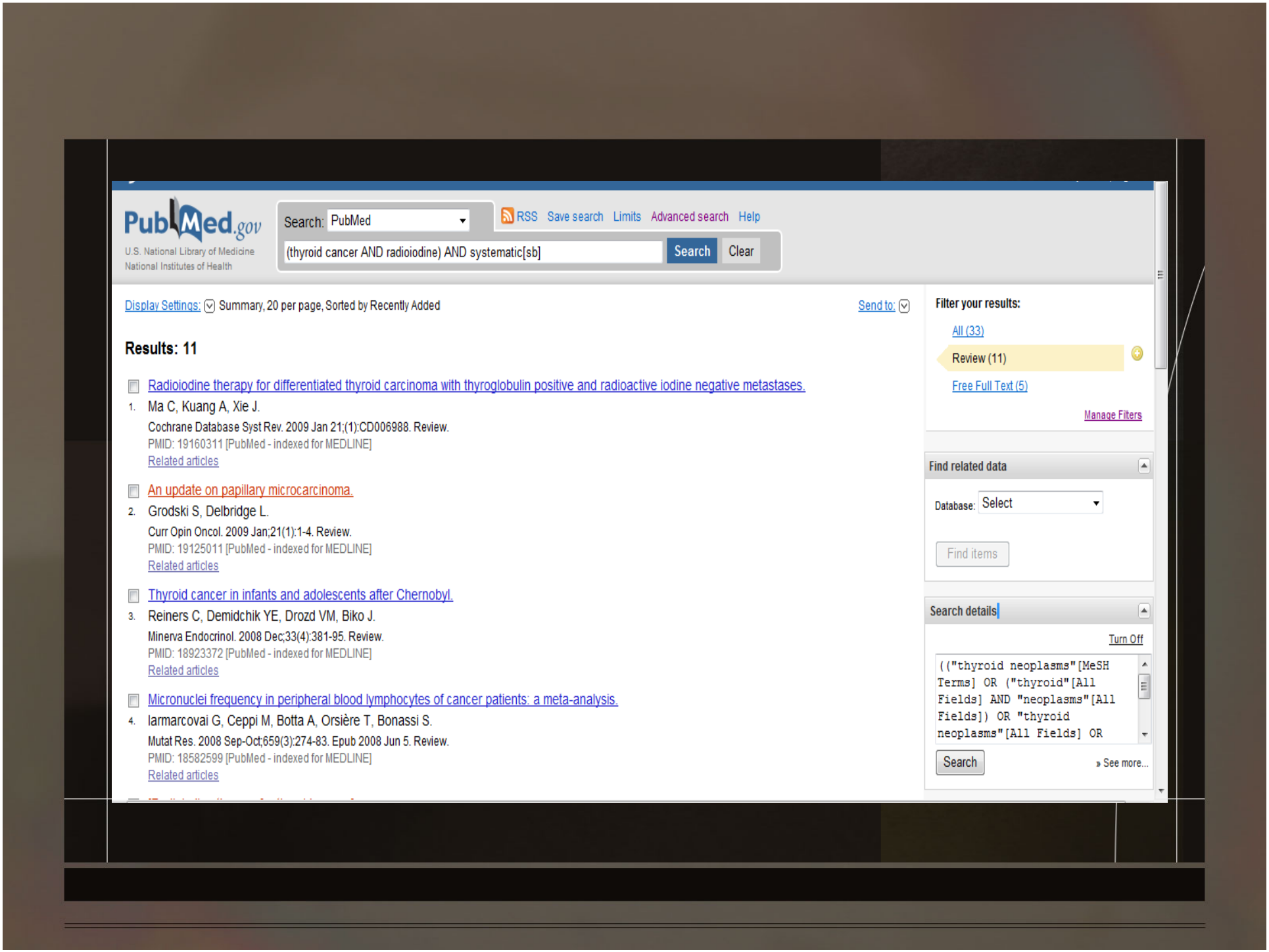
- Keyword:thyroid cancer,radioiodine
  - **Radioiodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases**
    Chao Ma, Anren Kuang, Jiawei Xie
    January 2009

- Background: Differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases has been observed in follow-up studies. The management of this condition remains controversial. Most studies support blind radioactive iodine treatment while others negate this approach.
- Objectives: To assess the effects of radioiodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases.
- Search strategy: Studies were obtained from computerised searches of MEDLINE, EMBASE, *The Cochrane Library*, China National Infrastructure (CNKI) and paper collections of conferences held in Chineses
- Selection criteria: Randomised controlled clinical trials and prospective controlled clinical trials.
- Main results: Because of the absence of any suitable randomised or prospective controlled trial in this area, results currently cannot be presented.
- Authors' conclusions: The currently available evidence is insufficient to reliably assess the potential of radioiodine treatment for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases.

PubMed

- Keyword:thyroid cancer,radioiodine

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Radioiodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases.
1. Ma C, Kuang A, Xie J.
Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006988. Review.
PMID: 19160311 [PubMed - indexed for MEDLINE]
Related articles
An update on papillary microcarcinoma.
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Curr Opin Oncol. 2009 Jan;21(1):1-4. Review.
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Related articles
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3. Reiners C, Demidchik YE, Drozd VM, Biko J.
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PMID: 18582599 [PubMed - indexed for MEDLINE]
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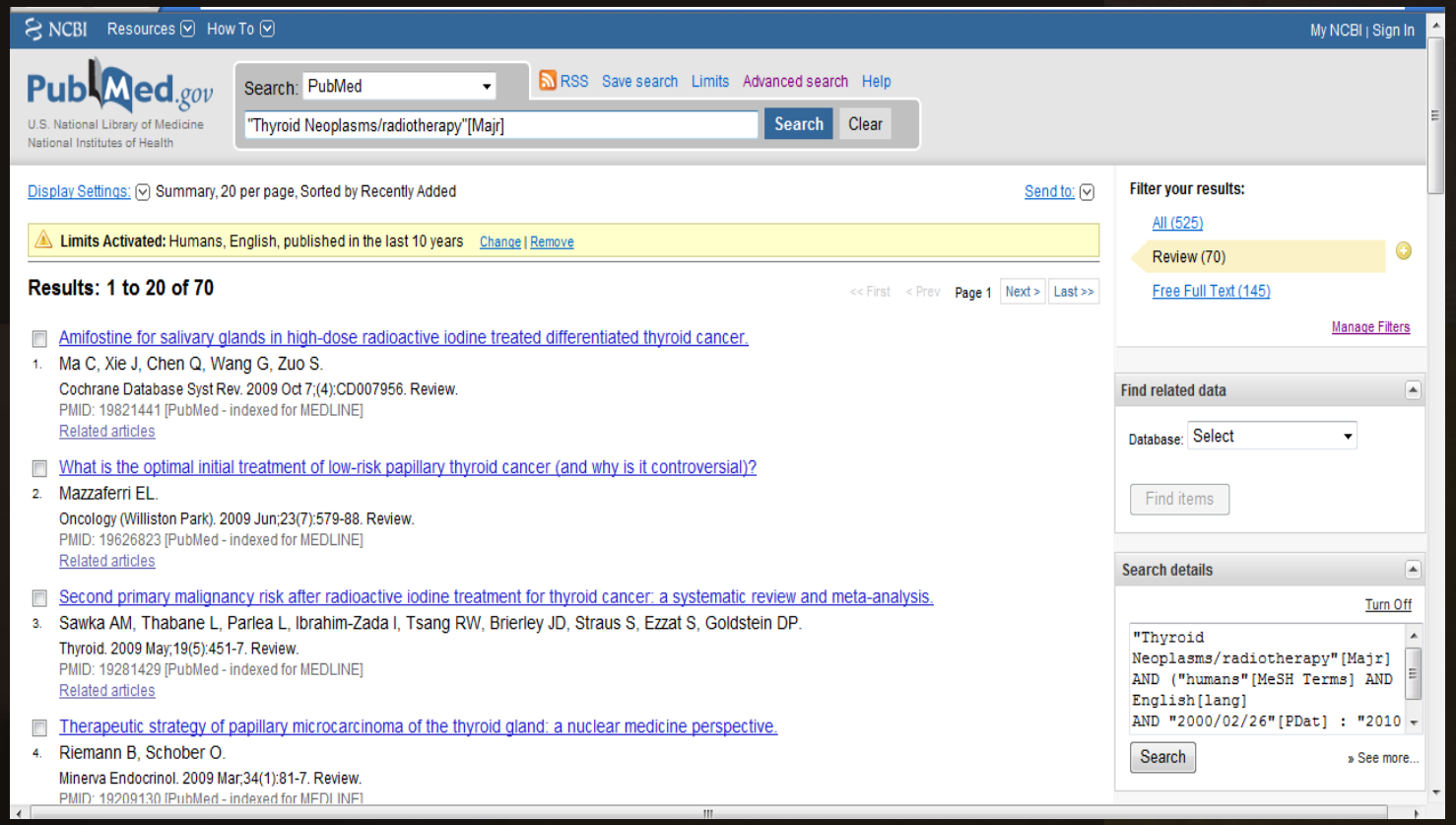
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Amifostine for salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer.
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What is the optimal initial treatment of low-risk papillary thyroid cancer (and why is it controversial)?
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Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis.
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Thyroid. 2009 May;19(5):451-7. Review.
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- **An Updated Systematic Review and Commentary Examining the Effectiveness of Radioactive Iodine Remnant Ablation in Well-Differentiated Thyroid Cancer**

  Endocrinol Metab Clin North Am. 2008 Jun;37(2):457-80, x.

- Radioactive iodine remnant ablation (RRA) is used to destroy residual normal thyroid tissue after complete gross surgical resection of papillary or follicular thyroid cancer. The article updates a prior systematic review of the literature to determine whether RRA decreases the risk of thyroid cancer-related death or recurrence at 10 years after initial surgery, including data from 28 studies.
- No long-term randomized trials were identified, so the review is limited to observational studies.
- The incremental benefit of RRA in low risk patients with well-differentiated thyroid cancer after total or near-total thyroidectomy who are receiving thyroid hormone suppressive therapy remains unclear.

- **A Systematic Review and Metaanalysis of the Effectiveness of Radioactive Iodine Remnant Ablation for Well-Differentiated Thyroid Cancer**

  J Clin Endocrinol Metab, August 2004, 89(8):3668–3676

- Radioactive iodine remnant ablation destroys residual thyroid tissue after surgical resection of papillary or follicular thyroid cancer. We systematically reviewed 1543 English references to determine whether remnant ablation decreases the risk of thyroid cancer-related death or recurrence after bilateral thyroidectomy for papillary or follicular thyroid cancer.
- In 18 cohort studies not adjusted for prognostic factors or interventions, the benefit of radioactive iodine ablation in decreasing the thyroid cancer-related mortality and any recurrence at 10 yr was inconsistent among centers. However, pooled analyses were suggestive of a statistically significant treatment effect of ablation for the following 10-yr outcomes: locoregional recurrence (relative risk of 0.31, 95% confidence interval, 0.2, 0.49) and distant metastases (absolute decrease in risk 3%, 95% confidence interval, risk decreases 1-4%).
- In conclusion, radioactive iodine ablation may be beneficial in decreasing recurrence of well-differentiated thyroid cancer; however, results are inconsistent among centers for some outcomes, and the incremental benefit of remnant ablation in low-risk patients treated with bilateral thyroidectomy and thyroid hormone suppressive therapy is unclear.

Appraisal (嚴格評讀)

Valid: systematic review worksheet

Importance: what were the result?

Applicability: population and feasibility

參考資料：

1. The GATE frame: critical appraisal with pictures
   ACP Journal Club March/April 2006 | Volume 144
2. JAMA,1994;271:1615-1619
3. Sackett Corrected 2 Dec 1996

A Systematic Review and Metaanalysis of the Effectiveness of Radioactive Iodine Remnant Ablation for Well-Differentiated Thyroid Cancer

Level:2a

P: 收集的文獻

What question did the systematic review addressed (PICO)
想要回答什麼問題？

systematically review to determine whether radioactive iodine remnant ablation *decreases the risk of thyroid cancer-related death, distant metastasis or recurrence* in adults who have had grossly complete resection of papillary or follicular thyroid carcinoma.

P: 收集的文獻

Systemic review worksheet

全面搜尋相關的文獻、不限英文、且涉及未出版文獻

•Electronic databases, including: Medline (1966–September 2002), Pre-Medline, Cochrane Database for Systematic Reviews, American College of Physicians Journal Club (September 1991–October 2002), Database of Abstracts and Reviews, The Controlled Clinical Trials Database, Cancerlit (1975–2002); Proceedings of the American Society of Clinical Oncology (1997–2002), Proceedings of the American Society for Therapeutic Radiology and Oncology (1997–2002), and Embase (1988 to August 2002).
The search was restricted to English-language publications.
•Online versions of: Thyroid (January 2001 through January 2002), Journal of Clinical Endocrinology & Metabolism (October 1996 through October 2002), Clinical Endocrinology (January 1998 through November 2002), and the Journal of Nuclear Medicine (January 1996 through November 2002) were included.
•Experts in endocrinology and nuclear medicine were also contacted to obtain further references
•Other sources for publications included“related articles” that were identified through PubMed as well as articles cited in guidelines from the British Thyroid Association, The Northern Cancer Network, The National Comprehensive Cancer Network, the American Association of Clinical Endocrinologists, and the American Thyroid Association.

P: 收集的文獻

Systemic review worksheet

文獻研究形式正確，排除或收錄標準明定

•Randomized controlled trials or cohort studies
•Adulat patients(>19 yr of age) who had:
1) well-differentiated thyroid cancer (defined as papillary, follicular, or follicular variant of papillary)
2) surgical treatment involving bilateral resection (*i.e. surgery that was more extensive than ipsilateral lobectomy* and isthmectomy)
3) RAI ablation given within 1 yr after the operation
4) a median or mean follow-up period of at least 5 yr
5) listing of the outcome(s) of cancer-related deaths, any cancer recurrence, local regional recurrence in the thyroid bed, or regional lymph nodes, or distant metastases (all at 10 yr for data unadjusted for prognostic factors or interventions).

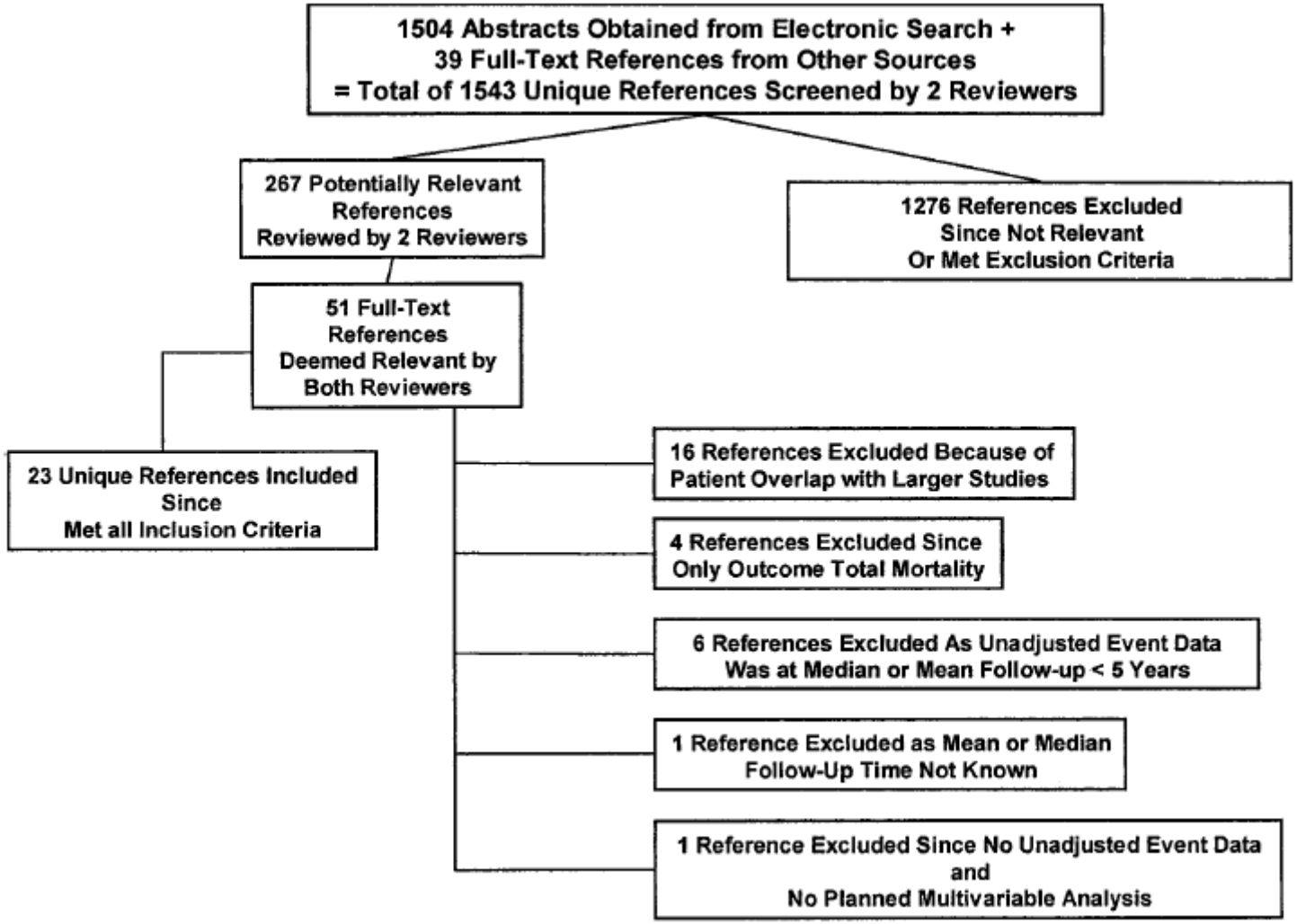

FIG. 1. Process of exclusion of studies.

Intervention and Control

Systemic review worksheet

I & C 是否清楚描述並且是可行的(Ascertain)

•If detailed information on completeness of resection of gross disease was absent in studies, we abstracted data from subgroup analyses comprised mainly of low-risk patients (as defined by the individual author or the standard staging system) because low-risk patients would typically have complete surgical resection of gross tumor.

•Data adjusted for prognostic factors or cointerventions was tabulated as presented in the primary studies, and pooling was not performed because variables adjusted for in individual models differed between Studies.

•For unadjusted data (consisting of crude data, without statistical adjustment for prognostic factors or cointerventions), pooled analyses were performed for the 10-yr outcomes of thyroid cancer-specific mortality, any recurrence, local recurrence (in the neck or upper mediastinum), and distant metastases, respectively.

Outcome

Systemic review worksheet

文獻的結果彼此之間是否相似(同質性)

•A chi-2 analysis was performed to assess for heterogeneity of treatment effect for each outcome and if present (*P <0.10), then a pooled estimate of treatment effect was not* presented

=>P=0.6 <1

Outcome

Systemic review worksheet

是否考慮所有重要的結果了(尤其我們想知道的問題)

•*Adjusted analyses: distant metastases. Postoperative RAI therapy* decreased the adjusted risk of distant metastatic recurrence in patients with papillary or follicular thyroid cancer in the largest study (n =1510). In individuals with distant metastases at the time of diagnosis, the hazard ratio was 0.6(95% CI 0.5, 0.8, *P=0.002) (. In a study of 587 patients with* papillary carcinoma, RAI ablation reduced the adjusted risk of distant metastases (adjusted RR 0.2, 95% CI 0.07, 0.64, *P* =0.006). However, the same investigators did not detect a reduced risk of distant metastatic recurrence in 135 patients with follicular thyroid cancer (median follow-up 10.8 yr) .

•*Pooled analyses: distant metastases*. For the outcome of distant metastases in patients of all histologies combined, the rate of distant metastases was 15 of 877 (2%) in ablated patients, compared with 41 of 1079 (4%) in nonablated patients; the pooled risk of distant metastases was decreased by 3% with ablation (95% CI decrease of 1 to 4%)

Outcome

Systemic review worksheet

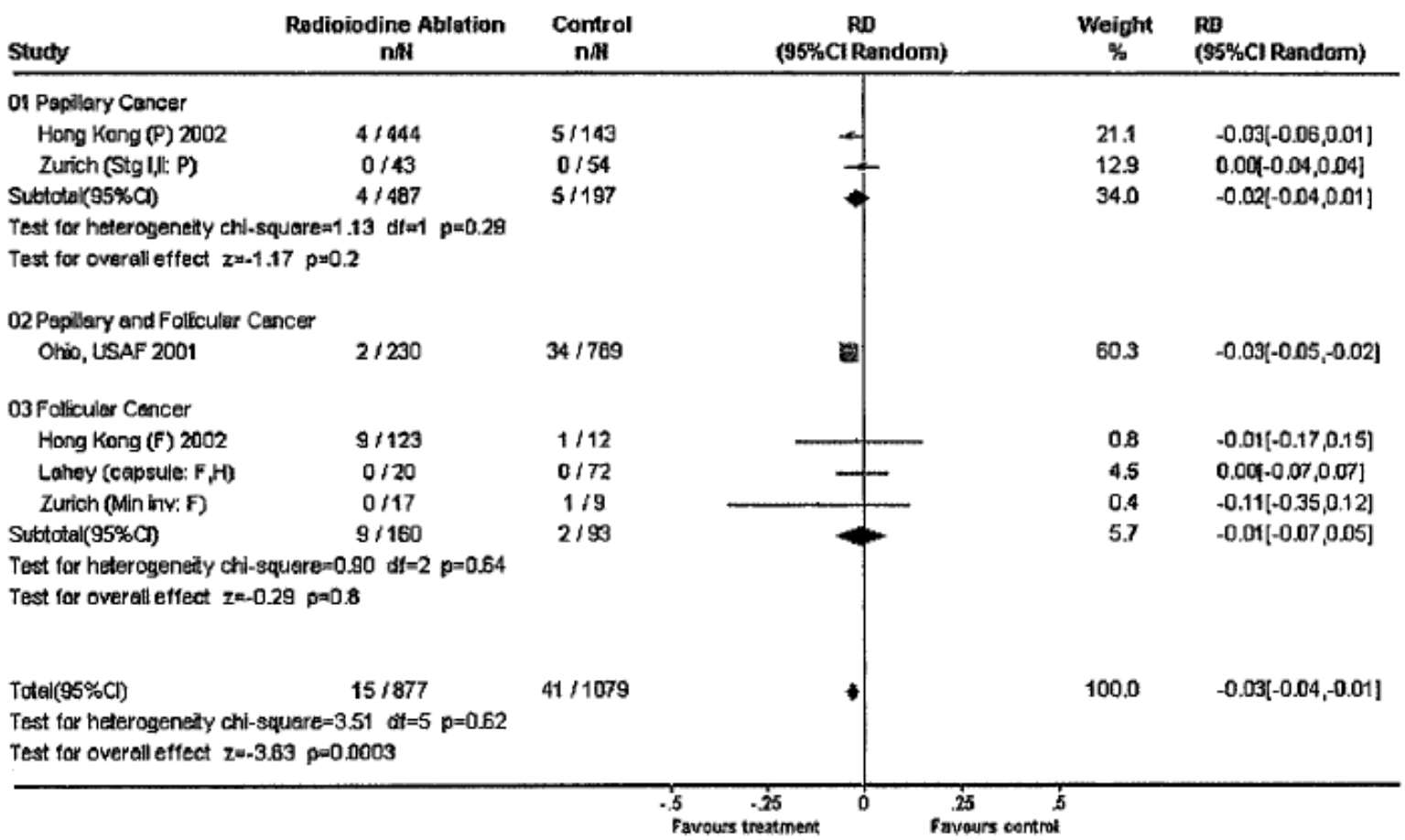

FIG. 4. Random effects model examining the RD of RAI ablation on development of distant metastases at 10 yr. n, Number of events; N, size of population studied; P, papillary; F, follicular; H, Hurthle cell; Stg I,II, stage I or II; Min inv, minimally invasive; capsule, only capsular invasion; node+, including cervical lymphadenopathy.

effectiveness

	Thrombosis		
	Event (+)	Event (-)	Total
control	41		1079
radioiodine	15		877

EER = 15 / 877 = 1.7 %

CER = 41 / 1079 = 3.7 %

RR = EER / CER = 45.9 %

RRR = (CER – EER) / CER = 54 %

ARR = CER – EER = 2 %

NNT = 1 / ARR = 50

(每50人，就有一人減少distant metastasis）

How large was the treatment effect
治療效果有多大？

呈現方式	
Relative Risk (RR): 相對風險 RR= EER / CER	45.9%
Absolute Risk Reduction (ARR): 絕對危險性降低度 ARR= CER – EER	2%
Relative Risk Reduction (RRR): 相對風險性降低度 RRR= CER – EER / CER	54%
Number Needed to Treat (NNT):益一需治數 NNT= 1 / ARR	50

Experimental event rate (EER): 實驗組事件發生率

Control event rate (CER): 對照組事件發生率

Time

Systemic review worksheet

測量結果的時間點是否合乎邏輯	unknown
追蹤是否夠久	in many studies there was lack of complete 10-yr data due to loss to follow-up or inclusion of patients less than 10 yr after their initial diagnosis

Apply

- Radioiodine remnant ablation *decreases the risk of thyroid cancer-related distant metastasis* in adults who have had grossly complete resection of thyroid carcinoma

Thank you~!