Impact of cervical lymph node dissection on serum TG and the course of disease in TG-positive, radioactive iodine whole body scan-negative recurrent/persistent papillary thyroid cancer[1]

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ABSTRACT. In the management of papillary thyroid cancer (PTC), surgery is indicated for locoregional recurrent/persistent disease. In this study, we examined the effect of such surgery on serum TG and the course of the disease in 21 patients with PTC (mean age 38.5 yr), who after the initial surgery and radioactive iodine (RAI) ablation developed high TG (>10 ng/ml) and negative ^{123}I whole body scan (DxWBS). All patients had neck persistent/recurrent PTC that was confirmed by ultrasound-guided fine needle aspiration. Prior to neck re-exploration, radiological studies (chest X-rays, CT scan of the chest, and fluoro-18-deoxyglucose positron emission tomography [FDG-PET]) showed no evidence of distant metastases. TG autoantibodies were negative in 19 patients. Second surgery consisted of unilateral (13 patients) or bilateral (8 patients) modified neck dissection. The mean±SE TG prior to neck re-exploration was 184.8±79.0 ng/ml and declined after surgery to 127.5±59.0 ng/ml (p=0.25). The corresponding TSH values were 150.6±23.0 and 143.4±20.0 mU/l, respectively (p=0.34). After a mean follow-up of 20.7±3 months, TG increased to 168±68.0 ng/ml. This increase, however, was NS (p=0.67). The corresponding TSH values were 143.4±20.0 and 132.0±22.0 mU/l (p=0.27). Following second surgery, only 4 patients achieved remission, the other 17 patients received one or more of the following therapies; RAI (10 patients), third surgery (5 patients), and/or external radiation (7 patients). Thirteen patients continued to have persistent disease and 4 patients showed progressive course of their disease (distant metastases or grossly palpable neck disease). In conclusion, second surgery for recurrent/persistent PTC leads to remission in only a minority of cases but the course of the disease tends to be stable in most cases.

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INTRODUCTION

Thyroid follicular cell has the ability to concentrate and organify radioactive iodine (RAI) and to produce TG molecules. These specific functions of thyroid follicular cells have been utilized in long-term monitoring of differentiated papillary thyroid cancer (PTC). After initial surgery and RAI ablation of the remnant thyroid tissue, patients are usually followed-up with periodic diagnostic RAI whole body scanning (DxWBS) and serum TG measurements (1-3). Absence of abnormal activity on DxWBS and undetectable or only minimally detectable TG levels generally indicate remission while a positive DxWBS and/or elevated TG usually points to recurrence or persistence of differentiated thyroid cancer (DTC) (1, 4, 5). In general, there is a high correlation between these 2 markers of disease activity, however, discrepancy occurs in about 15-20% of cases (1, 6). The situation of low or undetectable TG in the presence of significant disease rarely occurs and usually indicates that the tumor has dedifferentiated and lost its ability to produce TG (7, 8). On the other

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hand, negative DxWBS in the presence of significantly elevated TG level is not uncommon, occurring in about 15% of cases (6). The management of this situation is far from clear. 131-radioactive iodine (^{131}I) therapy has been reported to result in a variable degree of decline in TG level (6, 9, 10). However, the long-term effect of ^{131}I therapy on the progression of the disease and the patients' survival is not clear (11, 12). Despite the controversy, most experts would agree that when a significant recurrent or persistent disease is localized in the neck without evidence of distant metastases, surgical removal if possible is indicated (3, 13). However, the outcome of surgery in such a situation on the serum TG and the course of the disease are not clear.

The aims of this study were to assess the impact of second surgery on the serum TG and the long-term course of the disease in PTC patients with elevated TG level but negative DxWBS who subsequently underwent second neck exploration and lymph node dissection for locoregional recurrent/persistent disease.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of 21 patients (14 females and 7 males) with PTC, who after initial surgery and ^{131}I ablation developed high TG but negative DxWBS and subsequently underwent neck re-exploration and lymph node dissection for persistent/recurrent disease limited to the neck. The mean age was 38.5 yr (20-60 yr). The initial management consisted of total or near-total thyroidectomy in 19 patients and bilateral partial thyroidectomy in 2 patients. Based on clinical and intra-operative findings, further neck dissection was performed; if lymph nodes in the central compartment were positive or there was evidence of grossly palpable lymph nodes, modified neck dissection (MND) was performed. MND was performed in 14 cases: 8 bilateral and 6 unilateral. In 13 cases (all cases except 1 patient who had unilateral modified neck dissection), the pathological examination of the dissected lymph nodes showed evidence of metastases. Twenty cases had a classical type of PTC while one patient had the follicular variant of PTC; there were no signs of poor differentiation. The mean primary tumor size was 3.2 cm (0.8-6.5 cm). Thirteen patients (62%) were in pathological tumor node metastasis (pTNM) stage 1 while 8 cases (38%) were in stage 3. The low pTNM grade in a significant proportion of cases was mainly related to the young age of these patients; there was evidence of perithyroidal tumor extension in 17 cases (81%) and invasion of the surrounding muscles in 11 patients (52%). All patients received ^{131}I ablation about 2-4 months after initial surgery, with a mean dose of 134 mCi (84-163 mCi). External radiotherapy was not given after the first surgery probably because it was hoped that ^{131}I therapy would lead to remission. In addition, there was no convincing evidence of the efficacy of external radiotherapy. Furthermore, second neck exploration if needed after external radiotherapy carries a significant surgical risk due to the extensive adhesions that usually result from it. Three patients received second ^{131}I therapy (200-218 mCi). The time interval between last ^{131}I therapy and second neck exploration was at least 12 months (12-145 months).

Following initial surgery and ^{131}I ablation, patients were placed on levothyroxine suppression (TSH<0.006 mu/l). After initial management, only 5 patients achieved remission as defined above (see below). Patients were seen annually for follow-up. TG was measured at every visit and DxWBS was done 1 and 2 yr after ^{131}I therapy and, if negative, periodically thereafter.

On follow-up, all patients developed significantly elevated TG (defined as TG>10 ng/ml off thyroid hormone therapy). DxWBS done 24 h after oral doses of 10-15 mCi 123-radioactive iodine-(^{123}I) were negative in all patients (at our institution we use ^{123}I isotope for diagnostic DxWBS). The following definitions were used in this study: the patient is considered to be in remission when physical examination is negative for any palpable tissue or cervical lymphadenopathy, DxWBS is negative, and serum TG is <10 ng/ml off any thyroid hormone therapy. Persistent/recurrent disease is considered to be present when TG is >10 ng/ml off thyroid hormone therapy, neck disease found by US examination or other imaging techniques and confirmed by fine needle aspiration biopsy, and no evidence of distant metastases. Progression is considered when there is a new development of distant metastasis(es) or when the neck disease becomes grossly palpable.

After second surgery, patients were followed regularly every 6-12 months; physical examination, TSH and TG were performed with every visit chest X-rays (CXR); CXR and US were done at least once for all patients. CT scan of the chest, ^{123}I DxWBS, and fluoro-18-deoxyglucose positron emission tomography (FDG-PET) WBS were done in many patients as dictated by the clinical situation (see Results). All TG levels were obtained off levothyroxine for at least 5 weeks and off levothyronine for at least 2 weeks. To ensure that any difference in TG levels is real and is not related to different levels of stimulation of tumor cells by TSH, we compared TSH levels with of their corresponding TG levels. The TG and TSH changes are presented as mean±SE. Wilcoxon-paired non-parametric test was used to analyze TG and TSH changes. Mann-Whitney U test was used to compare TG levels in patients with unilateral *vs* bilateral recurrent/persistent disease. *P* value <0.05 was considered significant.

RESULTS

Management of high TG and negative WBS

Over a mean follow-up of 25.4 months (8.4-115.7 months) since the first ^{131}I ablation, all patients developed significantly high TG levels (>10 ng/ml off thyroid hormones) and had negative DxWBS. The mean TG level was 184.8±79 ng/ml. The corresponding mean TSH was 150.6±23.0 mU/l. Physical examination of the neck, however, did not reveal any palpable tissue or lymphadenopathy. TG autoantibodies were undetectable in 19 patients in whom they were measured (Table 1). Contamination with non-radioactive iodine was not screened for; however, there was no history of intake of high iodine diet or iv contrast injections. In ad-

Table 1 - *Results of pre-operative diagnostic work-up in 21 patients who underwent second lymph node dissection for TG-positive, ^{123}I whole body scan (DxWBS)-negative persistent/recurrent papillary thyroid cancer.*

Procedure	US neck	FNA	CXR	CT neck	CT chest	FDG-PET	TG abs
Positive	21	21		11		13	
Negative			21	3	12		19
Not done				7	9	8	2

Abs: autoantibodies; CXR: chest X-ray; FDG-PET: fluoro-18-deoxyglucose positron emission tomography; FNA: fine needle aspiration.

dition, patients were prescribed a low iodine diet for at least 1 week before DxWBS. All patients had high-resolution US of the neck, which suggested presence of persistent/recurrent disease in the form of significant unilateral or bilateral lymphadenopathy. There was no evidence of disease in the central compartment. In all cases the diagnosis of recurrent/persistent PTC was confirmed by US-guided fine needle aspiration biopsy. Posterior-anterior and lateral chest X-rays were normal in all patients showing no evidence of lung or mediastinal metastases. CT scan of the neck showed evidence of cervical lymphadenopathy in 11 out of 14 patients in whom it was done. CT scan of the chest showed no evidence of lung or mediastinal disease in all 12 patients in whom it was done. FDG-PET was done in 13 patients and showed in all of them areas of uptake limited to the neck, corresponding to the findings on US. Due to the significant cervical lymphadenopathy seen on US, reoperation rather than high dose ^{131}I therapy was chosen in these patients. The second surgery was guided by findings on US examinations and consisted of unilateral modified neck dissection in 13 cases and bilateral modified neck dissection in 8 cases. Patients who had bilateral disease tended to have higher TG level (321±180 ng/ml) than those who had unilateral disease (85.6±21.0 ng/ml); this difference, however, was not significant (p=0.62). Two cases had postoperative hypocalcemia and 1 patient had unilateral vocal cord palsy. The histopathologic examination of the dissected lymph nodes confirmed the presence of locoregional disease in all cases; there were no features of dedifferentiation.

Impact of second surgery on TG level

After a mean follow-up of 8.4+2.8 months after neck re-exploration, the TG level declined from 184.8±79.0 ng/ml to 127.5±59.0 ng/ml (Table 2). This decline in TG level, however, was NS (p=0.25). The corresponding TSH values were 150.6±23.0 mU/l and 143.4±20.0 mU/l (p=0.34), indicating similar levels of TSH stimulation of tumor tissue. Between the time of the second neck exploration and the last visit (follow-up 20.7±3 months), the TG gradually increased from a level of 127.5±59 ng/ml to 168±68 ng/ml (Table 2). This increase in TG level, however, did not reach a statistical significance (p=0.67). The corresponding TSH values were comparable, 143.4±20.0 mU/l and 132.0±22.0 mU/l, respectively (p=0.27). To exclude the possibility that the other modalities of treatment that were used after the second neck dissection may have affected TG, a comparison was made between the TG level before any of these modalities were employed (134.0±58.0 ng/ml) and the TG level after the second surgery (127.5±59.0 ng/ml) (Table 2). The difference was again NS (p=0.12). The corresponding TSH values were 145.0±23.0 mU/l and 143.4±20.0 mU/l (p=0.81).

Follow-up after second surgery

Following second neck exploration, patients were seen regularly every 6-12 months. All patients had one or more follow-up CXR; 1 patient showed 2 new lung nodules consistent with lung metastases and one patient had osteolytic rib lesions, also consistent with bone metastases. US showed cervical lymphadenopathy in 16 patients; three of them

Table 2 - *Impact of second lymph node dissection on TG level in 21 patients with TG-positive, ^{123}I whole body scan (DxWBS)-negative recurrent/persistent papillary thyroid cancer.*

	Before *vs* after second surgery			After second surgery *vs* last visit			After second surgery *vs* before additional therapies		
	A	B	*p* value	B	C	*p* value	B	D	*p* value
TG	184.8±79	127.5±59	0.25	127.5±59	168±68	0.67	127.5±59	134±58	0.12
TSH	150.6±23	143.4±20	0.34	143.4±20	132±22	0.27	143.4±20	145±23	0.81

A: before second surgery; B: after second surgery; C: at the last visit; D: before additional therapies were given.

have also shown evidence of distant metastases. One patient had a grossly palpable local neck recurrence. CT scan of the chest was done in 12 patients; one patient had evidence of lung metastases, one had lung and mediastinal metastases, and one had rib metastases. In 9 patients, FDG-PET was done and showed neck uptake in 6 of them. Fifteen patients had repeat withdrawal DxWBS in preparation for possible ^{131}I therapy. In all cases, these scans continued to be negative.

Other therapeutic interventions (Table 3)

Ten patients received an additional dose of ^{131}I for persistent elevation of TG. The mean ^{131}I dose was 184 mCi (150-202 mci). The post-therapy WBS were positive in only 2 of 9 patients in whom they were done. TG did not show a significant drop in any patient. Seven patients received external radiotherapy (3000-6000 Rad) and 5 patients had a third neck surgery for persistent disease. After these interventions, TG showed variable levels, but overall there was no significant decrease.

Long-term course of the disease

The total mean follow-up was 77.8±9.7 months. The mean follow-up after second surgery was 20.7±3.0 months. Following second surgery, 4 patients (19%) achieved remission without any further treatment; 4 other patients (19%) had a progressive course of their disease: 1 patient had grossly palpable neck disease and 3 patients had distant metastases (lungs, ribs, and mediastinum). Thirteen patients (62%) continued to have persistent disease but no evidence of new metastases. None of the 21 patients died during follow-up. There was no difference in the outcome between patients who had unilateral versus bilateral disease (odds ratio 0.139, 95% confidence interval 0.011-1.67).

Table 3 - *Management and course of the disease after second lymph node dissection in 21 patients with TG-positive, ^{123}I whole body scan (DxWBS)-negative Persistent/Recurrent papillary thyroid cancer.*

Therapy	Remission	Persistence	Progression	Total
Sx		1		1
RAI		3	1	4
XRT		1		1
Sx + XRT		1	1	2
Sx + XRT		1	1	2
RAI + XRT		3	1	4
None	4	3		7
Total	4	13	4	21

RAI: radioactive iodine (I^{131}) therapy; Sx: surgery; XRT: external beam radiotherapy.

DISCUSSION

In the management of PTC, the situation of elevated TG and negative DxWBS has been a highly controversial issue (11, 12, 14). Possible mechanisms proposed to explain this situation include small metastases that are of insignificant amount and activity to concentrate enough RAI to be seen on DxWBS, tumors that have dedifferentiated and became radio insensitive, overload with non-radioactive iodine, and falsely positive TG due to interference by TG autoantibodies (14). This study sheds some light on this controversial subject. First, in most cases, elevated TG and negative diagnostic WBSs represent a real recurrence or persistence of the disease rather than a mere elevation of TG. This has been found in other studies and points to the high specificity of TG as a disease marker in the follow-up of patients with DTC (4-6, 9, 10, 15). Second, as it is known about PTC, the most common site of disease recurrence is the neck area. However, Schlumberger *et al.* (15) found that about one-third of their patients who had negative DxWBS and elevated TG had lung metastases that were only demonstrable on large-dose post-^{131}I therapy WBS. Third, similar to other studies (16-18), high-resolution US examination is an excellent diagnostic modality for investigation of possible neck disease in PTC. In all patients in this study, neck US showed evidence of cervical lymphadenopathy, which was confirmed to contain metastatic PTC on fine needle aspiration and histopathological examination. Finally, second neck exploration and lymph node dissection in patients with high TG and negative DxWBS uncommonly results in significant reduction of serum TG level; however, the long-term course of the disease is stable in the majority of patients. There are a number of possible explanations for this low remission rate after second neck exploration: inadequate surgery, growth of small cervical lymph node metastases that were not detectable at the time of surgery or presence of microscopic distant metastases that were not apparent on imaging studies. In our patients, second surgical exploration was guided by pre-operative US findings. To improve the intra-operative detectability of recurrent/persistent neck disease, others have tried different strategies. Travagli *et al.* (19) administered therapeutic doses of ^{131}I and combined it with surgery 4-7 days later employing an intra-operative detector probe to localize the sites of the disease. Using this strategy, those investigators reported a

cure rate of 92% in patients with recurrent PTC. Other techniques that may increase the rate of detection and potentially the cure rate are the use of intra-operative US and other novel techniques to identify and surgically target those cervical lymph nodes in which there is evidence of metastases on cytological examination (17), measurement of TG (20) or PCR-based molecular analysis (21).

Apart from surgery, other therapeutic modalities have been used in the management of TG-positive, DxWBS-negative recurrent/persistent PTC. Large dose ^{131}I therapy has been reported to have some reducing effect on TG level (6, 9, 15). However, despite these encouraging results, there has not been any evidence that such ^{131}I therapy results in an improved patient final outcome. Furthermore, the potential risks of repeated doses of ^{131}I are of concern (12). In contrast to these reported results, our patients who were treated after second surgery with large dose ^{131}I rarely had positive post-therapy WBS. This could be related to the fact that this group of patients had poorly-differentiated subtypes of PTC. This is supported by the fact that a large proportion of these tumors showed a high metabolic activity on FDG-PET scanning. Abnormal uptake on FDG-PET scanning has been recently found to correlate with a higher degree of malignancy and poorer prognosis (22). However, pathological examination in our patients did not show any features of poor differentiation. Other possible explanations for the lack of activity on post-ablation scans in this study include significant reduction of tumor mass following second surgery or the use of large scanning doses of ^{123}I, which may have revealed all cases of radiosensitive tumors, leaving only those tumors which do not concentrate RAI. At our institution, we use ^{123}I isotope for diagnostic scanning; the high accuracy of this technique has recently been demonstrated (23, 24).

Apart from the 4 patients whose disease progressed, 17 had a stable course over a total mean follow-up period of 77.8±9.7 months and a mean follow-up of 20.7+3.0 months since second surgery. This stable course could be related to the second lymph node dissection and the other therapeutic interventions that were undertaken during this period. However, it may also reflect the natural course of PTC, which is generally favorable.

Despite the fact that this study, in most patients, did not demonstrate a significant reduction of serum TG following second lymph node dissection for TG-positive, DxWBS-negative locally recurrent/persistent PTC, one cannot exclude the possibility that second lymph node dissection may have stabilized the course of the disease (prevented or delayed the progression). In view of this potential effect of second neck dissection on the course of the disease and lack of more effective therapies for this subgroup of PTC patients, surgery, in our opinion, should continue to be the treatment of choice for those cases whenever possible. However, innovative diagnostic and therapeutic methods such as the one employed by Travagli *et al.* (19) (see above) should be sought to improve the outcome of this important subgroup of PTC patients.

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