



## Preoperative Neck Ultrasonographic Mapping for Persistent/Recurrent Papillary Thyroid Cancer

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**Abstract.** Surgical resection of persistent/recurrent (P/R) papillary thyroid cancer (PTC), when localized to the neck, is generally recommended; however, its impact on the course of the disease is not clear. We introduced a new technique in the form of preoperative neck ultrasonographic mapping (US-M) to improve the outcome of the surgical resection of P/R PTC. A total of 19 patients had undergone regional (central, lateral, or both) neck dissection before introducing the current technique (group 1, or G1), and 26 patients (group 2, or G2) had limited lymph node resection guided by US-M with findings accurately plotted on a standard diagram. All of the operations were performed by a single surgeon. The surgical outcomes of the two groups were compared. The resected lesions were positive for PTC in 17 patients (89.5%) in G1 and in 25 patients (96.2%) in G2. In G2, the intraoperative findings exactly matched the US-M in 23 patients (88.5%). Postoperatively, neck US became negative in 50% in G1 and in 83.3% in G2 ( $p = 0.02$ ). Thyroglobulin (Tg) became undetectable in 37.5% in G1 and 52.3% in G2 ( $p = 0.37$ ). Whole-body iodine scans (WBS) became negative in one of six patients (16.7%) in G1, and in three of four patients (75%) in G2, ( $p = 0.06$ ). After a mean follow-up of  $23.8 \pm 7.1$  months in G1 and  $9.8 \pm 4.7$  months in G2, 6 patients (31.6%) in G1 and 15 patients (62.5%) in G2 were in remission ( $p = 0.04$ ), whereas the disease persisted in 13 cases (68.4%) in G1 and 9 (37.5%) in G2 ( $p = 0.04$ ). In conclusion, US-M improved the surgical outcome, as evidenced by the postoperative US, Tg, and WBS findings and the higher remission rate for the G2 patients than for the G1 patients.

The management of recurrent/persistent (P/R) differentiated thyroid cancer, particularly when there is a discrepancy between the radioactive iodine whole body scan (WBS) and the serum thyroglobulin (Tg) level, is controversial [1–3]. When the P/R disease is significant and localized to the neck, surgery is usually indicated [1, 4–7]. However, in such a situation the impact of surgery on the course of the disease has not been consistently effective [8, 9]. The traditional approach is to perform unilateral or bilateral modified neck dissection, removing all grossly palpable disease. Our experi-

ence with that approach has not been quite satisfactory. In a previous study, we found that only about 20% of our patients with P/R disease achieved a complete remission with a low Tg level and negative imaging studies. Most patients continued to have evidence of persistent disease with elevated Tg or a positive WBS (or both) [9].

We have introduced a new technique in the form of meticulous preoperative neck ultrasonographic mapping (US-M) to localize P/R disease accurately followed by limited neck dissection and lymph node resection in the areas with abnormal findings on US-M. We now report our experience with this technique, comparing it with the standard approach in a cohort of patients who were reoperated for P/R disease.

### Materials and Methods

#### Patients

We retrospectively reviewed the medical records of 45 patients who underwent surgical reexploration for P/R papillary thyroid cancer (PTC). A single surgeon (S.A.) performed surgical resection in all patients. Patients were divided into two groups (Table 1): the control group (G1), which includes 19 nonselected patients (16 females, 3 males; mean  $\pm$  SD age  $41 \pm 14$  years) who underwent regional (central, lateral, or both) neck dissection for P/R PTC during the year before introducing the preoperative US-M technique, and the US-M group (G2), which includes 26 patients (19 females, 7 males; mean  $\pm$  SD age  $33.5 \pm 11.0$  years) who underwent limited surgery for P/R PTC guided by preoperative US-M. In G1, P/R disease was unilateral in 16 patients (15 jugular and 1 central) and bilateral central in 3 patients. In G2, the disease was unilateral in 17 patients (8 jugular and 9 central) and bilateral in 9 cases (5 jugular and 4 central). Remission was defined as no evidence of disease clinically, low Tg (undetectable on L-thyroxine or  $\leq 5$  ng/dl off L-thyroxine therapy), and negative WBS (if done). Persistent disease was defined as high Tg or positive WBS (or both). Disease was con-

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**Table 1.** Initial clinical, surgical, and pathologic characteristics and comparison between patients who underwent US-M and the control group.

| Parameter                      | Controls<br>(n = 19) | US-M group<br>(n = 26) | p       |
|--------------------------------|----------------------|------------------------|---------|
| Age (years)                    | 41.0 ± 14.0          | 33.5 ± 11.0            | 0.047   |
| Sex (Male:female)              | 3:16                 | 7:19                   | 0.480   |
| Pressure symptoms              | 1 (6.7%)             | 3 (11.5%)              | 0.620   |
| Duration of symptoms (months)  | 29.8 ± 32.0          | 17.5 ± 22.0            | 0.210   |
| Completion surgery             | 4 (21%)              | 6 (23%)                | 1.000   |
| <sup>131</sup> I dose (mCi)    | 211 ± 21             | 183 ± 19               | < 0.001 |
| Tumor size (cm)                | 2.15 ± 1.00          | 2.8 ± 1.7              | 0.250   |
| Extrathyroidal tumor extension | 9 (47.3%)            | 17 (65.3%)             | 1.000   |
| Tumor multifocality            | 8 (42.1%)            | 23 (88.4%)             | 0.020   |
| TNM stage                      |                      |                        | 0.180   |
| I                              | 13                   | 23                     |         |
| II                             | 1                    | 2                      |         |
| IV A                           | 4                    | 1                      |         |
| Nonstageable                   | 1                    | 0                      |         |

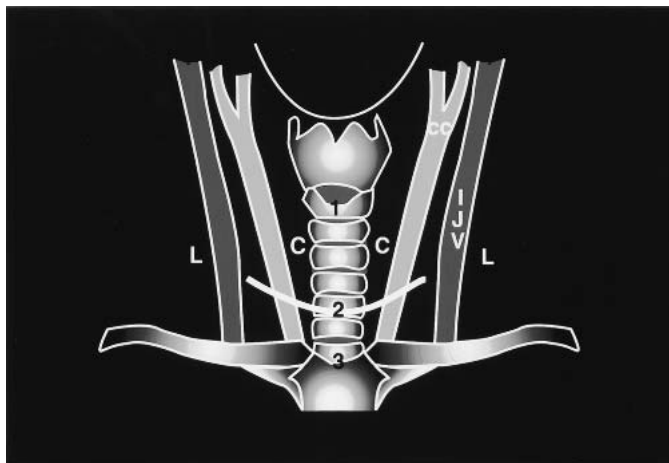
US-M: ultrasonographic mapping.

Continuous variables are expressed as the mean ± SD, and categorical variables are expressed in numbers and percents.

sidered recurrent when there was evidence of disease (as defined for persistent disease) after a period of remission.

**Group 1.** Nineteen nonselected patients who underwent unilateral or bilateral regional neck dissection for P/R disease before the introduction of the US-M technique were studied and compared with patients in G2 (Table 1). All patients presented with thyroid swelling, with a mean duration of symptoms of 29.8 ± 32.0 months. One patient had dysphagia. All patients underwent total thyroidectomy in one stage (15 cases) or two stages (4 cases). Eleven patients (57.9%) underwent modified lymph node dissection: six cases unilateral and five cases bilateral. The tumor size was 2.15 ± 1.00 cm; nine patients (47%) had tumor extrathyroidal extension, and eight (42%) had multifocal (two or more foci) tumors. Thirteen patients were in TNM stage I, one was in stage II, four were in stage IVA, and one could not be staged because of a lack of information. All 19 patients underwent iodine-131 (<sup>131</sup>I) ablation with a mean dose of 211 ± 21 mCi. Following surgery and <sup>131</sup>I ablation, patients were treated with suppressive doses of L-thyroxine to achieve undetectable thyroid-stimulating hormone (TSH) levels with high-normal levels of free thyroxine (FT<sub>4</sub>).

**Group 2.** All patients presented with thyroid swelling for a mean duration of 17.5 ± 22.0 months. Three had pressure symptoms in the form of vocal hoarseness or dysphagia. All patients underwent total thyroidectomy in one stage (20 cases) or two stages (6 cases). Unilateral (3 cases) or bilateral (6 cases) modified lymph node dissection was performed in nine patients (34.6%) with positive mid-jugular lymph node sampling (by frozen section). The pathology examination revealed PTC in all cases, with a mean tumor size of 2.8 ± 1.7 cm. In 23 patients (88.4%), the tumor was multifocal, and in 17 patients (65.3%), there was evidence of tumor extrathyroidal extension. Altogether, 23 patients were in TNM stage I, 2 were in stage II, and 1 patient was in stage IVA. All patients received one or two doses of <sup>131</sup>I for thyroid remnant ablation (mean dose 183 ± 19 mCi). One patient also received 4000 rad of external beam radiotherapy. Following surgery and radioactive iodine ablation, pa-



**Fig. 1.** Neck area used for ultrasonographic mapping (US-M). US findings were plotted, on this sketch, which was used intraoperatively to guide surgery. L: lateral; C: central; IJV: internal jugular vein.

tients were treated with suppressive doses of L-thyroxine to achieve undetectable TSH levels with high-normal FT<sub>4</sub>.

#### Persistent/Recurrent Disease

The diagnosis of P/R disease was based on positive US findings of suspicious soft tissue lesions in the neck (all patients), a high Tg level (37 patients), and a positive WBS (10 patients). The diagnosis was confirmed by positive US-guided fine-needle aspiration cytology in all patients. High Tg was defined as any detectable Tg in patients on thyroid hormones or > 5ng/ml in patients off thyroid hormone therapy.

#### Preoperative Ultrasonographic Mapping

In G2 patients, preoperative US-M was performed on the morning of surgery using a high-frequency (10–12 MHz), high-resolution ultrasound probe to scan the entire neck. All US examinations were performed by a single experienced radiologist (H.S.A.). The US findings were precisely plotted on a standard neck diagram (Fig. 1). The landmarks for the US-M diagram were four compartments (two lateral and two central neck compartments) and three levels (the level of the cricoid cartilage, the level of a previous thyroidectomy scar, and the level of the clavicle).

#### Surgery

Surgery for G1 was regional neck dissection in which the lateral (internal jugular lymph nodes) or central (peritracheal lymph nodes) compartments of the neck (or both) were fully explored at the involved site and all abnormal lesions were resected. For G2, the surgery was a more selective procedure; exploration was limited to the areas with abnormal US findings, which were resected without further exploration of the entire compartment or other regions.

#### Statistical Analysis

The data are presented as the mean ± standard deviation when continuous and as a percentage when categorical. The *t*-test was

**Table 2.** Comparison of the outcome after surgery for persistent/recurrent disease in patients who did and did not undergo US-M.

| Parameter          | Controls (n = 19) |                    |       | US-M group (n = 26) |                    |       | p    |
|--------------------|-------------------|--------------------|-------|---------------------|--------------------|-------|------|
|                    | Yes               | Total <sup>a</sup> | %     | Yes                 | Total <sup>a</sup> | %     |      |
| Negative US        | 9                 | 18                 | 50.0% | 20                  | 24                 | 83.3% | 0.02 |
| Undetectable Tg    | 6                 | 16                 | 37.5% | 11                  | 21                 | 52.3% | 0.37 |
| Tg decreased > 50% | 1                 | 10                 | 10.0% | 5                   | 10                 | 50.0% | 0.14 |
| Negative WBS       | 1                 | 6                  | 16.7% | 3                   | 4                  | 75%   | 0.06 |
| Remission          | 6                 | 19                 | 31.6% | 15                  | 24                 | 62.5% | 0.04 |
| Persistence        | 13                | 19                 | 68.4% | 9                   | 24                 | 37.5% | 0.04 |

P/R: persistent/recurrent; Tg: thyroglobulin; WBS: whole-body iodine scan.  
<sup>a</sup>Total number of patients with available data.

used to compare continuous variables and Fisher’s exact test or the  $\chi^2$  test for categoric data, as appropriate.

**Results**

*Initial Clinical and Pathology Data*

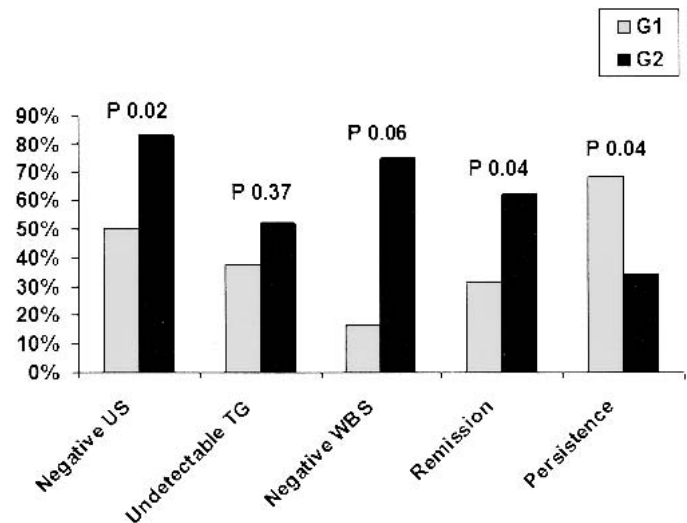
With the exception of age and tumor multifocality, the demographic and initial clinical and pathologic data were similar for the two groups (Table 1).

*Surgery for P/R Disease*

In G1, of a total of 129 lymph nodes removed from 19 patients (average of 6.8 lymph nodes/patient), 46 lymph nodes (35.7%) had metastatic PTC, and the other 83 lymph nodes (64.3%) were benign. The lymph node dissection was as follows: unilateral jugular in 15 patients (79%), unilateral central in 1 patient (5%), and bilateral central in 3 patients (16%). In G2, a total of 122 lymph nodes were removed from 26 patients (average of 6.4 lymph nodes/patient); 63 lymph nodes (52%) had metastatic PTC, and 59 (48%) were benign. The lymph node dissection was unilateral jugular in 8 patients (30.8%), unilateral central in 9 patients (34.6%), bilateral jugular in 5 patients (19.2%), and bilateral central in 4 patients (15.4%). The surgical findings for G2 were consistent with the US findings in 23 patients (88.5%) and different in only 3 (11.5%). The pathology examination of the resected specimens showed lymph node metastatic PTC in 17 patients (89.5%) in G1 and in 25 patients (96.2%) in G2. The rest of the lymph nodes were benign.

*Surgical Outcome*

The follow-up period was  $23.8 \pm 7.1$  months in G1 and  $9.8 \pm 4.7$  months in G2. The outcomes of surgery for both groups are summarized in Table 2 and Figure 2. Among 42 patients who had post-operative follow-up neck US data (18 in G1 and 24 in G2), US was negative in 9 cases (50%) in G1 versus 20 cases (83.3%) in G2; it was positive for residual lesions in 9 cases (50%) in G1 versus 4 cases (16.7%) in G2 ( $p = 0.02$ ). In 37 patients who had high Tg prior to surgery for P/R disease, Tg became undetectable in 6 of 16 patients (37.5%) in G1 and in 11 of 21 patients (52.3%) in G2. Among the remaining patients who continued to have elevated Tg levels after surgery for P/R disease, 1 of 10 patients (10%) in G1 versus 5 of 10 patients (50%) in G2 had a > 50% decrease compared to their Tg level prior to surgery. WBS became negative in one of six patients (16.7%) in G1 and in three of four patients (75%) in G2. Six



**Fig. 2.** Overall comparison between the patients who underwent US-M (G2) and those who did not (G1) regarding the outcome of surgical resection. TG: thyroglobulin.

patients (31.6%) in G1 and 15 (62.5%) in G2 were judged to be in remission ( $p = 0.04$ ), whereas the disease persisted in 13 patients (68.4%) in G1 and 9 patients (37.5%) in G2 ( $p = 0.04$ ). Two patients in G2 could not be categorized as being in remission or having persistent disease because of a lack of follow-up data (short follow-up). The TNM staging in those who continued to have persistent disease were not significantly different ( $p = 0.49$ ) between the two groups (in G1: seven in stage I, one in stage II, and four in stage IVA; in G2: seven in stage I, one in stage I, and one in stage IVA)

**Discussion**

Despite the high cure rate after initial therapy of PTC, P/R disease is not uncommon, and its management can be challenging [10, 11]. In this study, we examined the results of a newly adopted, US-guided, limited surgical approach for P/R PTC. Overall, we found that such an approach is associated with better surgical outcome; the rates of disappearance of US abnormalities, undetectable Tg, and negative WBS, as well as the remission rate, were higher than the same parameters when using the conventional surgical approach. Additionally, such an approach may offer better results and may decrease the risk of complications and the surgical time.

Overall, the risk of development of P/R disease in PTC is report-

edly 5% to 40% [10–12]. Most of these cases occur during the first few years after initial therapy, but recurrence has been reported after several decades [10]. The thyroid cancer mortality is mostly related to P/R disease rather than to the primary disease [10, 11]. Most of the patients with P/R disease have locoregional disease involving cervical lymph nodes [11–14]. To detect recurrence early, patients usually undergo periodic surveillance for P/R disease, with measurement of serum Tg and diagnostic WBS [4, 5]. The presence of even a slight elevation of serum Tg (e.g., > 5 ng/ml), uptake on WBS, or both usually indicates P/R disease and calls for further investigations and management. Because most of these patients have locoregional neck disease, high-resolution US is usually indicated. It has been found that this imaging technique has high accuracy for detecting P/R disease in the neck [15–17]. Furthermore, US-guided FNA has become the standard diagnostic approach to confirm P/R neck disease [15, 16].

Once diagnosed, various approaches have been described for management of P/R PTC depending on the status of the WBS and on whether the P/R disease is gross or minimal. Patients with positive WBS and minimal disease are generally treated with  $^{131}\text{I}$ . Those with significant P/R disease, especially when associated with elevated Tg and negative WBS, are generally treated surgically [6–8]. In the case of high Tg and negative WBS, surgery or radioactive iodine has been used with variable results [6, 8, 9].

High-dose  $^{131}\text{I}$  therapy has been reported to have some salutary effect on the Tg level [18–22]. Pacini et al. treated 17 patients who had high Tg and negative WBS with high-dose  $^{131}\text{I}$ ; 16 of the patients showed positive posttherapy WBSs. Among 12 patients for whom follow-up data were available, Tg decreased significantly in 7 patients, increased in 1, and did not change in the other 4 [18]. Pineda et al. treated 17 cases of PTC with high Tg and negative WBS with  $^{131}\text{I}$  in doses of 150 to 300 mCi q6–12 months until the posttherapy WBS became negative and Tg decreased to < 5 ng/ml. After the first  $^{131}\text{I}$  therapy, 16 of 17 posttherapy WBSs were positive, and in 13 patients there was a significant drop in serum Tg. Altogether, 13 patients had a second round of  $^{131}\text{I}$  therapy, 8 of whom had a positive posttherapy WBS. In the 5 patients who had negative posttherapy WBSs, there was a drop in the Tg level to < 5 ng/ml [20]. Schlumberger et al. treated 23 patients with  $^{131}\text{I}$  in doses of 100 mCi every 4 to 6 months until their posttherapy WBSs became negative. Prior to  $^{131}\text{I}$  therapy, all of these patients had normal chest radiographs and elevated Tg levels. Of the 23 patients, 12 had lung metastases shown only on the WBS obtained after  $^{131}\text{I}$  therapy [19].

Despite these encouraging results, there has not been any evidence that such  $^{131}\text{I}$  therapy results in an improved patient outcome [2, 3, 22, 23]. Some studies have shown no benefits from such therapy [22]. Furthermore, the potential risks of repeated doses of  $^{131}\text{I}$  are of concern.

Surgery remains the therapeutic modality of choice for resectable P/R disease, especially when it is clinically palpable or evident on US. The results of surgery, however, are not always satisfactory. We previously reported the results of neck reexploration and modified neck dissection of 21 patients who had P/R disease with high Tg and negative WBS [9]. Those patients had significant locoregional disease on US examination. In that study, the disease was localized to one or more regions in the neck, and unilateral (7 patients) or bilateral (14 patients) modified neck dissection was performed. Only 4 patients (19%) achieved complete remission with undetectable Tg and negative WBS, whereas 13 patients (62%) continued

to have persistent disease. In four patients (19%), the disease progressed with distant metastases or grossly palpable neck disease [9].

Various strategies have been used to guide and improve the accuracy and outcome of surgical resection for P/R disease, including administration of therapeutic doses of  $^{131}\text{I}$  followed 2 to 5 days later by radio-detector probe-guided surgery [24, 25]. Using this technique, Travagli et al. reported their experience with 54 patients who had recurrent disease. They found that the technique was decisive for surgery in 20 patients and facilitated the surgical procedure in 26. In 8 patients, the probe either showed no radioactivity or the radioactivity was falsely positive. Overall, the cure rate was reported to be 93% [24]. In another study, Salvatori et al. reported that the probe showed activity in 74 of 78 lymph nodes removed from 10 patients with P/R differentiated thyroid cancer. They judged this technique to be decisive in 20%, helpful in 60%, and irrelevant in 20% [25]. Despite the encouraging results with the technique, both groups recommended complete, rather than probe-guided limited dissection of the area of surgery, as some cases were not detected by the probe or by radioactive iodine WBS [24, 25].

The use of intraoperative US has also been described [26, 27]. In one study, intraoperative US was used in 13 patients and identified nonpalpable disease in 7 of them; 11 of the patients underwent complete resection, and Tg became undetectable in 7. The technique was particularly useful in patients who had undergone external beam radiotherapy, and when lesions were < 20 mm in size, or locally invasive or adherent to the airways [27]. In a case report, the use of intraoperative US localization successfully detected a small recurrence [26].

To our knowledge, our study is the first to compare retrospectively two surgical approaches to the management of P/R PTC. The results showed a better outcome of surgery in patients in whom US-M was used. Furthermore, the operative complications and the operating time are likely to be less with US-M, issues that were not addressed in this study.

## Conclusions

We found that preoperative US-M is a useful tool for guiding the surgical exploration and resection of P/R PTC. It has a positive impact on the surgical outcome as evidenced by a higher frequency of negative postoperative US and WBS and undetectable Tg. It also improves the remission rate.

**Résumé.** En cas de persistance ou de récurrence (P/R) d'un cancer papillaire de la thyroïde (CPT) au niveau du cou, on recommande habituellement la résection chirurgicale; l'impacte de cette résection sur l'évolution de la maladie, cependant, n'est pas clair. Notre nouvelle technique qui consiste en une cartographie du cou par échographie préopératoire (EPO) est destinée à améliorer l'évolution après résection chirurgicale du CPT P/R. Dix-neuf patients (G1) qui ont eu un curage ganglionnaire cervical central et/ou latéral avant l'introduction de cette technique alors que 26 patients (G2) ont eu un curage ganglionnaire limité guidé par les données de l'EPO, ensuite inscrites sur un schéma, et les résultats et l'évolution ont été comparés entre les deux groupes. Les 45 patients porteurs de P/R ont eu une exploration par un seul chirurgien. Les lésions réséquées étaient positives pour CPT chez 17 patients (89.5%) dans G1 et chez 25 patients (96.2%) dans G2. Dans G2, les constatations peropératoires correspondaient parfaitement avec celles de l'EPO chez 23 patients (88.5%). En postopératoire, on a constaté que l'examen échographique est redevenu normal chez 50% des patients dans G1, et chez 83.3% des patients dans G2 ( $p = 0.02$ ); la thyroglobuline (Tg) n'était plus détectable chez 37.5% dans G1 et chez 52.3% dans G2 ( $p = 0.37$ ); la scintigraphie du corps

entier (SCE) est devenue négative chez 1/6 patients dans G1 et chez 3/4 patients dans G2 ( $p = 0.06$ ). Après un suivi moyen de  $23.8 \pm 7.1$  mois dans G1 et de  $9.8 \pm 4.7$  mois dans G2, six patients (31.6%) dans G1 et 15 patients (62.5%) dans G2 étaient en rémission ( $p = 0.04$ ) alors que la maladie persistait chez 13 patients (68.4%) dans G1 et chez neuf patients (37.5%) dans G2 ( $p = 0.04$ ). En conclusion, l'EPO a amélioré l'évolution chirurgicale comme en témoignent les résultats postopératoires de l'échographie, de la Tg et de la SCE, ainsi que le taux de rémission constaté dans G2 par rapport au G1.

**Resumen.** La resección quirúrgica del cáncer papilar de tiroides (CPT) persistente/recurrente (P/R) es generalmente recomendada cuando se halla localizada en el cuello; sin embargo, no está claro su impacto sobre el curso de la enfermedad. Hemos introducido una nueva técnica en la forma del mapeo ultrasónico (M-US) preoperatorio con el fin de mejorar los resultados de la resección quirúrgica del CPT. P/R. Cuarenta y cinco pacientes con CPT fueron sometidos a disección cervical por P/R a cargo del mismo cirujano. Veintiséis pacientes (G2) tuvieron una disección linfática limitada guiada por M-US con los hallazgos graficados en un diagrama estándar y 19 pacientes tuvieron una disección cervical regional (central y/o lateral) con anterioridad a la introducción de esta técnica (G1). Se hizo la comparación de los resultados entre los dos grupos. En el G2, los hallazgos intraoperatorios coincidieron exactamente con los del M-US en 23 pacientes (88.5%). Las lesiones resecadas fueron positivas para CPT en 17 pacientes (89.5%) en el G1 y en 25 (96.2%) en el G2. La ultrasonografía postoperatoria del cuello (US) se hizo negativa en 50% en el G1 y en 83.3% en el G2 ( $p = 0.02$ ); la tiroglobulina (Tg) resultó no detectable en 37.5% en el G1 y en 52.3% en G2 ( $p = 0.37$ ). La centelleografía (gammagrafía) con yodo de cuerpo completo se hizo negativa en 1 de 6 pacientes (16.7%) en el G1 y en 3 de 4 (75%) en el G2 ( $p = 0.06$ ). Luego de un seguimiento promedio de  $23.8 \pm 7.1$  meses en el G1 y  $9.8 \pm 4.7$  meses en el G2, 6 pacientes (31.6%) en el G1 y 15 (62.5%) en el G2, se encontraban en remisión ( $p = 0.04$ ), en tanto que la enfermedad persistía en 13 (68.4%) en el G1 y en 9 (37.5%) en el G2 ( $p = 0.04$ ). En conclusión, el M-US mejora los resultados quirúrgicos a juzgar por el US postoperatorio, la Tg y la centelleografía con yodo de cuerpo entero, así como la mayor tasa de remisión en el G2 en comparación con el G1.

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