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Treatment of local and regional recurrences of differentiated thyroid cancer by radio-guided surgery with iodine-131

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ABSTRACT

BACKGROUND/MATERIAL AND METHODS: The aim of this study was to assess the reliability of radioiodine (^{131}I) and a gamma probe for radio-guided surgery (RGS) to detect and radically dissect lymph node recurrence (LNR) in 15 patients with differentiated thyroid cancer (DTC). The major inclusion criterion was the presence of a radioiodine-positive LNR after previous total thyroidectomy and at least two ineffective ^{131}I treatments. The protocol was designed as follows: Day 0 — all patients were hospitalized and received 3.7 GBq of ^{131} I while clinically hypothyroid. Day 3 — pre-surgery whole-body scan with a therapeutic ^{131}I dose (TxWBS) was acquired. Day 5 — neck surgery using a gamma probe (Navigator GPS, AutoSuture, Italy), recording the absolute counts and the lesion/background (L/B) counts ratio was performed. Day 7 — post-surgery TxWBS was performed using the remaining radioactivity.

RESULTS AND CONCLUSIONS: This protocol permitted us to identify neoplastic foci with high sensitivity and specificity, enabling us to remove lymph node metastases resistant to radioiodine therapy in a single session. The protocol also allowed detection of some additional tumoural foci in sclerotic areas or behind vascular structures that were not seen at the pre-surgery TxWBS evaluation.

Key words: radio-guided surgery, thyroid cancer, local regional recurrences, radioiodine

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Introduction

Total or near-total thyroidectomy followed by ^{131}I ablation of thyroid remnants is widely accepted as the most effective modality of treatment for most patients with differentiated thyroid carcinoma (DTC) [1]. However, after initial treatment neck recurrences can appear in the follow-up in 5% to 20% of patients, twice more frequently than distant metastases [2].

^{131}I is the treatment of choice in recurrent DTC but uptake may not be adequate and repeated therapy may fail to eradicate these foci. In these cases, surgery is the main modality of treatment, and an accurate preoperative work-up is mandatory to accurately localize the site and extent of the recurrences. Anatomical imaging modalities, such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI), offer a high spatial resolution, but are often difficult to interpret because of fibrous scarring and altered anatomic structures resulting from prior thyroidectomy [3].

Furthermore, US, CT and MRI remain limited in their ability to discriminate between tumour and scar, in determining whether mildly enlarged lymph nodes represent tumour or a non-malig-

nant process and in detecting cancer foci < 1 cm in diameter [4]. Scintigraphic imaging with radioiodine (^{131}I or ^{123}I) permits the distinction between residual tumoural foci and scar but suffers from inadequate sensitivity, primarily because of the limited intrinsic spatial resolution of the gamma cameras [5].

To overcome these drawbacks, some authors have proposed radioguidance with an intraoperative gamma probe following the administration of high doses of ^{131}I to detect and dissect lymph node metastases during re-operations for loco-regional recurrences in patients with DTC (3–6–7).

In the present work, following our previous experience [7], we report data obtained using this technique in 15 patients with loco-regional recurrences from DTC, with specific emphasis on the technical aspects of the procedure, and compare our results with those reported in other series (3–6–7).

Material and methods

Patients

The present study involves 15 patients submitted for neck dissection due to local and regional recurrence of DTC between January 1st 2000 and December 31st 2005 (Table 1).

They included 5 women and 10 men, ranging in age from 25 to 66 years (mean 47.5 years) at the time of the first thyroid surgery. All patients had undergone total thyroidectomy, and 10/15 had had cervical lymph node dissection.

The tumours were staged according to the 2002 TNM classification [8]. The stages are shown in Table 1. Lymph node metastases were found in all patients at the initial surgery and three patients (1, 3, 5) also presented with lung metastases. The histopathology of the tumours was papillary in 14 patients and poorly differentiated follicular in one patient.

After the initial surgery, all patients received two or three radioiodine doses (mean 2.4) to ablate any thyroid remnants and to treat any functioning metastases. The mean radioiodine cumulative dose was 11.9 GBq (range 4.6–20.3 GBq).

^{131}I administration was performed while the patients were in a hypothyroid state in 13 patients. Hypothyroidism was obtained by stopping treatment with levo-thyroxine (L-T4) and starting triiodothyronine (T3) until 2 weeks prior to administration of the radioiodine.

Serum thyroid stimulating hormone (TSH) levels measured prior to the time of the radioiodine administration were above 30 μUI/ml in all patients (mean 64, range 30–144 μUI/ml).

To avoid hypothyroidism in two patients with ischaemic heart disease we used exogenous TSH stimulation with rh — TSH (Thyrogen ©) under the manufacturer's compassionate use programme. We administered one intramuscular injection of 0.9 mg on each of two consecutive days given during thyroid hormone suppressive therapy (THST) with administration of ^{131}I on the third day.

TSH levels were measured using a commercial electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostic Co., Indianapolis, IN, USA) for Elecsys System 2010.

At the same time of TSH serum evaluation, serum thyroglobulin (Tg) levels and thyroglobulin autoantibodies (TgAb) were evaluated.

Serum Tg levels were measured using a commercial kit with a sensitivity < 0.1 ng/ml using an electrochemiluminescence immunoassay (ECLIA) kit (Roche Diagnostic, Indianapolis, IN, USA) for Elecsys System 2010.

TgAbs were measured by enzyme-linked immunosorbent assay (ELISA) with a lower limit of detection at 2 IU/ml and an inter-assay coefficient of variation of 14.2%.

The time elapsed from the initial total thyroidectomy to inclusion in the present study ranged from 14 to 60 months (mean 28.4 months).

Criteria for inclusion and preoperative evaluation

The main inclusion criterion in the present study was the presence of persistent or recurrent radioiodine-positive lymph node metastases after at least two radioiodine treatments. Other criteria were clinical evidence of lymph node metastases, positive neck ultrasonography (US) or neck and chest computed tomography (CT) studies or detectable serum Tg values. Only patients without serum TgAbs were included in the present study. Before RGS, all patients showed focal radioiodine uptake outside the thyroid bed at the last DxWBS or TxWBS. Four patients presented with enlarged lymph nodes at the clinical examination. Ultrasonography

Table 1. Patient and tumour characteristics

Patient no.	Sex	Age	Initial surgery	Stage[a]	Histology	^{131}I Tx[b]	^{131}I Tx no.[c]	Time[d] (months)
1	M	43	TT, LN	pT2mN1bM1	Papillary	16.3	3	53
2	F	57	TT	pT1mN1aM0	Papillary	7.4	2	14
3	F	52	TT	pT3N1aM1	Follicular	9.2	2	60
4	M	49	TT, LN	pT4N1aM0	Papillary	13	2	20
5	M	40	TT, LN	pT4N1bM1	Papillary	11	2	15
6	M	52	TT, LN	pT4N1bM0	Papillary	16.6	3	39
7	M	33	TT, LN	pT4N1bM0	Papillary	7.4	2	16
8	M	45	TT, LN	pT2mN1bM0	Papillary	11.1	3	21
9	F	66	TT	pT3N1aM0	Papillary	14.8	3	32
10	M	25	TT, LN	pT4N1bM0	Papillary	11.1	2	17
11	M	41	TT, LN	pT3N1bM0	Papillary	4.6	2	23
12	M	60	TT	pT4N1bM0	Papillary	16.6	3	29
13	M	65	TT, LN	pT2N1aM0	Papillary	9.2	2	19
14	F	39	TT, LN	pT3N1bM0	Papillary	20.3	3	54
15	F	30	TT	pT3N1aM0	Papillary	9.2	2	15

TT — total thyroidectomy; LN — lymph node dissection; [a]UICC pathologic TNM; [b]cumulative ^{131}I activity before radio-guided surgery (GBq); [c]number of radioiodine treatments; [d]time elapsed from TT to radio-guided surgery; M — male; F — female

performed using a 7.5-MHz linear probe (Logiq 700 MD; General Electric, Milwaukee, Wisconsin, USA) showed echographic findings suspicious for lymph node involvement in 11 of 15 patients.

Computed tomography performed with injection of contrast medium more than 6 weeks before administration of ^{131}I showed pathologic enlargement of cervical lymph nodes in 6 of 10 patients.

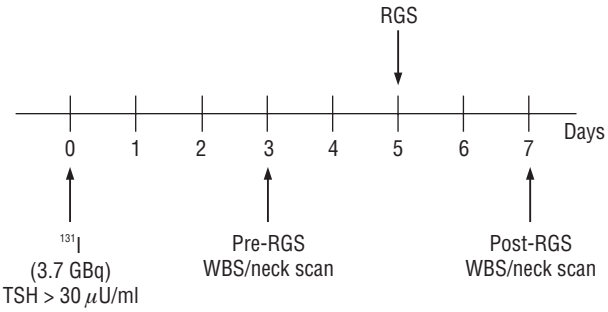
The present study was performed with the authorization of the local ethical committee, informed consent of the patients and permission of the health physics department.

Radio-guided surgery

Our protocol for RGS of persistent or recurrent lymph node metastases from a DTC is similar to that reported by Travagli et al. [3]. A summary of the protocol is shown in Figure 1 and consists of:

- **day 0** — all patients were hospitalized and received 3.7 GBq of ^{131}I while in a hypothyroid status obtained as previously reported. Patients were not placed on a low-iodine diet but were asked to avoid iodine-containing drugs. We did not routinely measure urinary iodine prior to ^{131}I administration, but patients were carefully screened by history for pharmacological or environmental iodine intake;
- **day 3** — patients were discharged from the isolation room 3 days later when the radiation emission was $< 30\ \mu$Sv/hr at 1 m. At the same time, a pre-surgery TxWBS with a neck spot view was performed using a rectilinear scanner that had double heads equipped with high-energy collimators;
- **day 5** — two days later, neck surgery using a hand-held gamma detection probe (Navigator GPS; AutoSuture, Milan, Italy) was performed. Under the guidance of the ^{131}I neck scan obtained on day 3, the patient's neck was scanned with the probe to localize the cutaneous projection of the radioiodine focal uptake sites. Before surgically removing the tumoural tissue, the probe was placed in direct contact with the pathologic sites, and the counts per second were recorded. The activities in normal adjacent soft tissues were counted as well and were used as the background value. The lesion/background (L/B) ratios of these measurements were thus obtained. After nodal excision, radioactivity was measured in the bed of the lesion to confirm the success of the dissection. At the end of the procedure, a scan of the operative field with the handheld gamma detection probe was repeated, looking for any residual activity of the tracer.

  The radiation doses to the surgeon's hands during surgery and the contamination of surfaces and surgical tools were measured by thermoluminescent dosimeters and a portable dedicated device, respectively. The amount of operator time necessary to perform the complete surgical procedure was recorded in each case. At the end of the operation, the surgeon made the following judgments on the usefulness of the gamma probe: it was a "decisive" procedure if it showed tumoural foci that had not otherwise been detected; a "favourable" procedure in cases where assisted intraoperative detection of tumoural foci had already been demonstrated by preoperative diagnostic methods; and "irrelevant" procedure if it made only an insignificant contribution to the operation. All surgical specimens were sent separately to the pathologist for a detailed histological examination. The recorded lymph node counts and the pathologist's reports were then compared;
- **day 7** — a postoperative neck scan was performed using the remaining radioactivity to evaluate the success of the surgery. Patients were then followed up with periodic TSH and Tg measurements (every 3–6 months) on L-T4 therapy and with clinical and US evaluation; a DxWBS and off L-T4 serum Tg evaluation 1 year later were planned for all patients.



RGS: radio-guiled surgery with intraoperative gamma probe
WBS: highly sensitive whole body scan

Figure 1. Protocol from radio-guided surgery of lymph-node metastases from Institut Gustave Roussy, Villejuif Cedex, France, modified by Salvatori et al. [7].

Results

Table 2 shows the results of TxWBS performed before and after surgery, the TSH- stimulated Tg levels and the lesion — background count ratio (L/B) of the most radioactive lymph nodes recorded pre- and post-surgery and the surgeons' judgments about the usefulness of the gamma probe. TxWBS performed before RGS was positive in all patients, with a total of 50 scintigraphic sites of radioiodine focal uptake (mean 3.3 sites per patient).

Focal radioiodine uptake was present in the laterocervical compartments in all 15 patients, in the central compartment in 3 patients and in the supraclavicular compartments in 2 patients.

Preoperative US and CT studies have been positive in 11 and 6 patients, respectively. Both of these diagnostic procedures showed fewer abnormalities and gave more equivocal results than TxWBS.

Before RGS, Tg on L-T4 was detectable in 11 patients, with a mean level of 29.30 ng/ml (range 2.5–163.0 ng/ml). Tg off L-T4 increased in 12 patients and remained undetectable in 3 patients.

The pre-excision absolute counts obtained by placing the probe in direct contact with all the pathologic sites (evident or not evident at TxWBS) showed a mean counts per second of 179.30 (18 cps minimum, 553 cps maximum). The mean L/B ratio was 12.30 (2.75 minimum, 27.6 maximum).

The post-excision absolute counts obtained by placing the probe in the bed of the removed lesion showed a mean counts per second of 29.60 cps (4 cps minimum, 49 cps maximum). The mean L/B ratio was 2.03 (0.8 minimum, 4.1 maximum).

After RGS, the TxWBS performed on day 7 showed a negative pattern in 11 patients, suggesting the efficacy of the surgical procedure, 4 patients (patients 3, 5, 10, 14) showed reduced radioiodine uptake owing to persistent residual neoplastic disease. Adjuvant external radiotherapy was planned for two patients (patients

Table 2. Results of radio-guided surgery

Patient no.	TxWBS: day 3rd	TxWBS: day 7th	TSH-stimulated Tg	L/B Ratio[a]: Pre	L/B Ratio: Post	Surgeon's opinion
1	3	0	51	2.75	0.8	Decisive
2	2	0	3.1	6.8	1.1	Favourable
3	2	1	804	17.8	1.7	Irrelevant
4	2	0	< 0.1	4.5	1.0	Irrelevant
5	4	1	15	9.8	1.3	Decisive
6	1	0	< 0.1	11	1.75	Favourable
7	9	0	7	13.5	1.5	Favourable
8	3	0	2.5	12.5	3.3	Favourable
9	2	0	5	20.3	4.1	Favourable
10	5	2	10	27.6	2.4	Favourable
11	1	0	< 0.1	4.7	1.3	Favourable
12	5	0	754	21.5	4.2	Favourable
13	2	0	4.5	9.6	1.3	Decisive
14	6	1	450	11.5	1.6	Favourable
15	3	0	9.1	10.5	1.1	Irrelevant

Tg — thyroglobulin; TxWBS — number of ^{131}I-positive lesions at initial (day 3) and final (day 7) whole body scans; L/B — lesion/background ratio;
[a]counts and L/B ratio — absolute counts and lesion/background counts ratio before and after excision, reported only for the most radioactive lymph node

5 and 10) owing to their pathologic stage (pT4N1b). After the operation, the surgeons judged the procedure "decisive" in 3 patients, "favourable" in 9 patients, and "irrelevant" in 3 patients.

The final histological examination showed the presence of 111 lymph node metastases; among them, 49 were evident by both TxWBS and gamma probe evaluation, 56 were demonstrated only by gamma probe and 6 were negative by both TxWBS and gamma probe evaluation.

The mean operating time necessary to perform the RGS was 100 minutes (range 58–180 minutes). No morbidity or complications were observed during surgery, and there were no transient or permanent injuries to the recurrent laryngeal nerve. None of the patients developed permanent hypoparathyroidism during the postoperative period.

The dosimetry and radioactivity measurements in all cases revealed extremely low levels of radioactive exposure to the surgeon's hands (< 40 μSv) and no radioactive contamination of surfaces or surgical tools.

During the subsequent follow-up, DxWBS, Tg off L-T4 and US showed an absence of locoregional disease in 14 of the 15 patients. Further radioiodine treatments have been planned for patients with distant functioning metastases.

Discussion

After initial treatment of DTC, local and regional recurrences can be found in the thyroid bed, in lymph nodes and in soft tissues, and the majority of these appear in the early follow-up, indicating either an incomplete initial treatment or the presence of an aggressive tumour [9].

The frequency of these recurrences is related to the size and histological type of the primary tumour, extent of lymph node dissection and method of histological analysis.

In most studies lymph node metastases are associated with a higher risk of distant metastases, while the impact on survival is still controversial [10].

The therapeutic tools for lymph node metastases include radioiodine therapy, surgery, and adjuvant external beam radiotherapy (EBRT) according to the size of the lesion, the radioiodine uptake and the clinical characteristics of the disease.

Lymph node size, radioiodine uptake and radiation dose absorbed by residual or recurrent thyroid tissue are the most important factors that influence the efficacy of radioiodine therapy. At Memorial Sloan-Kettering, New York, Robbins et al [11] found that a single dose of radioiodine can abolish subsequent uptake of radioiodine in approximately 65% of patients. However, for macroscopic tumour deposits and absorbed radiation doses below 3500 cGy, the chances of cure are compromised [12].

The role of EBRT in lymph node recurrence remains controversial and it is clearly not indicated in young patients (age < 45 years) with elevated ^{131}I uptake. However, EBRT can be recommended for patients older than 45 years of age, with papillary carcinoma and extra-thyroidal invasion in association with no significant ^{131}I uptake [13].

Therefore, surgery represents the main form of treatment for non-functioning local and regional recurrences appearing during early and long term follow-up and for functioning large lymph node metastases (> 1 cm in diameter) that are usually only partially responsive to ^{131}I treatment [11].

However, re-operation is often problematic when tumoural foci are present inside an area of sclerosis due to previous surgery, at unusual sites such as behind vascular structures or in the mediastinum. Surgery should be performed at a single session, thereby precluding the need for subsequent surgical procedures.

For these reasons, some authors have proposed radioguidance with an intraoperative gamma-probe following the administration of specific and non-specific tumour-seeking radiopharmaceuticals to detect and dissect lymph nodes during surgery for local and regional recurrences in patients with thyroid cancer. The radiopharmaceuticals used for RGS are different according to the type of cancer [3, 6, 7, 14–19] and are reported in Table 3.

Travagli et al. [3], from the Institute Gustave-Roussy in Villejuif,

Table 3. Radiopharmaceuticals for RGS in thyroid cancer

Tumour-seeking radiopharmaceuticals for RGS in thyroid cancer	Ref.
Differentiated thyroid carcinoma	
^{131}I-iodine	[3, 6, 7, 14]
^{123}I-iodine	[15]
Non functioning thyroid carcinoma	
^{99m}Tc-MIBI	[16–17]
Medullary thyroid carcinoma	
^{111}In-pentreotide	[18–19]
^{99m}Tc(V)-DMSA	
Monoclonal antibodies	

RGS — radio-guided surgery

France, proposed and designed a protocol combining the administration of high doses of ^{131}I and an intraoperative probe to detect and then radically dissect lymph node recurrences from DTC in a single session.

Following their experience, we used the same protocol on a smaller number of patients with local and regional recurrences from DTC, with only a minor difference from the original protocol, i.e. performing the pre-surgery TxWBS 3 days after ^{131}I administration (instead of 4 days) when the patients were discharged from the isolated rooms because the radiation exposure rate was $< 30\ \mu$Sv/hr at 1 m [7].

Our results confirmed that TxWBS is a useful pre-surgery diagnostic procedure for detecting lymph node metastases from DTC that is more sensitive and specific than US or CT. The gamma probe permitted us to look for neoplastic foci with high sensitivity and specificity and to remove metastatic lymph nodes resistant to radioiodine therapy. It allowed removal of pathological areas of uptake in the neck in most patients and allowed detection of some additional tumoural foci inside areas of sclerosis or behind vascular structures that were not seen during the pre-surgical evaluation.

In fact, in most cases the surgeons expressed a positive opinion about the procedure, describing it as "decisive" or "favourable."

In addition, the evidence that 6 lymph node metastases were only found at histological examination of surgical specimens, being undetected by neither TxWBS nor the probe, confirms other authors' suggestions that lymph node metastatic involvement displays insufficient or absent uptake [20].

Therefore, the possibility of false negative results implies that a complete excision to remove lymph nodes is needed irrespective of the count rate measured by the gamma probe and, probably, the most appropriate term for this technique is "radio-assisted surgery" instead of "radio-guided surgery", to highlight the assistance of the gamma-probe in the way of performing a more complete surgery.

Another advantage of this protocol is the possibility of early evaluation of the efficacy of surgery. In fact, the rapid decrease in radioactivity count shown by the gamma probe and the negative qualitative evaluation of the TxWBS on day 7 allowed us to evaluate the completeness of the tumoural excision at an early stage.

We did not observe significant lengthening of the normal operating times needed to perform a radical lymph node dissection, nor was there an increase in morbidity, particular risks or surgical complications. Both Travagli et al. [3] and Scurry et al. [6] confirmed the very low morbidity of this protocol, with only one reported haemo-mediastinum in a patient with a large mediastinal lymph node metastasis and a case of transient laryngeal nerve palsy [20].

Although we administered a high radioiodine dose 4 days before surgery, we always observed low levels of radioactive exposure to the surgeon's hands and no radioactive contamination of surfaces or surgical tools.

However, there are some limitations to this procedure that are worth mentioning. Firstly, owing to the physical properties of ^{131}I, the gamma probe involves a suboptimal performance with this radiopharmaceutical, and better performance has been obtained using a gamma probe after the administration of ^{123}I [17–21]. The half-life of ^{123}I (13 hours) allows optimisation of target-to-background ratio with a fairly strong target signal over a period of 12 to 24 hours, therefore permitting a flexible operating room scheduling. The gamma energy (159-kev gamma photon) is optimal for diagnostic purposes compared to the 364-kev of ^{131}I, and entails minimal radiation exposure both to patient and surgeon. However, high costs and difficult availability limit the extensive use of ^{123}I in common clinical practice.

Secondly, in most countries radioprotection regulations do not permit the use of large ^{131}I doses in outpatients. Hence, the dose used for the present study (i.e., 3.7 GBq) requires that the patient be hospitalized, with its consequent costs and patient discomfort.

Finally, even though we did not observe significant impact on myocardial contractility, nervous system function or increased operative risk, the surgery is performed on patients in subclinical hypothyroidism and achieved by withdrawal of L-thyroxine therapy. This, however, is not a problem if exogenous administration of recombinant human TSH (rhTSH) is performed.

Conclusions

This study confirms our previous results as well as other authors' (3–6–7) and suggests that RGS can be of substantial benefit when performing radical lymph node dissection in patients with local and regional recurrences of DCT in a single session. It permits accurate surgical results without significant lengthening of the normal operating times. It was not associated with any increase in morbidity or surgical complications, and delivered low levels of radioactive exposure to the surgeon's hands.

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