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Successful Treatment of Differentiated Thyroid Carcinoma with Transaxillary Robotic Surgery and Radioiodine: The First European Experience

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Cancer · Papillary thyroid carcinoma · Quality of life · Radioiodine ablation · Radioiodine therapy · Surgery · Thyroid cancer · Robotic surgery · Differentiated thyroid cancer · Oncological evaluation

Abstract
Objectives: Transaxillary robotic thyroidectomy surgery (TARS) has been reported to be a safe approach in patients with differentiated thyroid carcinoma, and oncological responses are promising. ***Study Design:*** This study aimed to evaluate the oncological outcomes of TARS followed by radioiodine (RAI) therapy in patients with differentiated thyroid carcinoma. Between 2011 and 2016, patients treated for differentiated thyroid carcinoma by TARS in a single institution, followed by RAI, were retrospectively included. The oncological response was performed according to the 2015 American Thyroid Association (ATA) guidelines 6–12 months later and at the last available visit. ***Results:*** A total of 42 patients (30 females) were included, with a median tumor size of 20 mm (12 cases of N1a and 5 cases of N1b on initial pathology report). According to ATA classification of recurrence risk after surgery, 17 and 25 patients were classified as low and intermediate risk, respectively. After RAI, all patients had a normal posttherapeutic whole body scan (except 1 patient, who had pathological lymph node uptake), but no unusual uptake was seen. At the 6- to 12-month evaluation (n = 37), 24 patients had excellent response, 8 had indeterminate response, and 5 had incomplete response (2 biological and 3 structural); no distant metastasis was found. At the last evaluation (median follow-up 15.9 months), 35 patients had no evidence of disease and 1 patient had a structural incomplete response. In total, a second open surgery was necessary for 3 patients to treat persistent lymph nodes (all intermediate risk). ***Conclusion:*** In this study, TARS followed by RAI therapy seems to be curative, even for patients with lymph node metastases, after good preoperative staging. More studies are required to confirm the findings.

Introduction

Thyroid cancer is the most common endocrine malignancy, accounting for 3.8% of new cancer diagnoses [1], and its incidence has increased faster than other malignancies in the last decade due to the better detection of

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early-stage small cancers. Most of these tumors are well differentiated and curable by surgery. Radioiodine (RAI) therapy is administered for remnant ablation in some cases, while in a few cases it is given as sole therapy or as adjuvant therapy. The American Thyroid Association (ATA) guidelines [2] for the management of thyroid cancer changed in 2015: they now advocate a more appropriate and risk-adapted approach to both the diagnosis and treatment of thyroid cancer. Regarding RAI therapy, the lowest activity is now needed to ensure successful treatment with the lowest risk possible. About 6–24 months after RAI treatment, oncological response to therapy is evaluated based on ultrasonography, as well as clinical and biological status.

Surgical resection remains the first-line therapy. Open thyroidectomy (OpenT), performed through an anterior neck dissection, is the most commonly practiced surgery. However, to improve cosmetic outcomes and to prevent nerve and muscle injury, transaxillary robotic thyroidectomy surgery (TARS) was developed by Korean surgeons in 2007 [3]. Since then, this technique has been used for both benign and malignant thyroid disease. The size limit is commonly set at >20–40 mm for low risk-differentiated thyroid carcinoma, and >50 mm for benign or indeterminate nodules. Morbidity and quality of life outcomes seem comparable in thyroid cancer patients undergoing either OpenT or TARS. Surgical completeness also appears similar. Moreover, the rates of locoregional recurrence and survival outcome at 5 years are similar between OpenT and TARS in Korean studies [4].

To our knowledge, most of the data about TARS effectiveness in thyroid cancer comes from Korea. No European studies have been published concerning robotic thyroidectomy treatment for cancer cases only, with or without RAI therapy. To address the lack of information, we analyzed the results of TARS combined with RAI treatment of differentiated thyroid cancer in a series of consecutive patients treated in a single surgery department in France. The oncological response was assessed according to the 2015 ATA guidelines [2].

Patients and Methods

Inclusion Criteria

We included consecutive patients treated by TARS for thyroid carcinoma in the Department of Otolaryngology Head and Neck Surgery of the American Hospital of Paris, followed by radioiodine (RAI) therapy between March 2011 and October 2016. Oncological response to therapy was evaluated 6–12 months after RAI.

Surgical Treatment

TARS was performed by a single surgeon (P.A.) via transaxillary approach, using the Da Vinci Si® surgical robot (Intuitive Surgical, Sunnyvale, CA, USA), as previously described [5]. Prophylactic ipsilateral or bilateral central lymph node dissection was performed when the analysis by specialized systematic neck ultrasonography suggested the presence of carcinoma before the operation. Postoperative complications were recorded. All patients signed an ethics statement at the time of surgery.

RAI Treatment Protocol

All patients received RAI therapy at least once within 12 months following surgery and were treated according to local practice at the time of treatment (in 2 different centers). The RAI (^{131}iodine) dose used was either low dose (1.1 GBq ^{131}iodine) for remnant ablation, or high dose (3.7 GBq ^{131}iodine) for adjuvant therapy. The choice of the dose was based on local practice, in agreement with the ATA guidelines in practice at the time of treatment (either 2009 [6] or 2015 [2] ATA guidelines). The RAI therapy was administered after preparation, using either levothyroxine withdrawal or thyrotropin (rhTSH) stimulation. Thyroid markers were measured in the serum, namely, TSH, stimulated serum thyroglobulin (Tg), and the presence of anti-Tg antibodies (anti-Tg Ab). Stimulated Tg was measured either on the day of RAI administration in the case of levothyroxine withdrawal, or on the peak 5th or 6th day after rhTSH stimulation. A posttherapeutic whole body scan combined with SPECT CT (single photon emission computed tomography) was performed 3 days after RAI administration. The site of uptake and conclusion of whole body scan (normal, indeterminate, suspicious) were recorded.

Oncological Response and Follow-Up

Oncological response to therapy was established 6–12 months after RAI therapy, based on clinical examination and morphological results on a neck ultrasonography. The following biological markers were also measured: serum Tg on levothyroxine treatment (basal Tg) or after TSH stimulation (stimulated Tg), and anti-Tg Ab. The oncological outcome was assessed according to the ATA 2015 recommendations [2], which describe four clinical statuses at any point during the follow-up:

- Excellent response: no clinical, biochemical, or structural evidence of disease. Cutoff for basal (suppressed) Tg <0.2 ng/mL and TSH-stimulated Tg <1 ng/mL.
- Biochemical incomplete response: negative imaging and basal Tg >1 ng/mL, stimulated Tg >10 ng/mL, or rising anti-Tg Ab levels.
- Structural incomplete response: structural or functional evidence of disease with any Tg level, with or without anti-Tg Ab.
- Indeterminate response: nonspecific biochemical or structural findings that cannot be confidently classified as either benign or malignant. Nonspecific findings on imaging studies. Nonstimulated Tg detectable (but <1 ng/mL) or stimulated Tg detectable (but <10 ng/mL), or anti-Tg Ab stable or declining in the absence of structural or functional disease.

For the follow-up, oncological outcomes were assessed based on clinical examination, thyroid markers (basal Tg and anti-Tg Ab), and latest neck ultrasonography. For patients with short follow-up without full oncological evaluation, thyroid markers were studied when available and added to the results of the ultrasonography performed at the time of RAI.

Table 1. Thyroid cancer staging

Parameter	Patients (n = 42)	%
ATA 2015 recurrence risk		
Low	17	40
Intermediate	25	60
Initial tumor staging after surgery		
Tumor staging		
T1a	2	5
T1b	6	14
T2	12	29
T3 with tumor size >40 mm	5	12
T3 with extra thyroid extension	17	40
Lymph node staging		
N0	17	40
N1a	12	29
N1b	5	12
Nx	8	19
Metastatic staging during follow-up		
M0	42	100
M1	0	

American Joint Committee on Cancer (AJCC) 7th edition of the TNM classification system for differentiated thyroid carcinoma was used to establish TNM staging in the study. ATA, American Thyroid Association.

Results

Clinical and Pathological Characteristics

In total, 42 patients with thyroid carcinoma histologically proven at the time of robotic thyroidectomy and then receiving RAI treatment were included for analysis. The patients' demographic and clinicopathological characteristics are shown in Table 1. The median age at the time of surgery was 46 years (range 26–71 years); 12 males (29%) and 30 females (71%) were included. The most common indication of thyroidectomy was pathological preoperative cytology (suspicious or malignant) in 27 cases, suspicious nodule on ultrasonography (with indeterminate cytology or without cytology) in 10 cases, and fortuitous pathological findings in 5 cases.

Pathological reports showed a median tumor size (greatest dimension) of 20 mm (range 5–70 mm). The 7th edition of the American Joint Committee on Cancer (AJCC) TNM classification system was used to establish the TNM staging in the study. Several foci were observed in 21 cases and minor/microscopic extrathyroidal extension (pT3) in 19 cases; 4 patients had aggressive subtypes of thyroid carcinoma: 1 poorly differentiated carcinoma, 1 oncocytic vesicular, 1 tall cell, and 1 sclerosing variant (focal). Lymphocytic thyroiditis lesions were found in 23 cases. Regarding the lymph node staging, patients were Nx and N0 in 8 and 17 cases, respectively, and N1a and N1b in 12 and 5 cases, respectively (Table 1). The median number of metastatic lymph nodes was 4 (range 1–11), with extracapsular nodal extension in 5 patients. According to the ATA classification of recurrence risk after surgery, 17 and 25 patients were classified as low and intermediate risk, respectively (Table 1). No patient had known distant metastases either before surgery or afterwards.

Surgical Outcome

The median duration of hospitalization was 3 days (2–10 days). Postoperative complications were observed in 12 cases. These complications were permanent unilateral vocal cord palsy (n = 1), transient hypoparathyroidism (n = 1), permanent hypoparathyroidism requiring calcium and α-calcidol vitamin D supplementation for more than 6 months (n = 2), and postoperative anterior chest pain or cervical discomfort (n = 8). Two patients had pulmonary embolism during hospitalization. Conversion to open procedure was required in 2 cases during the initial surgery (1 case each in 2011 and 2012).

RAI Treatment

The ^{131}iodine dose administered for RAI therapy was 1.1 GBq in 18 cases (43%) and 3.7 GBq in 24 patients (57%). TSH stimulation was done by levothyroxine withdrawal in 15 cases (36%) and rhTSH stimulation in 27 cases (64%). The results of RAI treatment are summarized in Table 2. At the time of RAI therapy, the median stimulated Tg level was 4.5 ng/mL (range 0.16–125 ng/mL) and 7 patients had anti-Tg Ab. At that time, 3 patients had a suspicious cervical lymph node on ultrasonography.

All patients had a normal posttherapy whole body scan with SPECT CT (except 1 patient, who had pathological cervical lymph node uptake, confirmed by ultrasonography). The median calculated cervical uptake was 1% (range 0.06–3.9%; data available for 17 patients), corresponding to thyroid remnants and/or physiological thyroglossal tract. Four patients had a cervical uptake of more than 2%. No unusual uptake, particularly in the chest wall, was seen in any of these patients.

Oncological Response and Follow-Up

At the 6- to 12-month posttherapy evaluation (median time 8 months), most patients (32/37; 87%) had a good

response to treatment and no evidence of disease. Of these, 24 (65%) had an excellent response and 8 (22%) had an indeterminate response (Table 3). Four of these patients were classified as having an indeterminate response because of persistent, but not rising, anti-Tg Ab. According to the ATA level of recurrence risk, the oncological response was excellent in 11/13 patients (84%) of the low-risk group and in 13/24 patients (54%) of the intermediate-risk group. In the intermediate-risk group, 2 patients (5%) had a biochemical incomplete response and 3 (9%) had a structural incomplete response with suspicious cervical lymph node; 2 of the 3 patients with a morphological incomplete response had an elevated stimulated Tg level (167, 125, and 16 ng/mL) at the time of adjuvant RAI therapy. Evaluation of the response was not possible in 2 patients because of insufficient follow-up (no second postoperative ultrasonography available) but both had already a very low Tg. Finally, 3 patients were not further evaluated after RAI treatment (lost to follow-up).

The median follow-up time was 15.9 months (range 5–62). At the last point of follow-up, no evidence of disease was found in almost all patients (37/39; 92%). Patients had an excellent response in 27 cases, an indeterminate response in 8 cases, and a good biological response in 2 cases (short follow-up, excellent or indeterminate response with normal ultrasonography at the time of RAI therapy) (Table 3). One patient had a biochemical incomplete response and another had a structural incomplete response with a cervical pathological infracentimetric lymph node (online suppl. Table 1; see www.karger.com/doi/10.1159/000487234). During that follow-up, 3 patients required a second surgery (using the OpenT technique this time) to remove suspicious persistent lymph nodes. Of note, those 3 patients had metastatic lymph nodes removed during the initial robotic intervention. Three patients were not followed up.

Discussion

Several studies have shown the advantages of TARS over traditional OpenT, such as better cosmetic outcomes, reduced postoperative pain, lower estimated

Table 2. RAI treatment

Parameter	Patients (n = 42)
Administered RAI activity	
1.1 GBq ^{131}iodine	18 (43)
3.7 GBq ^{131}iodine	24 (57)
TSH stimulation preparation	
rhTSH	27 (64)
Levothyroxine withdrawal	15 (36)
Stimulated Tg level, ng/mL	4.5 (0.1–125)
Positive anti-Tg Ab level	7 (16)
Uptake on the WBS	
Orthotopic residual thyroid tissue including thyroglossal tract	42
Cervical lymph node	1
Distant metastases	0
Median cervical uptake RAI (n = 17), %	1 (0.06–3.9)

Values are n (%) or median (range), as appropriate. RAI, radioiodine; WBS, whole body scan.

Table 3. Oncological outcome

Response to therapy	6–12 months after RAI (n = 42)	%	End of follow-up (n = 42)	%
Excellent response	24	57	27	64
Indeterminate response	8	19	8	19
Biochemical incomplete response	2	5	1	2.5
Structural incomplete response	3	7	1	2.5
Not yet available	2	5	2	5
Lost to follow-up	3	7	3	7
Median duration of follow-up, months	last follow-up (n = 15)		15.9 (5–62)	

Response to therapy according to ATA 2015 guidelines [2]. ATA, American Thyroid Association; RAI, radioiodine.

blood loss [7–10], and less dysphagia. Furthermore, the bilateral vagal automatic periodic stimulation use during surgery increases patient safety, as it prevents impending thermal or stretch-related injury to the recurrent laryngeal nerve [10–12]. Many systematic reviews and meta-analyses have been published regarding the safety and efficiency of robotic thyroidectomy. Those reviews relied mainly on Korean publications [13–15] showing that robotic thyroidectomy was as safe as OpenT for benign and cancer cases, with the same rate of complications, but a longer operative time. In our study, morbidity with TARS appears comparable to OpenT since the percentage of postoperative complications, such as hypoparathyroidism or recurrent laryngeal nerve injury, is similar to those reported in several meta-analyses [7, 10]. This could be due to the fact that all surgeries in this study were performed by a surgeon with a high level of expertise. It is also noteworthy that the vast majority of patients (90%) had a suspicion of cancer before surgery, and they chose the TARS to be cured. Systematic preoperative staging by specialized ultrasonography probably helped to achieve the excellent oncological outcome in our study.

In the literature, 2 cases of suspicious ectopic residual thyroid tissue located in the subcutaneous tissues used for the TARS pathway have been described [16], but a false iodine-positive test with inflammatory chest wall was not completely excluded. In contrast, in this current study, no unusual posttherapeutic imaging was found. The aspect on the whole body scan was the same as that usually seen in good open surgery, with small remnants, except in 4 cases with fixation of benign thyroid remnants of more than 2%.

In our study, even low-risk patients (especially pT1a [multiple] and pT1b patients), received RAI in agreement with local recommendations that were in use at the time. This has now been changed, and RAI is no longer recommended for low-risk patients [6].

The oncological response to therapy in our study is in line with previously published results with OpenT. Indeed, according to the results supporting ATA recommendations [2], an excellent response to initial therapy (stimulated Tg <1 ng/mL, in the absence of anti-Tg Ab) was achieved in 86–91% of ATA low-risk patients and in 57–63% of ATA intermediate-risk patients. We found an initial excellent response to therapy in 84% (11/13) of ATA low-risk patients and 54% (13/24) of ATA intermediate-risk patients (even when considering the 4 patients with persistently detectable anti-Tg Ab). Neither biochemical nor structural incomplete response was noted in our low recurrence risk group. Biochemical and structural incomplete response has been described in 22 and 19–28%, respectively, of ATA intermediate-risk patients in the literature [2]. We found lower numbers of 8 and 12%, respectively, after 6–12 months of follow-up in our series. Among the 3 patients with structural incomplete response at the 6- to 12-month evaluation, none had any remaining morphological disease at the last follow-up visit and 2 still had detectable levels of blood Tg (result obtained after second open surgery for 2 patients, and 1 patient had spontaneous size regression). The comparison of our oncological results with other TARS studies is difficult. One of the reasons is that most of the nodules in Korean publications are smaller than our series (largest diameter of around 10 mm vs. 20 mm in our series). American [15] and Chinese [13] meta-analyses of Korean articles showed that the postoperative Tg level after TARS was significantly higher than after openT, but the interpretation remains difficult because some patients had only lobectomy, the condition and the time of postoperative Tg dosage were not specified, and the use of RAI was not specified.

It has been published that TARS might be inferior to OpenT in terms of the number of central lymph nodes retrieved [3, 4, 10]. However, in the present study, a median of 6 lymph nodes were removed in cases of central dissection only (18 patients), and 18 lymph nodes (range 6–24) in cases of central plus lateral lymph node dissection (8 patients). Moreover, very few patients in our study needed to be operated on again (3/42), and all these patients already had metastatic lymph node at initial diagnosis. Robotic neck dissection via the transaxillary approach was also reported to be safe in patients with papillary thyroid carcinoma and lateral neck node metastasis (N1b) at 5 years postoperatively [17]. It is noteworthy that even aggressive histology has been treated by robotic surgery.

Nevertheless, the present study has several limitations. First, the data were retrospectively analyzed, which has a greater risk of missing data and loss to follow-up (7% in our study, but fewer than in other studies), and no comparison was performed with cases treated with OpenT. Second, our study was limited to a small number of patients due to the underdevelopment of TARS for thyroid cancer in France. Third, there was a relatively short follow-up period of around 16 months, while we acknowledge that thyroid cancer requires long-term surveillance (usually 1–5 years). In our study, patients were treated by RAI according to the local practice at the time of diagnosis. The results of follow-up of patients with a diagnosis of cancer after TARS and not treated by RAI are not known, but these patients had low-risk cancer. Further-

more, the local practice of RAI treatment changed recently during this period concerning indications (less indication in low-risk patients), iodine dose (more ablative than adjuvant dose) and type of preparation used (more rhTSH). Nowadays, fewer treatments are required, in particular for low-risk patients [18].

Conclusion

This study represents the first European report, beyond the pioneering studies done in Korea, of oncological outcome in patients who underwent TARS and RAI therapy for differentiated thyroid cancer. Despite the limited number of patients, our data show that TARS performed by an experienced surgeon is safe, if carried out in selected patients with well-differentiated carcinoma. We also conclude from this preliminary study that TARS is as efficient as OpenT surgery, even for patients with cervical metastatic lymph nodes after thorough preoperative ultrasonography staging. Based on these results, further randomized clinical trials with long-term follow-up are warranted to definitively evaluate the oncological long-term effectiveness of TARS.

Disclosure Statement

Patrick Aidan is a proctor for Intuitive Surgical. All other authors have no conflicts of interest to declare.

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