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ORIGINAL RESEARCH

Cost-effectiveness profile, organizational implications and patient preferences on the use of exogenous TSH therapy (Thyrogen®) vs. THW in thyroid residue ablation in Italy

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ABSTRACT

BACKGROUND: Radioiodine ablation is an adjuvant procedure used to treat patients with differentiated thyroid cancer. For ablation to be successful, patients must have elevated levels of thyroid stimulating hormone (TSH). This can be achieved by withholding thyroid hormone therapy (endogenous stimulation), or by administration of recombinant human thyroid stimulating hormone (rhTSH; Thyrogen®; exogenous stimulation) to patients in the euthyroid state.
AIM: To compare the estimated health benefits, cost and cost-effectiveness of TSH stimulation with and without Thyrogen® in the Italian setting.
METHODS: A cost-utility analysis was undertaken to assess the impact of exogenous vs. endogenous TSH stimulation before radioiodine remnant ablation of patients with newly diagnosed, well-differentiated papillary or follicular thyroid cancer who have undergone total or near-total thyroidectomy. A Markov model was developed to simulate treatment costs and health outcomes associated with exogenous and endogenous stimulation in four distinct health states: pre-ablation, ablation, post-ablation, and well/recovery. Treatment was stratified by patients who receive high- and low-activity (30-100 mCi, respectively) in the ablation state. The Italian National Health System perspective was adopted in the base case scenario while the impact of indirect costs was explored in a sensitivity analysis. Costs and quality adjusted life years (QALY) specific to each health state were estimated, summarized and converted into a corresponding incremental cost-effectiveness ratio (ICER).
RESULTS: We calculated a cost effectiveness ratio of 18,357.18 €/QALY gained whereas the inclusion of indirect cost and accident cost produced reductions of the ICER to € 14,609.51 and € 15,515.26 per QALY, respectively. Finally, all results in the sensitivity analysis are below the lower bound of national and international cost- effective threshold.
CONCLUSION: Thyrogen® represents a cost-effective option for patients with differentiated thyroid cancer who underwent total or near-total thyroidectomy in Italy. Our findings are consistent with other cost-utility analyses.

Keywords

Radioiodine ablation; Recombinant human thyroid stimulating hormone; Thyroidectomy

INTRODUCTION

Total, or near-total, thyroidectomy followed by 131I radioiodine ablation represents the gold standard treatment for differentiated thyroid cancer. The main purpose of performing ablation is elimination of normal thyroid cells, which facilitates detection of recurrent disease, by improving sensitivity of diagnostic tests, such as Tg (thyroglobulin) measurements or whole-body RAI (radioiodine) scans. Additional ablation goals are adjuvant therapy, by targeting potential residual disease with improvement of disease-free survival; and therapy, which may

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improve disease-free survival in higher risk patients [1].

Remnant ablation requires elevated thyroid-stimulating hormone (TSH) levels which increase radioiodine uptake by residual tissue and facilitate an effective ablation. TSH elevation can be achieved by discontinuation of thyroxine therapy (thyroid hormone withdrawal, THW) for at least 4-5 weeks or by administration of recombinant human TSH (rhTSH – Thyrogen®). The use of Thyrogen® allows the patient to continue T4 therapy, thus avoiding the consequence of iatrogenic hypothyroidism [2].

The benefits associated with the use of Thyrogen® include avoidance of the symptoms of hypothyroidism, which include fatigue, weakness, constipation, depression, impaired memory and bodily pain. Recently, hypothyroidism has been associated with cognitive and motor impairments that are likely to constitute hazards in the operation of motor vehicles and a public safety risk [3]. Avoidance of hypothyroidism via Thyrogen® therapy has been found to be associated with consequent better health-related quality of life, little or no productivity loss and a reduction in the need for GP visits or medications [4]. In addition, use of Thyrogen® has been shown to allow a shorter duration of the pre-ablative period and a faster radioiodine clearance rate [5,6] with the possibility of less radiation exposure to non-targeted organs and earlier discharge from radioprotective wards [7,8].

More importantly, such benefits are achieved with ablation efficacy comparable with thyroid hormone withdrawal. This was initially demonstrated in an international randomized controlled study showing similar success rates in exogenous- and endogenous-stimulated patients [5]. Furthermore, two phase III studies (HiLo [9] and ESTIMABL [2]) have independently confirmed similar efficacy for the two methods of TSH stimulation across two 131I activity levels (30 or 100 mCi). A meta-analysis performed in 2014 that included 7 randomized controlled trials (RCTs) with a total of 1535 patients came to the same conclusion [10].

In 2012, the use of Thyrogen® has been approved for an 131I dose range of 30-100 mCi for postoperative remnant ablation, instead of the previous approval of just 100 mCi 131I [11]. Due to this change, a pre-existing economic model [12,13] was adapted to compare exogenous TSH therapy (Thyrogen®) with thyroid hormone withdrawal in the Italian setting. Unlike all previous adaptations, including the most recent one in the Korean setting [14], our analysis takes into account both high- (100 mCi) and low-activities (30 mCi) of radioiodine. The aim of this study was to compare the estimated health benefits, cost and cost-effectiveness of TSH stimulation with and without Thyrogen® in the Italian setting.

METHODS

An Italian cost utility analysis was undertaken to assess the impact of exogenous vs. endogenous TSH stimulation before radioiodine remnant ablation of patients with thyroid cancer who have undergone total or near-total thyroidectomy. Consistent with the patient characteristics of the three pivotal

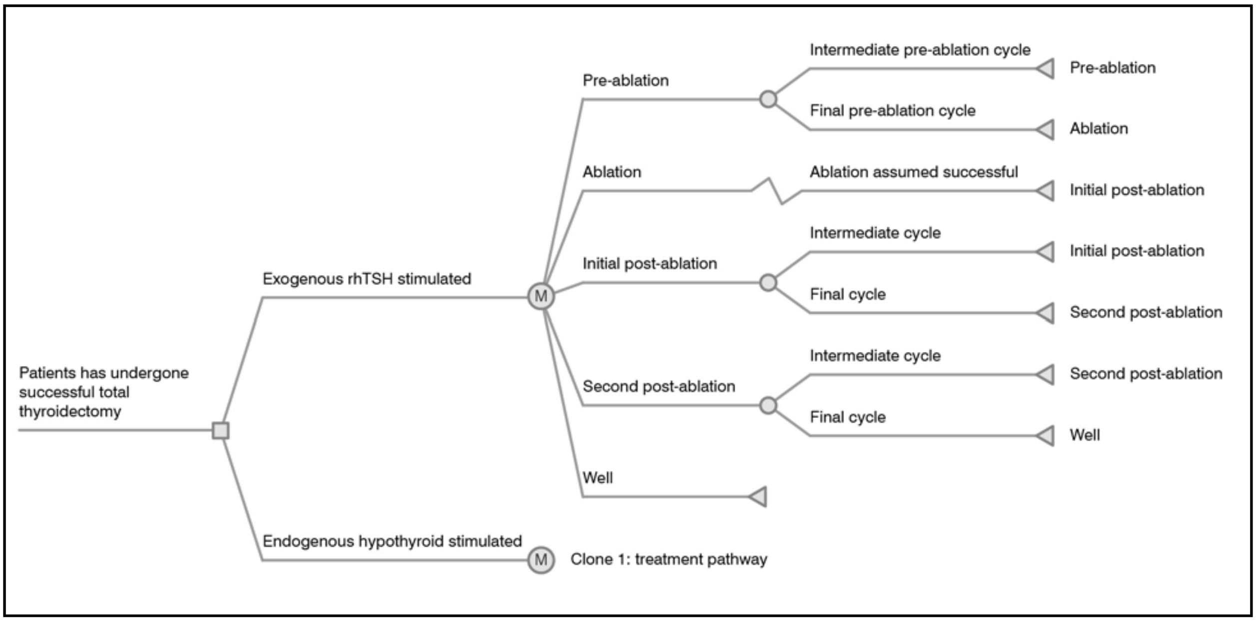

Figure 1. *Simplified model structure*

trials [2,5,9] patients with aggressive types of thyroid cancer or distant metastasis were not included in the model.

The local healthcare payer perspective was adopted in the base case scenario. Nevertheless, the impact of indirect costs (only appreciable within the societal perspective) is explored in a sensitivity analysis. In order to capture the differential costs and utilities associated with the short-term morbidity caused by induced hypothyroidism the economic model has a 17-week time horizon, assuming no differences beyond that point, as described elsewhere [13].

Model structure

The structure of the Markov model (Figure 1) is based upon the model originally developed by Mernagh et al. [13]. Briefly, treatment costs and health outcomes associated with exogenous stimulation and endogenous stimulation were computed in four distinct health states: pre-ablation (time between thyroidectomy and ablation), ablation, post-ablation (divided into two 4-week periods: initial and second post-ablation period), and well/recovery. Furthermore, in order to incorporate the extended indication of Thyrogen® for the use with a range of 30-100 mCi of radioiodine, treatment is stratified by patients who receive high- and low-activity in the ablation state. The cycle length of the model is one week. Costs and quality adjusted life years (QALY) specific to each health state were estimated, summarized and converted into a corresponding incremental cost-effectiveness ratio (ICER).

Clinical inputs

Local data provided from Italian clinicians via a survey of treatment practice (reported in Appendix A), were used to tailor the analysis to the Italian setting. Based on treatment survey responses, ≈40% of patients receive 30 mCi and ≈60% patients receive 100 mCi radioiodine. Consistent with previous economic evaluations [12,13], and according to the available body of clinical evidence the model assumed successful ablation in all the patients regardless of the method of preparation and administered radioiodine activity [2,5,9,10].

Length of time between thyroidectomy and radioiodine ablation

Since endogenously-stimulated patients can undergo ablation only after TSH levels have naturally elevated to a suitable level, the interval between thyroidectomy and ablation might vary from patient to patient. This will be further addressed in the discussion since it might impact the ward organization. In our base case, following recovery from total thyroidectomy (inclusive of histology results), the pre-ablation period (time between the decision to perform ablation and the ablation procedure) is about 4 weeks. This interval was calculated based on the answers provided by the centers involved in the survey and reflects our experience as well as real life medical practice. In contrast, exogenously-stimulated patients can experience a much shorter pre-ablation preparation period. A summary of the duration of each health state and the transition probabilities allowing patients to move from pre-ablation to ablation is shown in Appendix B.

Length of stay in radioprotective ward

Consistent with the results of the local treatment survey, the average length of stay used in the model was distinguished by the radioiodine activity, 2.6 and 3.0 days for 30 mCi and 100 mCi activities, respectively. The length of stay for exogenously and endogenously-stimulated patients, in absence of local data, were assumed to be the same. This assumption is conservative (thus penalizing Thyrogen®) since there is a solid body of evidence linking Thyrogen® to a faster clearance of 131I after radioiodine ablation [6,15,16], leading to a shorter stay in the radioprotective ward [7,8,17]. Differences in the length of stay, using literature data, were tested in the sensitivity analysis. The impact of length of stay on modeled outcomes is addressed in the discussion.

Utility weights

The time spent in each state was quality adjusted using utility weights. Utility weights for the pre-ablation and the initial post-ablation periods were derived from the SF-36 data collected during the initial pivotal RCT [5] and transformed into utility weights using the SF-6D method [18]. The mean disutility associated with thyroid hormone therapy withdrawal in the endogenously-stimulated arm compared to the exogenously-stimulated arm is a direct and expected consequence of the symptoms associated with hypothyroidism [5,19].

In order to reflect the disutility that patients may feel as a consequence of the ablation procedure and the associated time spent in the hospital, the ablation utility weights were based on those of pre-ablation, with an assumed extra disutility of 0.1 applied in each arm. The post-ablation period is divided into two sequential 4-week periods: in order to capture a gradual recovery, leading to the well health state, the initial period has a lower uti-

	Exogenously-stimulated arm		Endogenously-stimulated arm		Source
	30 mCi	100 mCi	30 mCi	100 mCi	
Patient (%)	40	60	40	60	Italian treatment survey
Time between surgery recovery and ablation (weeks)	1		4		Clinical opinion (rhTSH) and Italian treatment survey
Average length of stay in radioprotective hospital ward (days)	2.60	3.00	2.60	3.00	Italian treatment survey and Author assumptions
Utility weights					
Pre-ablation	0.714		0.548		[5] (week 4 data)
Ablation	0.614		0.448		Assumption (pre-ablation – 0.1)
Initial post-ablation	0.712		0.637		[20] (1-month post-ablation)
Second post-ablation	0.856		0.819		Assumption (average of initial post-ablation and well)
Well	1		1		Assumption

Table I. *Clinical input and utility weight in the base-case*

lity than the second. In particular, the utility for 0-4 weeks post-ablation was derived directly from 1-month post-ablation SF-36 data from pivotal trial, whereas the utility for 4-8 weeks post-ablation period was an average of the utility weights of the well and initial post-ablation period [5]. Finally, a conventional value of 1 was attributed to the well utility as representative of perfect health. As this may not be true for all the patients a lower value was tested in a sensitivity analysis. A summary of clinical input and utility weights used in the model are reported in Table I.

Resource	Unit cost (€)	Source
Drug costs		
Radioiodine ablative activity		
• 30 mCi	140.00	Personnal comunication Sant'Orsola hospital
• 100 mCi	287.00	Personnal comunication Sant'Orsola hospital
T4 (100 mcg, 1 tablet)	0.06	Codifa [22]
T3 (20 mcg, 1 tablet)	0.07	Codifa [22]
RhTSH (Thyrogen®, 2-vial kit)	720.46[1]	AIFA - Official Gazette [23]
Resourse costs		
Whole body scan using radioiodine	305.08	92.18.1 [21]
Cost of hospital stay for radioiodine ablation (1 day)	700.00	Assumption and [24]
Visit to specialist (endocrinologist or radiation oncologist)	22.50	89.7A.8 [21]
Visit to specialist (follow-up visit)	17.90	89.01.8 [21]
Visit to a practice nurse	22.50	Assumption
Visit to a general practitioner (GP)	22.50	Assumption
Visit to GP (follow-up visit)	22.50	Assumption
TSH quantification test (once only)	8.40	90.42.1 [21]
Serum thyroglobulin count	16.35	90.41.5 [21]
Antigen test	13.15	90.54.4 [21]
Daily productivity loss	25.60	See sensitivity analysis
Accident cost	100.00	[4]

Table II. *Unit costs used in the model and relative source*

[1] Official ex-factory price as published in the Official Gazette. The model considers purchase cost, after application of mandatory discounts.

Resource use and cost input

Unit costs applied to resource use are taken from the Tariff System of Lombardy [21], drug costs were derived from Codifa [22]. In the exogenously-stimulated arm the net acquisition cost of Thyrogen® plus administration was taken into account (a visit for each of the 2 injections). According to survey responses, an initial TSH quantification test would be performed 4 weeks after T4 withdrawal, in the case of endogenous stimulation. If the TSH level had not reached suitable levels, ablation would be postponed by approximately one week. The survey also reveals that on average 2.42% and 38.25% of endogenously-stimulated patients would seek additional treatment from a GP or specialist, respectively, looking for relief of symptoms related to iatrogenic hypothyroidism. Finally, the proportion of radioiodine ablation patients taking T3 (liothyronine sodium) during the period between their thyroidectomy and radioiodine ablation is also based on data from the treatment survey. Unit costs incorporated into the economic model and source, and total costs per health state in each arm are presented in Table II and Table III, respectively.

Sensitivity analysis

Individual one-way deterministic sensitivity analyses were performed to test the impact of key assumptions, and to better understand the main drivers of the economic analysis. In particular, we tested the impact of:

- Including indirect costs, thus adopting a societal perspective. This was done according to the friction cost methodology:

$$P = 0.8 \times (\omega \times \delta)$$

where P is the daily productivity loss, ω is the daily wage (calculated from total average weekly earnings divided by seven days) and δ is equal to the unemployment-adjusted labor force participation rate. As both ω and δ are likely to change substantially from one economy to another, the daily productivity loss is a sensitive variable. For Italy, the unemployment rate (12.3%), the labor force participation rate (64.4%) and the average daily wage (€ 56.65) were obtained from ISTAT – (2014). This results in a calculated daily productivity loss of € 25.60.

- Inclusion of accident costs for THW patients (€ 100 as per 1 month incremental risk as in Luster, 2005 [4]).
- Varying assumptions regarding the difference in time spent in the radioprotective ward between the two arms due to faster clearance of 131I with Thyrogen®, using various radiation discharge thresholds (see Appendix C).
- Reducing incremental utility difference in the pre-ablation health state and in the well health state.

Health state	Cost (€)	
	With Thyrogen®	Without Thyrogen®
Radioiodine activity = 30 mCi		
Pre-ablation	773.92	86.26
Ablation	2,298.66	2,298.26
Initial post-ablation	19.52	19.52
Second post-ablation	1.62	1.62
Well	2.83	1.62
Total	**3,096.55**	**2,407.27**
Radioiodine activity = 100 mCi		
Pre-ablation	773.92	86.26
Ablation	2,729.06	2,728.66
Initial post-ablation	19.52	19.52
Second post-ablation	1.62	1.62
Well	2.83	1.62
Total	**3,526.95**	**2,837.68**

Table III. *Total costs per health state in each arm of the model*

	With Thyrogen®	Without Thyrogen®	Incremental difference
Cost per patient(€)	3,354.04	2,664.46	689.58
Benefit per patient (QALY)	0.281	0.243	0.038
ICER (€/QALY gained)			**18,357.18**

Table IV. *Results of the analysis*

RESULTS

Base case

The results presented in Table IV illustrate the cost of treatment with Thyrogen® in the Italian setting when compared with endogenous stimulation of TSH before ablation. The incremental cost-effectiveness ratio is € 18,357.18 per each QALY gained, meaning that Thyrogen® represents a cost-effective solution.

Sensitivity analysis

The sensitivity analysis identified as the most critical variable the potential reduction in length of stay in the radioprotective ward (Figure II). When a 1 day difference was assumed for both high- and low-activity radioiodine, Thyrogen® dominates endogenous stimulation as it still produced greater health gains whilst costing less. In parallel, if it is assumed that this difference is seen only for the percentage of patients receiving high activity 131I, consistent with Mallick et al. results [9], we calculated an incremental cost-effectiveness ratio of € 5,815.46 per QALY. Relatedly, the ICERs are sensitive to radioiodine discharge thresholds because of differences in length of hospital stay. At all considered discharge thresholds (40, 20, 10.8 and 5.4 mCi, see Appendix C for details) the ICER was lower than the base case. Across the scenarios tested, the threshold at 20 mCi had an ICER of € 9,825.86 per QALY and was the most cost-effective result. Sensitivity analyses investigating the inclusion of indirect cost and accident cost produced reductions of the ICER to € 14,609.51 and € 15,515.26 per QALY, respectively.

We further combined the effect of these assumptions in a multivariate sensitivity analysis (Table V). In particular, the first analysis shows the impact of reducing the utility score in the well health state as well as reducing the utility difference in the pre-ablation health state by 50%. The QALY gain shifts from 0.038 to 0.028 and the ICER increased to € 24,372.27 per QALY. The cost of hospitalization had no impact in the base case analysis because we assumed that the length of stay was only dependent on the activity of radioiodine received. The daily cost of hospitalization was therefore tested using length of stay estimates from Borget et al. [7] at the

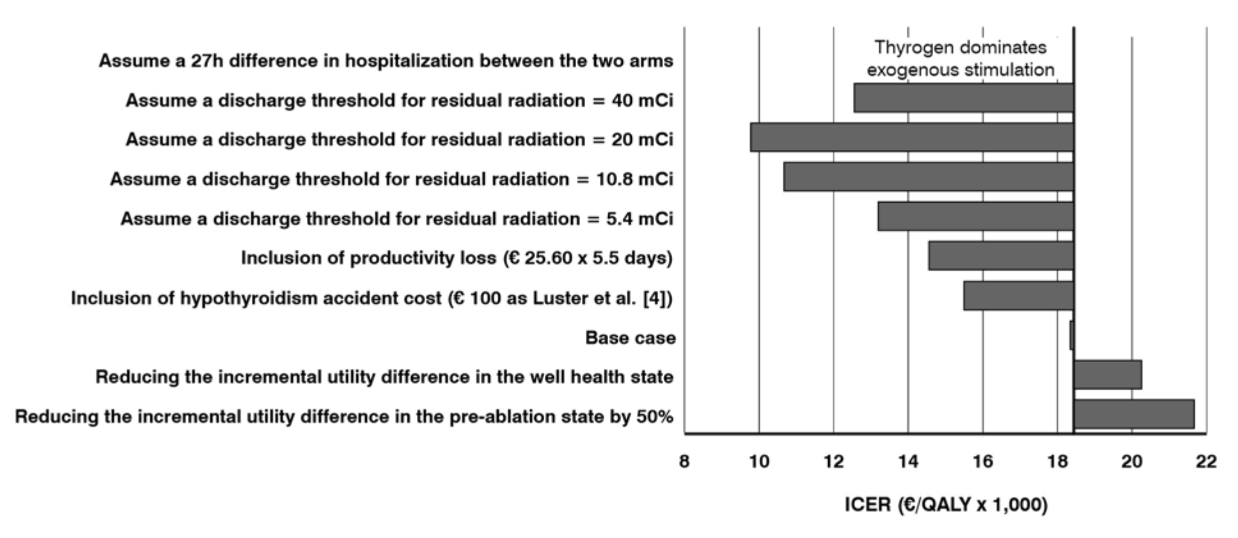

Figure 2. *Results of the univariate sensitivity analysis*

discharge threshold for residual radiation of 20.0 mCi. As shown in Table V, a 50% increase in cost per day in hospital stay translates to a more favorable ICER.

Further multivariate sensitivity analysis was undertaken using the discharge threshold for residual radiation of 20.0 mCi and amending the utility scores. Consistent with previous sensitivity analyses the ICERs increased when the incremental difference in utility was reduced between patients who received Thyrogen® and those that received endogenous stimulation. When we simulate what is closer to reality, higher cost per hospital stay, possibility of earlier discharge and inclusion of additional relevant costs such as indirect costs and costs associated with accidents, Thyrogen® becomes dominant.

In Italy, there is no official cost-effectiveness threshold. Therefore, as many other authors, we compare our results with a benchmark of € 35,000 per QALY, equal to what is in use in UK [25] and within the range (€ 25,000-40,000 per QALY) recommended by the Italian Health Economics Association [26]. All results calculated in the sensitivity analysis, both one-way and multivariate, are below the lower bound of the above mentioned range, supporting Thyrogen® value for money.

Assumption 1	Assumption 2	Assumption 3	ICER (€/QALY)
Reducing the incremental utility difference in the well health state (1 → 0.929)	Reducing the incremental utility difference in the pre-ablation health state by 50% (0.548 → 0.631)	-	24,372.27
Reducing the incremental utility difference in the well health state	Reducing the incremental utility difference in the pre-ablation health state by 50%	Assume difference in LoS and a discharge threshold for residual radiation = 20 mCi	13,045.50
Inclusion of productivity loss (€ 25.60 x 5.5 days)	Inclusion of hypothyroidism accident cost (€ 100, as Luster 2005 [4])	-	11,810.53
		Assume a discharge threshold for residual radiation = 20 mCi	3,376.84
Reducing the cost of hospitalization per day by 50%	Assume a discharge threshold for residual radiation = 20 mCi	-	14,091.52
		Inclusion of productivity loss and hypothyroidism accident cost	7,593.78
		Variations in utilities (1 → 0.929; 0.548 → 0.631)	18,708.89
Increasing the cost of hospitalization per day by 50%	Assume a discharge threshold for residual radiation = 20 mCi	-	5,560.20
		Inclusion of productivity loss and hypothyroidism accident cost	Thyrogen® dominates THW
		Variations in utilities (1 → 0.929; 0.548 → 0.631)	7,382.11

Table V. *Results of the multivariate sensitivity analysis*
LoS = Length of Stay

DISCUSSION

Thyrogen® avoids daily life disruptions and preserves patients' QoL, whereas thyroid hormone withdrawal (THW) has been shown to produce a QoL deterioration greater than that of heart failure, depression and migraine headache [19,27]. The patients' perspective on the desirability of these two alternatives is evidenced by the finding that between 86% and 97% of interviewed patients favored rhTSH over THW [28,29]. As indicated by our analysis, the use of Thyrogen® is cost-effective according to the Italian conventional willingness to pay (WTP) thresholds (25,000-40,000 €/QALY) [26]. To our knowledge this is the first study assessing cost-effectiveness of Thyrogen® in the Italian setting in patients who receive either high- (100 mCi) or low-activity (30 mCi) radioiodine for remnant ablation post-thyroidectomy.

A number of cost-effectiveness analyses of Thyrogen® have been conducted previously, however it is well known that results cannot be transferred directly across different countries [30]. Our findings are consistent with three cost-utility analyses conducted using the same model in the German, Canadian and Korean settings in which ICERs were equal to 958 €/QALY, 1,520 Canadian $/QALY and 26,697,361 W/QALY, respectively [12-14].

Most recently, a cost-effectiveness analysis performed in France alongside the ESTIMABL trial adopted a longer time horizon and considered the consecutive use of Thyrogen® in both ablation and follow up procedures [31]. Results cannot be directly compared for a number of reasons. First, clinical pathways, clinicians' attitudes and/or reimbursement mechanism in France might be different from Italy and might imply differences in term of time and costs. Secondly, as a consequence of the longer time horizon adopted in the French study (8 +/- 2 months vs 17 weeks), the QoL estimates, including both physical and mental components, should be compared only in the initial 3 months, which are common to both simulations. Within such period the QoL scores are quite comparable, however, after this point, in the French study there appears to be some sort of a prolonged "rebound effect" in the THW cohort. Authors did not comment on the length and extent of this phenomenon. In addition, neither the hospital length of stay (2.6 vs 2.8 days) nor the sick leave time (23 vs. 24 days) appeared to be significantly different, in contrast to other retrospective reports [7,8]. We remind that length of stay is mainly driven by how each nuclear medicine ward is organized (number of beds, use of beds - 7/7 or just Monday to Friday-presence/absence of waiting lists) and, above all, by the remuneration system. Culturally in Italy there is the common misconception that identifies remuneration tariffs such as Disease Related Groups (DRGs) with real costs. Additionally, the DRG applied for ablation is calculated on a minimum length of stay of two nights, so any earlier discharge, even if feasible and desirable, might be internally perceived as a productivity loss instead of a competitive advantage.

The aim of our research is twofold: on the one hand, to support informed decisions with the most conservative modelling approach (even though less favorable to Thyrogen®), and on the other hand, to stimulate constructive debate. Therefore, we decided to run the base case scenario under the most conservative assumptions, assuming no difference in length of stay. However, in the sensitivity analysis we relaxed our hypothesis and assumed an earlier discharge for Thyrogen® treated patients (Borget reported a reduction from 3.5 to 2.4 days in 2008 [7], whereas Vallejo-Casas in 2011 documented 1.41 vs. 2.02 days [8]); in this scenario, Thyrogen® dominates endogenous stimulation by providing better QoL outcomes along with cost savings.

In a strict analogy and despite their paramount importance, we excluded societal benefits such as productivity gains in the base case analysis. This might be counterintuitive given the considerable body of evidence suggesting that endogenous stimulation results in greater work absenteeism [4,28,32,33]. Albeit not in ablation but in the follow up, Dietlein et al. [28] reported workday loss in 70% of THW patients in follow-up (40% with Thyrogen®); Luster et al. [4], back in 2005, reported a similar figure (65%). In both studies the average workday loss was between 11 and 12 days (vs. 3 to 4 days in case of Thyrogen® use). Borget et al. [32] documented a 8.1 days difference in 2007 whereas the ESTIMABL study [31] reported no difference. We speculate that sick leave duration is highly dependent of the clinical practice: in some cases is set on the basis of the disease (thyroid cancer) and not on the basis of the treatment. In other words, the use of a standard protocol, possibly defined on general DTC patients characteristics such as age, sex, comorbidities, would totally prevent to appreciate the maintenance of a state of wellbeing that is compatible with normal productivity in most patients. With the inclusion of such indirect costs, the cost-effectiveness of Thyrogen® would further improve to 14,695.67 €/QALY when compared with endogenous stimulation.

There are some additional potential Thyrogen® advantages that we were not able to address in our analysis. The intensity of individual symptoms of iatrogenic hypothyroidism may vary from patient to patient; however, the cognitive, motor and psychological deficits – linked to severe hypothyroidism and resulting in the impaired ability to operate machinery or drive vehicles – might have been underestimated. Driving motor vehicles such as cars or motorbikes, should be avoided in the severe hypothyroid state because of decreased fine-motor performance and processing speed, and slowed reaction times (braking times were increased by 8.0%, equivalent to the motor slowing caused by alcohol ingestion at a blood concentration of 0.082 g/100 ml; this concentration is above the levels allowed within EU for driving) [3]. This is quite relevant since driving habits appear to be difficult to change in at least 30% of THW cases, irrespectively of a strong negative medical advice [4].

The use of Thyrogen® may also improve overall ward efficiency, lowering fixed costs and halve waiting lists, in analogy of what measured in other countries [8,24]. Little is known about the real organizational aspects related to ablation and isolation rooms in Italian hospitals, as a consequence of the shorter length of stay and the more exact scheduling of admissions and discharges.

In conclusion, Thyrogen® represents a good treatment option for patients as well as a difficult exercise for any healthcare professional operating in a scenario with limited resources: by training, physicians have to keep patients from harm, and this should strongly advise against inducing hypothyroidism, even if temporary, when an alternative, such as Thyrogen®, is available. We strongly advocate for future studies about broader aspects related to hypothyroidism, since this would allow more informed decision making. Retrospective analysis on administrative claim databases as well as specific patient interviews might shed some light whether the use of Thyrogen® is able to improve patient safety by reducing accidents, either at home or related to driving, as well as unscheduled use of healthcare resources in the emergency departments.

AUTHORS DISCLOSURES

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APPENDIX A

The survey (Table IA) was conducted amongst clinical experts in endocrinology, nuclear medicine and surgery, currently practicing in Italy. The objective of the survey was to establish the current practice of radioiodine ablation (both high and low-dose) for well differentiated thyroid cancer in those patients who are endogenously-stimulated prior to ablation.

How many newly diagnosed patients undergo ablation each year:	Response
100 mCi	889
30mCi	597
What proportion of patients are treated with:	
100 mCi	59.83%
30 mCi	40.17%
What proportions of patients are withheld from T4 replacement therapy straight after their thyroidectomy in preparation for scheduled radio-ablation?	
T4 withheld after surgery	18.33%
T4 withdrawn at a later time	81.67%
What TSH level must be attained before radio-ablation is performed?	30
How many weeks after starting withholding/withdrawal is the patient's TSH level first measured?	5
If the patient's TSH level has not reached the required value for ablation when first tested, is it measured again?	1
How many weeks later?	1
What proportion of patients are ablated within the following timeframes in practice	
< 3 weeks	22.11%
3 weeks	12.11%
4 weeks	24.56%
5 weeks	27.33%
6 weeks	13.89%
> 6 weeks	0.00%
Average Pre-ablation Time	3.99
Time left	4.01
Other than time required to reach target TSH, list other factors that influence the delay between surgery & ablation:	
What proportion of radioiodine ablation patients take T3 (liothyronine sodium) during the period between their thyroidectomy and radio-ablation?	50.1%
On average, for how many weeks would T3 be taken by patients?	2.33
What percentage of patients visits their primary care physician to seek treatment or reassurance due to symptoms of hypothyroidism?	2.42
What percentage of patients visits their specialist to seek treatment or reassurance due to symptoms of hypothyroidism?	38.25
Do you have radio-protective facilities for patient isolation?	Y
In your unit, is the patient's external radiation routinely measured after radioiodine ablation?	Y
If so, does this measure influence when the patient is discharged from hospital?	Y
What is the nearest radiation threshold for discharge?	
40 mCi	14.3%
20 mCi	71.4%
10.8 mCi	0.0%
5.4 mCi	14.3%
Following ablation with I131 , what proportion of patients are released from hospital within the following timeframes (for 30mCi:	
Within a day	0.63%
2 days	64.75%
3 days	9.00%
4 days	25.63%
5 days	0.00%
Average	2.60

Table continues>

Table continued>

Following ablation with I131 , what proportion of patients are released from hospital within the following timeframes (for 100mCi:	
Within a day	0.00%
2 days	28.44%
3 days	43.56%
4 days	27.44%
5 days	0.56%
Average	3.00
If patients are to receive Thyrogen®, what health professionals would be involved in the administration of Thyrogen® (NB. administration is by intramuscular injection)?	
Practice nurse alone	56%
GP Alone	0%
Specialist alone	11%
Practice nurse and specialist	33%
Practice nurse and GP	0%

Table IA. *Treatment survey conducted amongst clinical experts in endocrinology, nuclear medicine and surgery, currently practicing in Italy*

APPENDIX B

Length of time between thyroidectomy and radioiodine ablation

Health state	Exogenous stimulation	Endogenous stimulation
Pre-ablation (time between clinical decision and ablation procedure)	1	4
Ablation	1	1
Initial post-ablation period	4	4
Second post-ablation period	4	4
Patient recovered and considered well	7	4

Table IIA. *Duration of health states (weeks)*

Duration time	Transition probabilities
Less than 3 weeks	0.2211
3 weeks	0.1211
4 weeks	0.2456
5 weeks	0.2733
6 weeks	1.0000

Table IIIA. *Transition probabilities of endogenous thyroid stimulation patients from pre-ablation to ablation states*

APPENDIX C

Sensitivity analysis

Radiation threshold (mCi)	Radioablative dose (mCi)	N	Time spent in hospital/radioprotective ward (days)	
			Exogenous stimulation (rhTSH)	Endogenous stimulation (hypothyroid)
5.4	30	357	0.87	0.99
	100	1,484	2.90	3.29
10.8	30	357	0.61	0.78
	100	1,484	2.02	2.59
20	30	357	0.33	0.52
	100	1,484	1.09	1.73
40	30	357	0.09	0.22
	100	1,484	0.29	0.72

Table VA. *Time spent in hospital stratified by radiation threshold following radioiodine ablation for patients prepared with exogenous vs. versus endogenous stimulation*