



Evidence Summary Report 14-3 EDUCATION AND INFORMATION 2013

I-131 Remnant Ablation after Thyroidectomy for Papillary or Follicular Thyroid Cancer

*A Sawka, A Driedger, S Ezzat, C Lochrin, G Bauman, K Thepamongkhon, M Charette, and
members of the Therapeutic Radiopharmaceutical Guidelines Group*

Report Date: July 20, 2005

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I-131 Remnant Ablation after Thyroidectomy for Papillary or Follicular Thyroid Cancer

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An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base practice recommendations.

SUMMARY

Question

Does I-131 remnant ablation decrease long-term rates of disease-related mortality, loco-regional recurrence in the neck, or distant metastases in patients with papillary or follicular thyroid carcinoma (well-differentiated thyroid carcinoma) who have undergone total-, near-total-, or sub-total thyroidectomy (surgery more extensive than resection of the affected lobe and isthmus) with gross complete resection of disease?

Target Population

This evidence summary applies to adult patients with papillary or follicular thyroid carcinoma (well-differentiated) who have undergone total-, near-total-, or sub-total thyroidectomy (surgery more extensive than resection of the affected lobe and isthmus) with gross complete resection of disease. This evidence summary does not apply to patients with medullary, anaplastic, thyroglossal duct, or familial thyroid carcinoma, or to patients with a history of therapeutic radiation exposure prior to diagnosis of thyroid cancer. The evidence summary also does not apply to patients with concurrent thyrotoxicosis, pregnancy, or renal failure.

Opinions of the Therapeutic Radiopharmaceutical Guidelines Group

The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Therapeutic Radiopharmaceutical Guidelines Group offers the following opinions based on the evidence reviewed:

- There are no long-term randomized controlled trials examining the effectiveness of radioactive iodine remnant ablation in decreasing, well-differentiated, thyroid cancer-related mortality or recurrence.

- The body of current observational evidence suggests that this intervention may be associated with a reduced risk of recurrence of thyroid cancer in terms of any recurrence or locoregional recurrence, or distant metastases, as well as possibly thyroid-cancer related mortality for well-differentiated thyroid cancer. However, results are inconsistent among a relatively small number of centres and not always consistent between papillary and follicular histologies (the former representing the majority of patients studied). Of note, the current body of observational evidence has not adequately adjusted for thyroid hormone suppressive co-therapy, and the incremental benefit of radioiodine ablation with such therapy is unclear. Furthermore, some studies were underpowered to detect a survival benefit, given low mortality rates.
- For patients with well-differentiated thyroid cancer who do not fall into the “good prognosis” category (age <45 years, with unifocal tumour <1.5 cm, no vascular invasion, no tall cell, pink cell or insular variant component, clear resection margins, and no regional nodal involvement) I-131 ablation post-thyroidectomy with the intent of decreasing disease recurrence is a reasonable therapeutic option. Clinicians should discuss the risks and potential benefits of this intervention, including the relative uncertainty of the existing observational evidence, with patients when considering such therapy, and treatment must be individualized. Foregoing remnant ablation in low-risk patients is also an acceptable practice, particularly if patients are aware of the potential risk of recurrence.

Key Evidence

- Thirteen observational cohort studies examining whether postoperative radioactive iodine ablation affected the outcomes of thyroid cancer-related mortality or recurrence (any, loco-regional, or distant metastatic recurrence) were reviewed. In each of those studies, multivariable analyses adjusting for prognostic factors and/or co-interventions were performed.
- Seven studies provided data on the outcome of thyroid cancer-related mortality. One study including 1,510 patients reported a statistically significant association in the reduction of thyroid cancer-related mortality with I-131 ablation. No statistically significant differences were found in the remaining six studies.
- Of six studies examining the outcome of any recurrence of thyroid cancer, post-operative I-131 ablation was associated with a decreased risk in three studies and no difference in the remaining three studies.
- Three studies provided data on loco-regional recurrence of thyroid cancer, and all three reported a decreased risk associated with the use of I-131 ablation.
- Postoperative I-131 was associated with a decrease in the rate of distant metastatic recurrence in two of the three studies examining this outcome.

Treatment Alternatives

- The main treatment alternative is not administering radioactive iodine remnant ablation and considering treatment with thyroid hormone, with the dose adjusted to keep the thyrotropin concentration sub-normal. The effectiveness of thyroid hormone suppressive therapy alone compared to radioactive iodine remnant ablation (with or without suppressive doses of thyroid hormone) is not clear.

Future Research

- In order to definitively clarify whether I-131 remnant ablation is effective in decreasing thyroid cancer recurrence, prospective trials, preferably randomized controlled trials are needed. Given the low mortality rate, in particular with localized papillary cancer, the

outcome of interest needs to include fatal and non-fatal recurrence. Furthermore, quality-of-life measurements should be performed in such a trial.

- The optimal treatment regimen for ablation (dose of I-131, fixed dosing or tailored dosimetry) in terms of maximizing potential benefit and minimizing potential side effects has yet to be determined.
- Determining whether remnant ablation is equally effective when performed after thyroid hormone withdrawal compared to recombinant thyrotropin is also important.
- The potential benefits of co-interventions such as thyroid hormone suppressive therapy (and degree of suppression) as well as external beam radiation therapy should also be determined prospectively, preferably through randomized controlled trials.

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*The Program in Evidence-based Care (PEBC) is sponsored by:
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Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681.*

PREAMBLE: About Our Evidence Summary Reports

The Program in Evidence-based Care (PEBC) is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups using the methodology of the Practice Guidelines Development Cycle.¹

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. For example, the evidence comes from uncontrolled studies, from studies with control groups that are not relevant to current practice in Ontario, or from subgroup analyses, or the evidence consists solely of preliminary results from ongoing trials. The PEBC will monitor the scientific literature and will develop a practice guideline on this topic when more evidence becomes available.

This evidence summary report has been formally approved by the PEBC Guideline Approval body. Formal approval of the document does not necessarily mean that the evidence summary has been adopted as a practice policy of CCO. The decision to adopt an evidence summary as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

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FULL REPORT

I. QUESTION

Does I-131 remnant ablation decrease long-term rates of disease-related mortality, locoregional recurrence in the neck, or distant metastases in patients with papillary or follicular thyroid carcinoma (well differentiated) who have undergone total-, near-total-, or sub-total thyroidectomy (surgery more extensive than resection of the affected lobe and isthmus) with gross complete resection of disease?

II. CHOICE OF TOPIC AND RATIONALE

Thyroid cancer is the most common endocrine malignancy, with an age-standardized incidence of 5.47/100,000 persons in Canada and an estimated 2,800 new cases in 2004 (1,2). Furthermore, in Canada, about 57% of subjects diagnosed with thyroid cancer are younger than 50 years of age (median age at diagnosis 46 years) (1). Thus, thyroid cancer affects many people in the prime of life. The most frequent histologic subtype of thyroid carcinoma is papillary (accounting for 80.2% of cases) followed by follicular carcinoma (11.4% of cases), which are commonly collectively referred to as well-differentiated thyroid cancer (3). Currently, in the United States, 64.8% of patients with papillary carcinoma and 54.5% of patients with follicular carcinoma are treated with total or near-total thyroidectomy (3). According to an American national cancer database, approximately 38% of such patients also receive postoperative radioactive iodine-131 (RAI, I-131) ablation or therapy, although that estimate may be low due to lack of physician registration of that intervention (4).

Radioactive iodine ablation (or remnant ablation) refers to the destruction of residual macroscopically normal thyroid tissue after complete gross surgical resection of cancer. The theoretical goals of radioactive iodine ablation are 1) to destroy any residual microscopic thyroid carcinoma and 2) to facilitate follow-up and early detection of recurrent or metastatic disease by measurement of serum thyroglobulin or radioactive iodine scanning (thereby enabling earlier treatment of recurrent disease).

The effectiveness of radioactive iodine ablation in preventing thyroid cancer-specific death and recurrence has been debated for many years, with no consensus in current practice. For example, the British Thyroid Association has suggested that “for most adult patients with tumours greater than 1 cm in diameter, radioactive iodine ablation should be carried out following thyroidectomy”, the Northern Cancer Network guidelines indicate that “uptake in the thyroid bed or elsewhere is an indication for ablation using high dose I-131”, and the National Comprehensive Cancer Network suggests that “there are compelling reasons” to perform thyroid remnant ablation (5-7). In contrast, the American Association of Clinical Endocrinologists has suggested that the issue of remnant ablation in low-risk patients “remains unsettled” and recommends a “case-by-case decision”, and the American Thyroid Association recommends an “individualized” approach based on “clinical experience” (8,9).

Our aim was to systematically review the literature to determine whether radioactive iodine remnant ablation (RRA) decreases the risk of thyroid cancer-related death, loco-regional recurrence (in the thyroid bed or cervical lymph nodes), distant metastases, or any recurrence in adults who have had grossly complete resection of papillary or follicular thyroid carcinoma. This review is focussed on I-131 remnant ablation after thyroid hormone withdrawal and not after pharmacologic stimulation (such as using recombinant thyrotropin injections prior to ablation). This review does not include treatment of persistent or recurrent disease. This topic was chosen as a priority given the increasing incidence of thyroid carcinoma, particularly in patients at low risk of death from the disease in whom remnant ablation is typically considered.

III. METHODS

Guideline Development

This evidence summary report was developed by the Cancer Care Ontario's Program in Evidence-based Care (PEBC), using methods of the Practice Guidelines Development Cycle (10). Evidence was selected and reviewed by one member of the PEBC's Therapeutic Radiopharmaceutical Guidelines Group and methodologists. Members of the Therapeutic Radiopharmaceutical Guidelines Group disclosed potential conflict-of-interest information.

The evidence summary report is a convenient and up-to-date source of the best available evidence on I-131 remnant ablation in papillary and follicular thyroid cancer, developed through systematic reviews and evidence synthesis and input from practitioners in Ontario. In contrast to the practice guidelines, the body of evidence in an evidence summary is less mature and is comprised of data primarily from non-randomized controlled trial data or data available only in abstract form. This precludes the development of definitive recommendations and instead, opinions of the Group are offered. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey consisting of items that address the quality of the evidence summary report, the interpretation of the available evidence, and whether there is a need to develop an evidence-based practice guideline when sufficient evidence is available. Final approval of the evidence summary report is obtained from the PEBC Guideline Approval body.

The PEBC has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original information.

Literature Search Strategy

Searches were performed in the following databases: MEDLINE and MEDLINE in Process (1966 through March 2004), CANCERLIT (1975 through October 2002), EMBASE (1988 to 2004 week 15), and the Cochrane Library (2004, Issue 1). The following terms were used for MEDLINE, CANCERLIT, and the Cochrane Library: "iodine radioisotopes" (Medical Subject Heading (MeSH) and text word), "iodine isotopes" (MeSH, text word), "radio-iodine:" (text word), "radioiodine:" (text word), "radioactive iodine:" (text word), "I-131" (text word), "131-I" (text word), "131I" (text word), "I131" (text word) combined with "thyroid neoplasms" (MeSH, text word), "thyroid cancer:" (text word), "papillary carcinoma" (MeSH, text word), "follicular carcinoma" (MeSH, text word), "thyroid carcinoma:" (text word). These terms were then combined with search terms to locate studies reporting multivariable analyses, proportional hazards or logistic models, survival analyses, or reporting on disease-free survival or loco-regional recurrence.

Conference proceedings of the American Society of Clinical Oncology (1997-2003) and the American Society for Therapeutic Radiology and Oncology (1997-2003) were searched. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. Cross-referencing of included studies as well as contact of experts was performed to obtain additional citations.

Eligibility Criteria

At the outset, randomized controlled trials or other suitably controlled prospective studies were considered the preferred design for inclusion in this systematic review. None were found. Therefore, given a lack of long-term randomized controlled trials in this field, cohort studies, presenting one or more analyses for the outcomes of thyroid cancer-related mortality or loco-regional/distant/any recurrence, adjusted for known prognostic factors and/or co-interventions,

were selected. All included articles were published reports or published abstracts meeting the criteria described below.

Population - Inclusion Criteria:

- Studies focussing on adult non-pregnant patients with papillary or follicular thyroid carcinoma who have undergone total-, near-total-, or sub-total thyroidectomy (surgery more extensive than resection of the affected lobe and isthmus) with gross complete resection of disease were included.
- Both the treatment and control group had to each contain at least five patients, and median follow-up period for the study population had to be at least 5 years.

Population - Exclusion Criteria:

- Studies in which more than half the population studied were 18 years or younger and in which the adult data were not provided separately.
- Patients with medullary or anaplastic carcinoma.
- Papers in which more than 10% of patients had Hurthle cell carcinomas were excluded. If outcomes of Hurthle-cell patients were presented separately, the Hurthle-cell subgroup was excluded.
- Papers in which more than half of the studied patients underwent lobectomy with isthmectomy or less extensive surgery (without completion thyroidectomy).
- Papers focussing on patients with gross invasion of the trachea or esophagus or grossly unresectable local disease or distant metastases were excluded. (Papers examining patients with lymph node metastases to the neck or upper mediastinum were not excluded).
- Papers focussing on patients with concurrent cancers (other than thyroid) or pituitary disease.
- Studies focussing on thyroglossal duct carcinoma or familial thyroid carcinoma or thyroid carcinoma in association with a familial syndrome (such as Cowden's disease, Gardner's syndrome, or familial adenomatous polyposis) or insular thyroid carcinoma.
- Studies focussing on patients who had previous radiation exposure or patients who were thyrotoxic (secondary to metastases or autoimmune thyroid disease).
- Studies focussing on patients with nodular or autoimmune thyroid disease or acromegaly and concurrent thyroid cancer.
- Studies focussing on patients with renal failure (on hemodialysis or peritoneal dialysis).
- In the case of studies of overlapping groups of patients (such as updates of a cohort study), only the study with the largest number of patients meeting the inclusion criteria for our study was included, and the overlapping studies were excluded unless they provided information that did not overlap (such as examination of different outcomes).

Intervention - Inclusion Criteria:

- The intervention studied was I-131 remnant ablation (first I-131 treatment after thyroidectomy, given to patients with no known residual gross disease and no known distant metastases). Fixed doses or dosimetry could be included. Ablation must have been performed within one year of either total-, sub-total, or near-total thyroidectomy or completion procedure).

Intervention - Exclusion Criteria:

- Studies of patients pre-treated with recombinant (or other form of) thyrotropin (TSH), lithium, or retinoids.

- Studies focussing on use of external beam radiation therapy (EBRT) compared to or in combination with I-131 ablation. If a subgroup that received EBRT was described in any study, that subgroup would be excluded, if possible.

Outcomes - Inclusion Criteria:

- Studies must have provided information on one (or more) of the following outcomes:
 - Cause-specific mortality
 - Any recurrence of disease
 - Loco-regional recurrence in the neck, or lymph nodes of the neck or upper mediastinum
 - Distant metastases
- Secondary malignancies (such as leukemia) or side effects of I-131 therapy or quality of life measurements were not an outcome for analysis but would be noted if mentioned.

Outcomes - Exclusion Criteria:

- Abnormal thyroglobulin measurements in absence of any clinical, radiologic, or biopsy-proven recurrence were not considered an outcome (i.e., thyroglobulin positive/ scan-negative disease).
- I-131 diagnostic scan within one year following ablation showing persistent uptake in the neck (incomplete ablation) was not considered an outcome, whereas new uptake in the neck (following previously negative scan) was considered an outcome (recurrence after complete ablation). Thus, studies focussing only on results of diagnostic scans within the first year of therapy following ablation were excluded (since they focus on successful ablation rates, not long-term outcomes).
- Studies examining only the outcome of total mortality.

Methodology - Inclusion Criteria:

- Since randomized controlled trials examining long-term outcomes of I-131 remnant ablation were not available, studies were selected where patients who received, or who did not receive, the intervention could be compared statistically (prospective comparative cohort studies, case series containing a control group).
- In the absence of prospective comparative cohort studies, studies were included only if a multivariable model predicting disease recurrence or mortality was constructed and I-131 ablation was entered into this model, the effect of I-131 on outcome within the model could be recorded. In the case of a conditional multivariable model, if I-131 ablation was examined a priori in a univariate analysis, was found not to be significant, and was not entered into the model (based on the lack of significance), the result of the univariate analysis could be recorded. The multivariable model would incorporate prognostic indicators and/or co-interventions for papillary and/or follicular thyroid cancer.

Methodology - Exclusion Criteria:

- Case-control studies, case series (without a control group), case reports, or narrative reviews (without a search history or that do not provide previously unpublished cohort data) were excluded. Outcomes unadjusted for any prognostic factors or co-interventions were excluded.

Synthesizing the Evidence

Data were abstracted from multivariable analyses examining the association of treatment with radioiodine (or in which an a priori multivariable analysis, incorporating radioactive iodine ablation was planned, depending on significance level in univariate analysis) on either thyroid cancer-specific mortality or recurrence. If, within included papers, multiple sub-group analyses

were provided, and it was not explicitly stated whether all patients had complete surgical resection of all gross tumour, the sub-group analysis pertaining to “low-risk” patients, as defined by the staging system used in each paper, was abstracted for either the pooled or multivariable analyses.

IV. RESULTS

Literature Search Results

Two reviewers independently reviewed 1,504 abstracts and titles obtained through the electronic search (originally performed in the last week of September, 2002) and, of those, 228 full-text papers that were deemed potentially relevant by either reviewer were retrieved. Both reviewers also reviewed another 39 full-text articles retrieved through hand-searching. Thus, a total of 267 unique full-text papers were independently reviewed, and 51 of those studies were deemed relevant by both reviewers (11-61). After excluding studies that met the exclusion criteria or in which overlap of patients was noted, 23 studies were left for inclusion in the systematic review. Only 13 of those studies performed a multivariable analysis examining the treatment effect of radioiodine (or indicated an intention to perform a multivariable analysis when radioactive iodine was used as a variable in a preceding univariate analysis) and were included in the final evidence summary (11,13,15,20,24-26,30,36,43,56,58,61). Of the 13 studies included, seven reported on thyroid cancer-related mortality, six reported on recurrence of thyroid cancer, three reported on loco-regional recurrence of thyroid cancer, and three reported on distant metastatic recurrence.

The electronic search was updated in all listed databases in July 2003 and April 2004, and all retrieved abstracts were reviewed by one reviewer. No new papers meeting all inclusion criteria were found using the updated electronic search.

Outcomes

Thyroid Cancer-Related Mortality

A summary of adjusted analyses examining the outcome of thyroid cancer-related mortality for patients with papillary and follicular thyroid carcinoma is shown in Table 1. The only study to report a statistically significant association between the intervention and thyroid cancer-related mortality was that of Mazzaferri et al (11). In that study, 1,510 patients were followed for a median of 16.6 years, with an unspecified treatment dose of postoperative radioactive iodine (Cox regression model adjusted for time to treatment, age, histology, lymph node metastases, tumour size, local tumour invasion, gender, and surgical extent) (hazard ratio, 0.5; 95% confidence interval [CI], 0.4-0.7). However, the co-intervention of thyroid hormone suppressive therapy was not adjusted for in the model. Moreover, the thyroid cancer-related mortality rate was not clearly stated for the patients included in the Mazzaferri analysis. Statistical power in smaller studies may have been too limited to detect such an association, given relatively low event rates (Table 1). Based on those limited data, the cause-specific mortality rate of well-differentiated thyroid cancer appears to be relatively low, and, although there may be a survival advantage in patients who have undergone postoperative radioactive iodine ablation, that result is not reproducible between studies. The ability to detect such a treatment effect is currently limited by low statistical power due to relatively low event rates, small population sizes studied, and the suboptimal study designs used.

Any Recurrence of Thyroid Cancer

Postoperative radioactive iodine therapy was reported to be associated with a decreased risk of any recurrence in the two largest studies (1,501 and 1,599 patients, respectively) (11,58) as well as a smaller study (187 patients) (26) examining the outcome of any thyroid cancer recurrence using a multivariable Cox proportional hazards or regression model. All adjusted for extent of surgery, with or without adjustment for other prognostic variables and co-interventions (Table 2). Of note, no adjustment for the co-intervention of thyroid hormone suppressive therapy was performed in any of those three analyses. All of the studies that suggested a positive treatment effect for

radioactive iodine had recurrence rates of over 20% with median follow-up periods ranging from 10.6 to 16.6 years. However, a positive association between treatment with radioactive iodine and any recurrence was not observed in three smaller studies (including 177, 273, and 229 patients, respectively) (26,30,56). Of note, the one study in which thyroid hormone suppressive therapy was adjusted for did not show a treatment advantage for radioactive iodine ablation (overall event rate 15%, median follow-up period five years) (30). Overall recurrence rates ranged from 3.9% (in a study of patients with microcarcinoma of the thyroid, often with lymph node metastases) (56) to 23.5% (in the Mazzaferri study, in which patients with distant metastases at presentation were included in the model) (11). Based on those data, it appears that radioactive iodine may be beneficial in decreasing the risk of any recurrence in patients with well-differentiated thyroid cancer. However, the studies with positive analyses may have included patients at high risk (given the relatively high event rates) and moreover, the incremental benefit of radioactive iodine ablation in low-risk patients treated with thyroid hormone suppressive therapy was unclear.

Loco-Regional Recurrence of Thyroid Cancer

Postoperative radioactive iodine ablation was associated with a reduction in the adjusted risk of loco-regional recurrence in three studies of 135, 587, and 382 patients with papillary or follicular thyroid cancer (relative risks [RR], 0.05; 95% CI, 0.005-0.51 in follicular patients (61); RR, 0.29; 95% CI, 0.17-0.51 in papillary patients (13); and RR, 0.4; 95% CI, 0.2 -0.7 in papillary and follicular patients (24)) (Table 3). However, thyroid hormone suppressive therapy was not adjusted for in any of those models. Event rates ranged from 3.6% in follicular cancer patients with completely resected gross disease in a study from Hong Kong (median follow-up period 10.8 years) (61) to 14% in the papillary and follicular patients studied at the University of Toronto (median follow-up period 10.8 years) (24). Based on those data from only two centres, it appears that radioactive iodine ablation may be beneficial in decreasing loco-regional recurrence of papillary and follicular thyroid cancer, but the incremental benefit of this intervention in addition to thyroid hormone suppression is unclear.

Distant Metastatic Recurrence of Thyroid Cancer

Postoperative radioactive iodine therapy was reported to be associated with a reduced risk of distant metastatic recurrence in patients with papillary or follicular thyroid cancer in the largest study from Mazzaferri et al (1,510 patients included in the analysis, event rate 7.5% in all). Those with distant metastases at time of diagnosis were included in the analysis, (median follow-up 16.6 years) with a hazard ratio of 0.6 (95% CI, 0.5-0.8; $p=0.002$) in those ablated after adjustment in a Cox regression model for age, follicular histology, lymph node metastases, tumour size, local tumour invasion, gender, extent of surgery, and "treatment with radioiodine (presumably for residual disease) (Table 4) (11). In a study of 587 patients with papillary carcinoma from Hong Kong (median follow-up period 9.2 years), radioactive iodine ablation was also associated with a decrease in distant metastases after adjustment for age, gender, tumour size, multicentric disease, extrathyroidal extension, lymph node metastases, distant metastases at presentation, postsurgical loco-regional residual disease, and extent of surgery (relative risk in a Cox regression model 0.2 95% CI, 0.07-0.64; $p=0.006$) (13). The Hong Kong group, however, did not detect a benefit in decreasing distant metastatic recurrence in 135 patients with follicular thyroid cancer (61). The 10-year event rates were 1.6% (papillary) (13) and 9% (follicular) (61) in the respective Hong Kong studies and 7.5% in the Mazzaferri study (11). None of those studies adjusted for thyroid hormone suppressive therapy in their multivariable analyses. Thus, the event rates for distant metastatic disease are relatively low for well-differentiated thyroid cancer, but there may be some benefit for radioactive iodine ablation therapy, based on data from a small number of centres.

Table 1. Thyroid cancer-related mortality.

Study (Type of Analysis) (Ref)	Number of Patients in Model (% events if given)	Patients Treated with Radioiodine Ablation	Histology	Median Follow-up (Years)	Prognostic Variables Adjusted for in Model	Co-interventions Adjusted For in Model	Effectiveness of Radioiodine Ablation
Ohio State, USAF 2001* (MCR) (11)	1510 § (unclear)	Unclear	Papillary, Follicular	16.6	Time to treatment, age, follicular histology, lymph node mets, tumour size, local tumour invasion, gender	Surgery more extensive than lobectomy	Hazard Ratio for radioiodine ablation: 0.5 (95% CI, 0.4-0.7); p<0.0001
Liverpool 1994* (Univariate, Chi- Square, multivariable model if significant) (36)	249 (15.3%)	81 (ablation), 75 (therapy of residual or recurrent disease)	Papillary, Follicular	8.7	None	None	NS
UCSF 1997† (CPH) (25)	187 (7% at 10 years)	305	Papillary, Follicular, Hurthle Cell	10.6	None	Extent of surgery, other modalities (external radiation, immunotherapy, chemotherapy)	Risk Ratio (No radioiodine compared to radioiodine): 1.1 (95% CI, 0.5-2.3); P=0.76
Hong Kong (Follicular) 2002‡ (MCR) (61)	135 (1.9% at 10 years)	123 §	Follicular	10.8	Age, gender, tumour size, extrathyroidal extension, lymph node mets, distant mets at presentation, postsurgical loco- regional disease	Type of thyroid surgery	NS
Hong Kong (Papillary) 2002‡ (MCR) (13)	587 (1.3% at 10 years)	444	Papillary	9.2	Age, gender, tumour size, multicentric disease, extrathyroidal extension, lymph node mets, distant mets at presentation, and postsurgical loco-regional residual disease	Type of thyroid surgery	NS
U of Toronto 1998 (CPH) (24)	382 (7% at 10 years for papillary and 15% at 10 years for follicular)	222	Papillary, Follicular	10.8	Age> 60 Years, tumour size>4 cm, poor differentiation, postoperative residuum, metastatic disease at presentation	Total compared to subtotal thyroidectomy, external beam radiation therapy	Relative risk of radioiodine compared to no radioiodine: 0.7 (95% CI, 0.4-1.4); P=0.34
Illinois Cancer Registry 1990 (CPH) (43)	2,282 (not given)	1,278	Papillary, Follicular	6.5	Age, stage (AJC – TNM staging), race, sex	Postoperative thyroid hormone	Relative odds ratio of total or thyroid cancer-related survival in patients not treated with radioiodine to those treated with radioiodine: 1.54 (95% CI, 1.01-2.35); P=0.05

NOTES: AJCC = American Joint Committee on Cancer; CI = confidence interval; CPH = Cox proportional hazards; MCR = multivariable Cox regression; mets = metastases; NS = not significant (p>0.05); Ref = reference; U = University; USAF = United States Air Force; UCSF = University of California, San Francisco.

* Excluded patients with distant metastases at presentation from analysis

† Includes only patients with primary tumours larger than 1 cm

‡ Excluded patients with distant metastases, no gross nor microscopic residual disease after thyroid surgery

§ Information obtained from author

Table 2. Any recurrence of thyroid cancer.

Study (Type of Analysis) (Ref)	Number of Patients in Model (% events if given)	Patients Treated with Radioiodine Ablation	Histology	Median Follow-up Period (Years)	Prognostic Variables Adjusted for in Model	Co-interventions Adjusted For in Model	Effectiveness of Radioiodine Ablation
Ohio State, USAF 2001* (Multivariable Cox Regression) (11)	1510 ‡ (23.5% for 1528 pts, including pts with distant metastases)	Unclear	Papillary, Follicular	16.6	Age, follicular histology, tumour size, local tumour invasion	Surgery more extensive than lobectomy, therapy with I131 for residual disease	Hazard Ratio: 0.8 (95% CI, 0.7-0.97); P=0.016 (In patients with completely resected disease)
Gunderson/Lutheran 1997 (Multivariable Logistic Regression) (26)	177 (13% of papillary, 8% of follicular, 7% of Hurthle cell)	"Frequently"	Papillary, Follicular, Hurthle Cell	7.2	Age, tumour size, presence of cervical lymph node metastases, local neck invasion, gender	Operation less extensive than near-total thyroidectomy	NS
Gustave-Roussy (France) 1998*† (Multivariable Logistic Regression) (56)	273 (3.9%)	117	Papillary, Follicular	7.3	Previous external radiation therapy, gender, mode diagnosis (incidental), neck lymph node metastases, histology, extrathyroidal and extranodal extent, multifocality, uni- or bilaterality, vascular invasion	Extent of surgery (total thyroidectomy compared to lobectomy or isthmectomy), lymph node dissection	NS
UCSF 1997† (Cox Proportional Hazards Model) (25)	187 (20.5%)	305‡	Papillary, Follicular, Hurthle Cell	10.6	None	Extent of surgery, other modalities (external radiation, immunotherapy, chemotherapy)	Risk Ratio (No Radioiodine compared to Radioiodine): 2.1 (95% CI, 1.5-3.1); p=0.0001
MD Anderson 1992 (Multivariable Cox Regression) (58)	1599 (23%)	447	Papillary, Follicular, Hurthle Cell	11	Gender, pathology, extent of disease, age	Surgery, external radiotherapy	"The most significant single factor was radioiodine treatment (p<0.001)."
Mexico 1996 (Cox Proportional Hazards Model) (30)	229 (15% at 10 years)	149	Papillary, Follicular	5	Sex, age, extent and size of tumour, nodal metastases, coexistence benign thyroid nodules or thyroiditis, presence Hurthle cells or tall cells, ploidy	Type of surgical resection, thyroid hormone suppression	NS

NOTES: CI = confidence interval; NS = not significant (p>0.05); pts. = patients; Ref = reference; USAF = United States Air Force; UCSF = University of California, San Francisco.

*Excluded patients with distant metastases at presentation from analysis

†Primary tumour ≤ 1cm in diameter

‡Information obtained from authors

Table 3. Loco-regional recurrence of thyroid cancer.

Study (Type of Analysis) (Ref)	Number of Patients in Model (% events if given)	Patients Treated with Radioiodine Ablation	Histology	Median Follow-up (Years)	Prognostic Variables Adjusted for in Model	Co-interventions Adjusted For in Model	Effectiveness of Radioiodine Ablation
Hong Kong (Follicular) 2002* (Multivariable Cox Regression) (61)	135 (3.6% at 10 years)	123 †	Follicular	10.8 (provided for a larger group of 215 patients)	Age, gender, tumour size, extrathyroidal extension, lymph node metastases, distant metastases at presentation, postsurgical loco-regional disease	Type of thyroid surgery	Relative Risk 0.05 (95% CI, 0.005-0.51); p=0.01
Hong Kong (Papillary) 2002* (Multivariable Cox Regression) (13)	587 (7.4% at 10 years)	444	Papillary	9.2	Age, gender, tumour size, multicentric disease, extrathyroidal extension, lymph node metastases, distant metastases at presentation, and postsurgical loco-regional residual disease	Type of thyroid surgery	Relative Risk comparing radioiodine ablation to no ablation: RR 0.29 (95% CI, 0.17-0.51); p<0.001
U of Toronto 1998 (Cox Proportional Hazards Model) (24)	382 (14% at 10 years for papillary and 44% at 10 years for follicular)	222	Papillary, Follicular	10.8	Age>60 Years, tumour size>4 cm, poor differentiation, postoperative residuum, metastatic disease at presentation	Total compared to subtotal thyroidectomy, external beam radiation therapy	Relative Risk of radioiodine compared to no radioiodine: 0.4 (95% CI, 0.2-0.7); p=0.002

NOTES: CI = confidence interval; NS = not significant (p>0.05); Ref = reference; U = University.

*Excluded patients with distant metastases, no gross nor microscopic residual disease after thyroid surgery

†Information obtained from author

Table 4. Distant metastatic recurrence of thyroid cancer.

Study (Type of Analysis) (Ref)	Number of Patients in Model (% events if given)	Patients Treated with Radioiodine Ablation	Histology	Median Follow-up (Years)	Prognostic Variables Adjusted for in Model	Co-interventions Adjusted For in Model	Effectiveness of Radioiodine Ablation
Ohio State, USAF 2001* (Multivariable Cox Regression) (11)	1510 ‡ (7.5% of 1528 patients, including those with distant metastases at diagnosis)	Unclear	Papillary, Follicular	16.6	Age, follicular histology, lymph node metastases, tumour size, local tumour invasion, gender	Surgery more extensive than lobectomy, therapy with I-131 (presumably for residual disease)	Hazard Ratio: 0.6 (95% CI, 0.5-0.8); p=0.002
Hong Kong (Follicular) 2002† (Multivariable Cox Regression) (61)	135 (9% at 10 years)	123	Follicular	10.8	Age, gender, tumour size, extrathyroidal extension, lymph node metastases, distant metastases at presentation, postsurgical loco-regional disease	Type of thyroid surgery	NS
Hong Kong (Papillary) 2002† (Multivariable Cox Regression) (13)	587 (1.6% at 10 years)	444	Papillary	9.2	Age, gender, tumour size, multicentric disease, extrathyroidal extension, lymph node metastases, distant metastases at presentation, and postsurgical loco-regional residual disease	Type of thyroid surgery	Relative Risk comparing radioiodine ablation to no ablation: 0.2 (95% CI, 0.07-0.64); p=0.006

NOTES: CI = confidence interval; NS = not significant (p>0.05); Ref = reference; USAF = United States Air Force;

* Excluded patients with distant metastases at presentation from analysis

† Excluded patients with distant metastases, no gross nor microscopic residual disease after thyroid surgery

‡ Information obtained from author

V. INTERPRETIVE SUMMARY

There are no long-term randomized controlled trials examining the effectiveness of radioactive iodine remnant ablation in decreasing well-differentiated thyroid cancer-related mortality or recurrence. The body of current observational evidence suggests that this intervention is associated with, and therefore may decrease the risk of, any recurrence, locoregional recurrence, or distant metastases, as well as possibly thyroid cancer-related mortality for well-differentiated thyroid cancer. However, results are inconsistent across a relatively small number of centres and are not always consistent between papillary and follicular histologies (the former representing the majority of patients studied). The current body of observational evidence has not adequately adjusted for thyroid hormone suppressive co-therapy, and the incremental benefit of radioiodine ablation with such therapy is unclear.

VI. ONGOING TRIALS

The Therapeutic Radiopharmaceutical Guidelines Group was not aware of any ongoing long-term randomized controlled trials examining the efficacy or effectiveness of radioactive iodine ablation in decreasing mortality or recurrence in papillary or follicular thyroid cancer. The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of ongoing trials but none were located.

VII. DISCUSSION

An initial draft report was reviewed and discussed during a teleconference with the entire Therapeutic Radiopharmaceutical Guidelines Group in October 2003. The group was in agreement that the data did not allow for the development of treatment recommendations on the role of I-131 remnant ablation for papillary or follicular thyroid cancer.

The Group acknowledged, however, that, although there is much variation in practice, ablation is commonly offered to patients in Canada belonging to the target population defined in this evidence summary. Members of the Group also discussed characteristics of a low-risk group where it might be reasonable to defer ablation with I-131. The group decided to add this information to the section entitled *Treatment Considerations*.

The Group also discussed the role of recombinant thyrotropin in remnant ablation. The members decided that the evidence is too premature to recommend routine pre-treatment with recombinant thyrotropin prior to ablation at this point, although recommendations may be devised at a later date with the publication of additional information.

VIII. TREATMENT CONSIDERATIONS

- In practice at many Canadian institutions, patients are administered I-131 following total-, near-total, or sub-total thyroidectomy. I-131 is given after a period of thyroid hormone withdrawal.
- In patients with good prognosis (typically defined as: age <45 years, with unifocal tumour <1.5 cm, no vascular invasion, no tall cell, pink cell or insular variant component, clear resection margins, and no regional nodal involvement), I-131 remnant ablation may not be required. Nevertheless, long-term follow-up is still indicated in this patient group.
- In patients who do not meet the good prognostic criteria, I-131 ablation is a reasonable therapeutic option.

IX. IMPLICATIONS FOR POLICY

This document was included on the agenda of the March 30, 2004 meeting of the Policy Advisory Committee. While the effect on cancer-related mortality is less clear, I-131 ablation appears to be associated with reduction in disease recurrence, both distant and locoregional, and I-131 ablation post-thyroidectomy is common practice within Ontario. Currently, in Ontario,

funding for I-131 ablation is borne within the global nuclear medicine or radiation therapy budgets of hospitals treating patients for thyroid cancer. An increasing incidence of thyroid cancer and increasing diagnostic budgetary demands for nuclear medicine in particular are limiting access to thyroid ablation for that group of patients. To address this growing need, and recognizing the potential benefits of I-131 ablation, it is proposed that funding for I-131 through the Ontario New Drug Funding Program (NDFP) be provided for patients who meet the criteria as outlined in the *Target Population* and *Treatment Considerations* sections of this evidence summary.

After review of this evidence summary, the Policy Advisory Committee concluded that I-131 should not be reimbursed through the NDFP, based on the fact that it is an older agent that has been used for many years and paid for through hospital budgets.

X. EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT

Based on the evidence reviewed, the Therapeutic Radiopharmaceutical Guidelines Group drafted the following opinions:

Target Population

This evidence summary applies to adult patients with papillary or follicular thyroid carcinoma (well-differentiated) who have undergone total-, near-total-, or sub-total thyroidectomy (surgery more extensive than resection of the affected lobe and isthmus) with gross complete resection of disease. This evidence summary does not apply to patients with medullary, anaplastic, thyroglossal duct, or familial thyroid carcinoma or to patients with a history of therapeutic radiation exposure prior to diagnosis of thyroid cancer. This evidence summary also does not apply to patients with concurrent thyrotoxicosis, pregnancy, or renal failure.

Draft Opinions

The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Therapeutic Radiopharmaceutical Guidelines Group offers the following opinions based on the evidence reviewed:

- There are no long-term randomized controlled trials examining the effectiveness of radioactive iodine remnant ablation in decreasing well-differentiated thyroid-cancer related mortality or recurrence.
- The body of current observational evidence suggests that this intervention may be associated with a reduced risk of recurrence of thyroid cancer in terms of any recurrence or locoregional recurrence, or distant metastases, as well as possibly thyroid-cancer related mortality for well-differentiated thyroid cancer. However, results are inconsistent across a relatively small number of centres and not always consistent between papillary and follicular histologies (the former representing the majority of patients studied). Of note, the current body of observational evidence has not adequately adjusted for thyroid hormone suppressive co-therapy and the incremental benefit of radioiodine ablation with such therapy is unclear. Furthermore, some studies were underpowered to detect a survival benefit given low mortality rates.
- For patients with well-differentiated thyroid cancer who do not fall into the “good prognosis” category (age <45 years, with unifocal tumour <1.5 cm, no vascular invasion, no tall cell, pink cell or insular variant component, clear resection margins and no regional nodal involvement) I-131 ablation post-thyroidectomy with the intent of decreasing disease recurrence is a reasonable therapeutic option. Clinicians should discuss the risks and potential benefits of this intervention, including the relative uncertainty of the existing observational evidence, with patients when considering such therapy and treatment must be individualized.

Practitioner Feedback

A draft version of this report was reviewed by Ontario practitioners. Any changes made to the report as a result of practitioner feedback are described in the “Modifications” section below.

Methods

Practitioner feedback was obtained through a mailed survey of 113 practitioners in Ontario (30 radiation oncologists, 13 medical oncologists, 61 surgeons and 9 nuclear medicine physicians). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on May 25, 2004. Follow up reminders were sent out at two weeks (postcard) and four weeks (complete package mailed again). The Therapeutic Radiopharmaceutical Guidelines Group reviewed the results of the survey.

Results

Sixty-three responses were received out of the 113 surveys sent (56% response rate). Responses included completed surveys as well as phone, fax and email responses. Of the practitioners who responded, 38 indicated that the report was relevant to their clinical practice and completed the survey. Results of the practitioner feedback survey are summarized in Table 5.

Table 5. Results of the practitioner feedback survey.

Item	Number (%)		
	Rated “strongly agree” or “agree”	Rated “neither agree nor disagree”	Rated “disagree” or “strongly disagree”
The rationale for developing an evidence summary, as stated in the “Choice of Topic” section of the report, is clear.	38 (100)	0 (0)	0 (0)
There is a need for an evidence summary on this topic.	37 (97)	1 (3)	0 (0)
The literature search is relevant and complete.	35 (92)	2 (5)	1 (3)
I agree with the methodology used to summarize the evidence.*	36 (95)	1 (3)	1 (3)
I agree with the overall interpretation of the evidence.†	37 (97)	0 (0)	0 (0)
The <i>Opinions of the Disease Site Group</i> section of this evidence summary is useful.*	34 (90)	3 (8)	1 (3)
An evidence summary of this type will be useful for clinical decision making.*	34 (90)	4 (11)	0 (0)
At present, there is insufficient evidence to develop a practice guideline on this topic.	20 (53)	7 (18)	11 (29)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.*‡	31 (82)	4 (11)	1 (3)
How likely would you be to use I-131 in your practice?	Rated “likely” or “very likely”	Rated “unsure”	Rated “not at all likely” or “unlikely”
	1 (3)	2 (5)	35 (92)

*Numbers do not add to 100% because of rounding.

†One practitioner did not respond to this question.

‡Two practitioners did not respond to this question.

Summary of Written Comments

Thirteen respondents provided written comments. The main points contained in the written comments were:

1. Studies with less than 10 years of follow-up show no difference. Studies with mixed groups of patients and small numbers show no difference. The disease is well known to be slowly progressive; one has to look at 20 year follow-up often to get some idea of recurrences. Therefore, studies with short-term follow-up (i.e., <10 years) are less helpful.
2. The evidence suggests that high-risk patients (i.e., high-grade, extra thyroidal extension and advanced age) likely benefit, but low-risk patients do not and should not be treated.
3. Other issues that should be looked at include: the efficacy of TSH suppressive therapy and the extent of surgery in low-risk patients.
4. The inclusion of patients studied should be only those who have had complete 'macroscopic disease clearance' as stipulated in your methodology. However, patients who had 'near-total' or subtotal thyroidectomy were included in the analysis—this seems to contradict the methodology described.
5. Patients in the best prognostic category, particularly those surviving more than 10 years (when reoccurrence can occur) are being frightened when they are clinically clear, by mild elevations in serum thyroglobulin titres and borderline uptakes (with or without thyrogen). The objective is to provide evidence that will help clinical judgement.
6. It would be helpful to have some input on this document from internationally known thyroidologists. There is not enough coverage of the European literature.
7. There are several problems with this topic as it relates to practice guidelines.
 - a) I-131 is delivered by non-oncologists—endocrinologists and nuclear medicine physicians who have an enormous stake in it. Unless there is a fundamental change in their thinking, practice will not change.
 - b) I-131 is a patient-driven treatment in many cases.
 - c) The role of total thyroidectomy as opposed to hemithyroid in low-risk patients—if I-131 remnant ablation is not effective.
 - d) The importance of patient monitoring of thyroglobulin levels.
 - e) These guidelines are not helpful in that they fail to address the prime question—should we give I-131 for low-risk patients? We will all give it for high-risk patients regardless of level of evidence since randomized controlled trials are not going to happen!

Modifications/Actions

It is important to note that the evidence summary was based solely on published observational data as long-term randomized controlled trial data does not exist to answer whether remnant ablation is beneficial in the treatment of patients with well-differentiated thyroid cancer. As the data collected was observational, this data was summarized in an evidence summary report and opinions of practitioners in the field were gathered, to reflect opinions of experts as well as current practices. In the absence of randomized controlled trial data, this report cannot be truly deemed a guideline. Specific questions and recommendations of practitioners are addressed below:

1. We agree that 20-year follow-up would be of interest but given that the median follow-up of all included studies ranged from five to 16.6 years (as listed in Table 4), a meaningful estimate of 20-year cancer-related outcomes is not possible based on the available data. Most patients in published series have not been followed 20 years or longer.
2. This evidence was restricted to relatively low-risk patients undergoing remnant ablation. A separate review of high-risk patients, particularly those with residual or distant metastatic disease would be needed to address the effectiveness of I-131 in the treatment of such individuals. The following sentence will be added to the *Draft Opinions*

section of the Evidence summary, *“Foregoing remnant ablation in low-risk patients is also an acceptable practice, particularly if patients are aware of the potential risk of recurrence.”* This statement reflects the uncertainty of benefit in low-risk patients as reflected by the practitioner’s comment.

3. We agree with the practitioner that the benefits of TSH suppressive therapy and the extent of surgery in low-risk patients are also important topics for future evidence summaries or practice guidelines by other disease site groups. These issues are not covered here as this evidence summary was produced by the radiopharmaceutical guidelines group, and, therefore, only the topic of I-131 ablation was covered.
4. The practitioner has expressed a concern that patients who have undergone “near-total” or “subtotal” thyroidectomy may have residual macroscopic disease. We have taken great effort in excluding groups of patients with residual macroscopic disease in this review as the topic is remnant ablation (which is defined by lack of residual macroscopic disease). We suspect the practitioner may be referring to the potential for microscopic disease in patients with “near-total” or “subtotal” thyroidectomy, and, frankly, the aim of ablation is to try to eliminate such microscopic disease.
5. We appreciate the clinical input from this practitioner, reflecting current issues in management of thyroid cancer. Of note, we reviewed only clinically relevant outcomes and did not consider thyroglobulin positivity in the absence of clinical recurrence as a reasonable outcome for review. We agree that the clinical importance of biochemically positive recurrence in the absence of clinical recurrence is questionable in importance.
6. The reviewer has commented that he/she feels that we have quoted insufficient European literature (German/French). It is important to note that our search was restricted to only the English language, and we have added that point to the Methods section. Given that the search was restricted to the English language, it is possible that relevant papers in other languages may have been missed. The reviewer has suggested sending our data to an expert such as Drs. Mazzaferri or Langsteger. In fact, we published the data collected in this review (as well as supplemental exploratory pooled analyses) in the *Journal of Clinical Endocrinology and Metabolism* (2004, volume 89, issue 8, pages 3668-3676) and Dr. Mazzaferri has written an editorial on the paper in the same issue of the journal (pages 3662-3664). A second editorial on the paper was written by Dr. Haugen in the same issue of the journal (pages 3665-3667). Thus, our work has been scrutinized not only by the journal peer review process but also by two prominent thyroidologists specializing in care of thyroid cancer patients.
7. The reviewer has concerns about the topic as relating to the implementation of practice guidelines in this clinical area. We again highlight that, given the lack of long-term randomized trial data, we have not provided a strict guideline but instead an evidence summary incorporating some opinions from the Therapeutic Radiopharmaceutical Guidelines Group. We agree that issues such as beliefs expressed by stakeholders or patients as well as the quality of available evidence and risk profile of the individual patient must be balanced in determining the appropriateness of remnant ablation on a case-by-case basis. We agree that monitoring of thyroglobulin levels is generally considered important in the care of patients with well-differentiated thyroid cancer but it was not the objective of this evidence summary to systematically examine the effectiveness of programs of follow-up testing. The reviewer has commented that it is still unclear whether I-131 should be given to low-risk patients. We agree that the current body of observational evidence does not definitively answer this question, and only a long-term randomized trial can clarify this issue. By highlighting the deficiencies of currently available observational evidence, we have made the first step in defining the need for a randomized controlled trial.

Final Approval Process

The final evidence summary was reviewed by one member of the PEBC Guideline Approval body and was approved without further modification.

XI. OPINIONS OF THE THERAPEUTIC RADIOPHARMACEUTICALS GUIDELINE GROUP

The lack of sufficient high-quality evidence precludes definitive recommendations from being made. Instead, the Therapeutic Radiopharmaceutical Guidelines Group offers the following opinions based on the evidence reviewed. The opinions reflect the integration of the draft opinions with feedback obtained from the external review process.

- There are no long-term randomized controlled trials examining the effectiveness of radioactive iodine remnant ablation in decreasing well-differentiated thyroid cancer-related mortality or recurrence.
- The body of current observational evidence suggests that this intervention may be associated with a reduced risk of recurrence of thyroid cancer in terms of any recurrence or locoregional recurrence, or distant metastases, as well as possibly thyroid-cancer related mortality for well-differentiated thyroid cancer. However, results are inconsistent among a relatively small number of centres and not always consistent between papillary and follicular histologies (the former representing the majority of patients studied). Of note, the current body of observational evidence has not adequately adjusted for thyroid hormone suppressive co-therapy and the incremental benefit of radioiodine ablation with such therapy is unclear. Furthermore, some studies were underpowered to detect a survival benefit, given low mortality rates.
- For patients with well differentiated thyroid cancer who do not fall into the “good prognosis” category (age <45 years, with unifocal tumour <1.5 cm, no vascular invasion, no tall cell, pink cell or insular variant component, clear resection margins and no regional nodal involvement) I-131 ablation post-thyroidectomy with the intent of decreasing disease recurrence is a reasonable therapeutic option. Clinicians should discuss the risks and potential benefits of this intervention, including the relative uncertainty of the existing observational evidence, with patients when considering such therapy and treatment must be individualized. Foregoing remnant ablation in low-risk patients is also an acceptable practice, particularly if patients are aware of the potential risk of recurrence.

XII. CONFLICTS OF INTEREST

The members of the Therapeutic Radiopharmaceuticals Guideline Group disclosed potential conflicts of interest relating to the topic of this evidence summary. No potential conflicts were declared.

XIII. JOURNAL REFERENCE

This document will not be published in journal format; however, it is available on the CCO Web site at <http://www.cancercare.on.ca>.

XII. ACKNOWLEDGEMENTS

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For a complete list of the Therapeutic Radiopharmaceuticals Guidelines Group, please visit the CCO Web site at: <http://www.cancercare.on.ca>.

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Education and Information