A Systematic Review of Adjuvant Interventions for Radioiodine in Patients with Thyroid Cancer

Gangzhu Xu¹, Tao Wu¹, Liqiao Ge², Wen Li²

¹Department of Surgery, First Affiliated Hospital of Xi’an Medical University, Xi’an, China; ²Department of Otorhinolaryngology, First Affiliated Hospital of Xi’an Medical University, Xi’an, China

Introduction
Thyroid cancer is the most common endocrine cancer, and its incidence has increased continuously in recent decades [1]. The principal standard treatment for thyroid cancer includes total or near-total thyroidectomy, when appropriate followed by radioiodine-131 (¹³¹I) post-surgical thyroid remnant ablation, and lifelong thyroid hormone-suppressive therapy [2]. Despite an excellent prognosis and recent advances in radioiodine therapy for thyroid cancer, the risk-benefit balance of radioiodine therapy remains unclear in many thyroid cancer patients.

Therefore, additional studies are required to improve thyroid remnant ablation in patients with thyroid cancer. Much effort has been made to optimize radioiodine therapy. Accordingly, we performed a systematic review of all relevant randomized controlled trials (RCTs) in the literature to estimate the effectiveness of adjuvant interventions for radioiodine therapy in patients with thyroid cancer.

Materials and Methods
Search Strategy and Selection Criteria
We systematically searched EMBASE and MEDLINE through Ovid SP, PubMed, and the Cochrane Central Register of Controlled Trials without language or year restriction, on July 9, 2014. The following search terms were used: ‘thyroid cancer’, ‘radioiodine AND ablation’, ‘combined OR adjuvant’, ‘neoadjuvant combined modality therapy’, and ‘pharmaceutic’. The reference lists of all eligible studies and relevant reviews were manually searched to retrieve any relevant articles missed by the electronic searches. Studies were included if they were RCTs in which patients with thyroid cancer had undergone total or near-total thyroidectomy as an initial treatment and had radioiodine ablation after surgery. In addition, the trials were required to include another adjuvant treatment. We excluded non-randomized studies and randomized studies that were only presented at meetings and have not been published as full text.

Keywords
Thyroid cancer · Radiation therapy, adjuvant

Summary
Aims: The purpose of this study was to assess the effects of adjuvant interventions for radioiodine in patients with thyroid cancer. Materials and Methods: A systematic search was undertaken on July 9, 2014. RevMan 5 software was used to synthesize data. Results: 13 randomized controlled trials were included. The pooled risk ratio of 0.99 (95% confidence interval (CI): 0.96–1.02, p = 0.58) indicated no significant difference in successful thyroid remnant ablation between recombinant human thyroid-stimulating hormone (rhTSH) and thyroid hormone withdrawal in 7 trials. The percentage of patients who had successful ablation was significantly higher in the oral-lithium group than in the control group (p = 0.017). A computerized decision aid improves informed decision-making in patients with early-stage papillary thyroid cancer (PTC) who are considering adjuvant radioiodine treatment (p < 0.001). Amifostine pretreatment did not prevent parenchymal damage to the major salivary gland function after radioiodine treatment (p = 0.2461).

Conclusions: The present systematic review suggests that rhTSH, lithium, and computerized decision aids maybe act as beneficial adjuvant interventions for radioiodine in patients with thyroid cancer; however, amifostine does not exhibit helpful effects in thyroid cancer patients treated with radioiodine.

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Data Extraction
Data were extracted and cross-checked independently by T.W. and W.L. by means of a standard data extraction form. Any discrepancies during data extraction were resolved by consensus, with the involvement of a third investigator (L.G.) if necessary.

Study Quality Assessment
The risk of bias of the included studies was assessed by G.X. and T.W. independently by using the Cochrane risk of bias tool. Disagreements were resolved by consensus, with the involvement of a third party (L.G.) if necessary.

Outcome Measures
The primary outcome of this study was the successful ablation rate and mortality between intervention and control groups. The secondary outcomes were quality of life (QoL), radiation exposure of blood and bone marrow, effects on organs including the salivary glands and the gastrointestinal and hematopoietic systems, and psychological satisfaction.

Statistical Analysis
Dichotomous data are expressed as risk ratios with 95% confidence intervals (CIs). Continuous data were analyzed using weighted mean differences with 95% CIs. Summary statistics were calculated by the Mantel-Haenszel method for fixed effects using RevMan 5 software as supplied by the Cochrane Collaboration. Heterogeneity was examined according to the I² statistic alongside the χ² test; if I² was greater than 50%, the random-effects model was applied. A funnel plot was used to detect potential publication bias.

Results
Search Results
A total of 690 records were identified from the search process. A total of 45 full-text articles were retrieved. Ultimately, 13 trials meeting the inclusion criteria were included in the review (fig. 1, table 1).

Table 1. Characteristics of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Participants</th>
<th>Interventions and grouping</th>
<th>Outcomes</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacini et al. 2006</td>
<td>Europe and North America</td>
<td>DTC</td>
<td>I: rhTSH (n = 33); C: THW (n = 30)</td>
<td>ablation rate, QoL, cost-effectiveness</td>
<td>8 months</td>
</tr>
<tr>
<td>Pilli et al. 2007</td>
<td>Italy</td>
<td>DTC</td>
<td>(1) rhTSH + 1.850 MBq ¹³¹I (n = 36), (2) rhTSH + 3.700 MBq ¹³¹I (n = 36)</td>
<td>ablation rate</td>
<td>6–8 months</td>
</tr>
<tr>
<td>Vaiano et al. 2007</td>
<td>Italy</td>
<td>DTC</td>
<td>I: rhTSH (n = 17); C: THW (n = 29)</td>
<td>red marrow-absorbed dose, cumulative activity</td>
<td>72 h</td>
</tr>
<tr>
<td>Chianelli et al. 2009</td>
<td>Italy</td>
<td>PTC</td>
<td>I: rhTSH (n = 21); C: THW (n = 21)</td>
<td>ablation rate, TSH, Tg, TgAb</td>
<td>6–12 months</td>
</tr>
<tr>
<td>Emmanouilidis et al. 2009</td>
<td>Germany</td>
<td>DTC</td>
<td>I: rhTSH (n = 13); C: THW (n = 12)</td>
<td>ablation rate, absolute urinary iodine, Tg, overall time of sick leave</td>
<td>3–12 months</td>
</tr>
<tr>
<td>Taieb et al. 2009</td>
<td>France</td>
<td>DTC</td>
<td>I: rhTSH (n = 37); C: THW (n = 37)</td>
<td>ablation rate, QoL, anxiety and depression scales, Tg, TgAb</td>
<td>9 months</td>
</tr>
<tr>
<td>Lee et al. 2010</td>
<td>Korea</td>
<td>DTC</td>
<td>I: rhTSH (n = 69); C: THW (n = 89)</td>
<td>ablation rate, QoL</td>
<td>12 months</td>
</tr>
<tr>
<td>Schlumberger et al. 2012</td>
<td>France</td>
<td>DTC</td>
<td>(1) rhTSH + 1.1 GBq ¹³¹I (n = 187), (2) rhTSH + 3.7 GBq ¹³¹I (n = 187), (3) THW + 1.1 GBq ¹³¹I (n = 189), (4) THW + 3.7 GBq ¹³¹I (n = 189)</td>
<td>ablation rate, adverse events, QoL</td>
<td>6–10 months</td>
</tr>
<tr>
<td>Mallick et al. 2012</td>
<td>United Kingdom</td>
<td>DTC</td>
<td>(1) 1.1 GBq ¹³¹I + rhTSH (n = 110), (2) 1.1 GBq ¹³¹I + THW (n = 110), (3) 3.7 GBq ¹³¹I + rhTSH (n = 109), (4) 3.7 GBq ¹³¹I + THW (n = 109)</td>
<td>hospitalization days, adverse events, tumor recurrence, QoL, socioeconomic factors</td>
<td>6–9 months</td>
</tr>
<tr>
<td>Bohuslavizki et al. 1998</td>
<td>Germany</td>
<td>DTC</td>
<td>I: 500 mg/m² amifostine (n = 25); C: physiologic saline solution (n = 25)</td>
<td>xerostomia questionnaire, adverse effects, uptake of Tc-99m-pertechnetate in parotid and submandibular glands</td>
<td>3–12 months</td>
</tr>
<tr>
<td>Kim et al. 2008</td>
<td>Korea</td>
<td>DTC</td>
<td>I: 300 mg/m² amifostine (n = 42); C: placebo (n = 38)</td>
<td>xerostomia questionnaire, adverse effects, uptake of Tc-99m-pertechnetate in parotid and submandibular glands</td>
<td>3–12 months</td>
</tr>
<tr>
<td>Sawka et al. 2012</td>
<td>Canada</td>
<td>PTC</td>
<td>I: DA with usual care (n = 37); C: usual care alone (n = 37)</td>
<td>medical knowledge about PTC, radioactive treatment, decisional conflict</td>
<td>6–12 months</td>
</tr>
<tr>
<td>Yamazaki et al. 2012</td>
<td>Brazil</td>
<td>DTC</td>
<td>I: 30 mCi ¹³¹I + lithium (n = 29); C: 30 mCi ¹³¹I (n = 32)</td>
<td>whole-body scan, TSH, Tg, TgAb</td>
<td>12 months</td>
</tr>
</tbody>
</table>

DTC = Differentiated thyroid cancer, PTC = papillary thyroid cancer, I = intervention, C = control, rhTSH = recombinant human thyroid-stimulating hormone, THW = thyroid hormone withdrawal, QoL = quality of life, TSH = thyroid-stimulating hormone, Tg = thyroglobulin, TgAb = thyroid autoantibody, DA = decision aid.
Characteristics of the Included RCTs
The details of the included trials are summarized in table 1. There were 4 types of interventions in these included trials. 8 studies compared recombinant human thyroid-stimulating hormone (rhTSH) with conventional thyroid hormone withdrawal (THW) to stimulate TSH in order to prepare for the ablation of post-surgical thyroid remnants [3–10]. In these, 2 trials were randomized not only to 2 different methods for TSH stimulation (rhTSH or THW), but also to high versus low radioiodine doses [8, 9]. 1 study compared the effects of high and low radioiodine doses under rhTSH [11]. 2 studies investigated the cytoprotective effect of amifostine on the salivary glands in radioiodine-treated differentiated thyroid cancer (DTC) [12, 13]. Another study determined if an oral dose of lithium enhances the effect of radioiodine [14]. Finally, another study examined the impact of a patient-directed computerized decision aid (DA) on the medical knowledge and decisional conflict of patients with papillary thyroid cancer (PTC) considering the choice of receiving adjuvant radioiodine or not [15].

Quality Assessment
In general, the overall methodological quality of the studies was good (fig. 2). Most of the studies comparing rhTSH with THW applied randomization and provided enough data for analysis, but the other 3 types of intervention studies are not suitable for a meta-analysis because of too few studies. Funnel plots were unnecessary due to the low number of studies.

Primary Outcomes
Seven studies indicated a successful ablation rate when comparing rhTSH and THW [3–9]. The pooled risk ratio showed no statistically significant difference in the successful thyroid remnant ablation for rhTSH versus THW (risk ratio = 0.99, 95% CI = 0.96–1.02, p = 0.58; fig. 3). These studies included 3 activity doses: 1.1, 2, and 3.7 GBq. The trial by Pilli et al. [11] compared 2 activity doses (1,850 and 3,700 MBq) under rhTSH stimulation; the results showed no significant difference in the thyroid remnant ablation rate (p = 1.0). 1 study showed significantly different success rates for the follow-up whole-body scan (WBS) between the oral lithium treatment and the control group (p = 0.017) [14]. In addition, no study reported mortality as an outcome criterion.

Secondary Outcomes
Five trials compared health-related QoL between rhTSH and THW. However, the assessment criteria were not uniform, so they could not be combined [4, 6–9]. On the basis of the descriptions of these studies, the QoL of patients undergoing radioiodine remnant ablation was better preserved in the rhTSH group than in the THW group.

Three trials reported the effects on the blood and bone marrow [10, 16, 17]. But the study parameters were not identical in these trials. The dose to the blood was significantly lower in the euthyroid group compared to the hypothyroid group (0.109 ± 0.028 vs. 0.167 ± 0.061 mGy/MBq; p < 0.0001) [16]. The red-marrow doses...
in rhTSH- and THW-treated patients were 0.06 ± 0.02 and 0.09 ± 0.03 mGy/MBq, respectively (p = 0.003) [10]. The absorbed dose estimates were lower in the rhTSH arm for bone marrow (0.07 ± 0.01 vs. 0.06 ± 0.01 mSv/MBq, p = 0.006) [17].

Two trials compared amifostine with placebo regarding the effects of amifostine on DTC patients [12, 13]. Amifostine versus placebo showed no statistically significant differences in the incidence of xerostomia (p = 0.2461). No health-related QoL and other patient-oriented outcomes were evaluated in the 2 trials.

One trial explored the impact of a computerized DA on the medical knowledge and decisional conflict in patients with early-stage PTC considering the choice of being treated with radioactive iodine treatment or not [15]. The results indicate that medical knowledge about the prognosis of early-stage PTC and radioactive iodine treatment was significantly greater in the DA group (mean score: 9.7 ± 0.6) than in the control group (mean score: 7.8 ± 1.3; mean difference: 1.9; 95% CI: 1.4–2.3; p < 0.001). Conflict related to the decision to accept or reject radioactive iodine treatment was significantly lower in the DA group (mean score: 25.2 ± 13.4) than in the control group (mean score: 52.1 ± 21.9; mean difference: 26.8; 95% CI: 18.4–35.3; p < 0.001) [15].

### Discussion

This systematic review examined recent results from RCTs investigating adjuvant interventions for radioactive iodine treatment in patients with thyroid cancer. The results of 7 RCTs suggest that rhTSH is as effective as THW for radioactive iodine remnant ablation. In addition, the success rates improved with an oral dose of lithium. DA improves informed decision-making in patients with early-stage PTC who are considering radioactive iodine treatment. However, amifostine pretreatment did not prevent the parenchymal damage to the major salivary gland function after radioactive iodine treatment.

A Cochrane systematic review [18] of 4 RCTs of rhTSH-aided radioactive iodine treatment for residual or metastatic DTC suggests that rhTSH is as effective as THW with radioactive iodine remnant ablation. The recent systematic review by Tu et al. [19] found that the administration of rhTSH has an ablation rate similar to THW, regardless of whether low- or high-dose iodine-131 is used, and the application of rhTSH can obtain higher QoL during the early period of radioactive iodine treatment. The results regarding the success rates of the different therapies in the present systematic review are in agreement with those of the Cochrane review [18] and Tu et al. [19].

In addition to the above-mentioned 2 reviews, our review includes 2 further RCTs, reported by Pilli et al. [11] and Vaiano et al. [10]. Pilli et al. compared the effects of 2 doses of 131I (1,850 or 3,700 MBq) on DTC patients under the same rhTSH dose [11]. Although the study by Vaiano et al. evaluates rhTSH and THW, the study parameters were the red-marrow absorbed dose and the remnant cumulated activity, but not the ablation rate [10]. So they could not be included in the meta-analysis.

Compared to THW, rhTSH treatment showed significant benefits on the dose absorbed by the blood and blood retention as well as the marrow dose. rhTSH is associated with a longer remnant half-life of radioactive iodine and with reduced radiation exposure of the rest of the body and of the general public who come into contact with the patients [16, 17]. These findings are in accordance with the Cochrane review [18] regarding the exposure of blood and bone marrow to radiation.

The results from the 2 trials suggest that amifostine has no significant radioprotective effects on the salivary glands for patients with DTC treated with radioactive iodine. These findings were also in agreement with those of Ma et al. [20]. The beneficial cytoprotective effect of amifostine might have been obscured by the dose effects of radioactive iodine.

In the present review, besides the above-mentioned studies on THW, rhTSH, and amifostine, our comprehensive search also found other adjuvant interventions for radioactive iodine in patients with thyroid cancer.

With regard to lithium, the present results show that the success rate of remnant ablation by lithium adjuvant treatment is greater than that of radioactive iodine alone. Furthermore, few adverse effects were reported in patients who received lithium. Therefore, lithium can be used as an adjuvant with 30 mCi 131I in patients who have undergone thyroidectomy for low-risk DTC [14].

DAs are instruments used to inform patients about the available healthcare options, including evidence of potential treatment benefits and risks [21]. Sawka et al. [15] developed and pilot-tested a patient-directed computerized DA explaining the choice to accept or reject radioactive iodine treatment for patients with early-stage PTC; as a result, DA improved the medical knowledge and reduced the decisional conflict of patients with early-stage PTC. However, access to the DA did not appear to significantly impact the ultimate radioactive iodine treatment choice.

The present systematic review has several limitations that must be mentioned. First, the included trials used different definitions of successful ablation, possibly inducing comparatively more hetero-

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Fig. 3. Pooled analysis examining successful thyroid remnant ablation.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>rhTSH Events</th>
<th>THW Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Risk Ratio MLE Fixed 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padini 2006</td>
<td>28</td>
<td>28</td>
<td>56</td>
<td>1.00 (0.94, 1.07)</td>
<td>2006</td>
</tr>
<tr>
<td>Talabi 2009</td>
<td>32</td>
<td>36</td>
<td>68</td>
<td>0.92 (0.80, 1.04)</td>
<td>2009</td>
</tr>
<tr>
<td>Chansbili 2009</td>
<td>19</td>
<td>21</td>
<td>40</td>
<td>0.90 (0.80, 1.12)</td>
<td>2009</td>
</tr>
<tr>
<td>Elmaneoufida 2009</td>
<td>10</td>
<td>13</td>
<td>23</td>
<td>1.15 (0.90, 1.49)</td>
<td>2009</td>
</tr>
<tr>
<td>Lee 2010</td>
<td>81</td>
<td>88</td>
<td>169</td>
<td>1.00 (0.90, 1.10)</td>
<td>2010</td>
</tr>
<tr>
<td>Malick 2012</td>
<td>183</td>
<td>210</td>
<td>393</td>
<td>1.00 (0.93, 1.08)</td>
<td>2012</td>
</tr>
<tr>
<td>Burk-Kenfig 2012</td>
<td>319</td>
<td>348</td>
<td>667</td>
<td>0.90 (0.86, 0.95)</td>
<td>2012</td>
</tr>
</tbody>
</table>

Total Events: 672, Total Events: 652, Heterogeneity: CH² = 23.32, df = 8 (p = 0.05), I² = 0%.

Test for overall effect: Z = 2.05 (p = 0.05).

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genity. Second, the quality of the studies varied greatly. This could affect the validity of the present results. Third, heterogeneity may exist because of differences in study interventions, study parameters, and outcome measurements, impeding comparability among studies. Therefore, the results of the present analysis may be inconclusive.

In conclusion, this systematic review of RCTs suggests that rhTSH, lithium, and DAs may act as beneficial adjuvant interventions for radioiodine in patients with thyroid cancer; however, amifostine does not exhibit helpful effects in thyroid cancer patients treated with radioiodine.

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Disclosure Statement

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References