

## CONTROVERSIES IN THE SURGICAL THERAPY OF DIFFERENTIATED THYROID CARCINOMA: A REPLICATION STUDY REVIEWING 32 CASES

By

Alaa M. El-Erian MD, Reda Saad MD, \* Maher Fathy MD.

Department of surgery, teaching institutes & hospitals, \*Department of surgery, Ain shams University.

**Objective:** reevaluation of experience with total versus near total thyroidectomy (TT) in treatment of differentiated thyroid carcinoma.

**Design:** 32 cases of differentiated thyroid carcinoma (21 papillary and 11 follicular) were allocated to receive either total thyroidectomy (TT) or near total thyroidectomy (NTT) from 1994 through 1997. In TT group, thyroid bed biopsies were taken intraoperatively and the postoperative RAI131 study was assessed to evaluate thoroughness of TT, also extensive histopathologic examination of the contralateral lobe was done to detect multicentric foci. Patients were followed up clinically, biochemically and radiologically to detect complications and recurrences.

**Results:** In TT group, 15 of 16 cases (93.8%) showed residual uptake in the neck. Also thyroid bed biopsies revealed thyroid tissue in 12 (75%), and contralateral lobe revealed cancerous foci in 6 (37.5%). 4 of TT group (25%) developed permanent hypoparathyroidism and one developed permanent RLN palsy.

In NTT group one developed transient hypoparathyroidism and one developed RLN palsy. 7 cases (20.8%) developed recurrences, 3 in TT group and 4 in NTT group. And 5 (15.6%) have died during follow up period, 2 in TT group and 3 in NTT group, all were follicular carcinomas. All cases with papillary carcinoma are still alive.

**Conclusion:** TT Vs NTT appear to bear no significant difference regarding recurrences and overall survival, despite an increased rate of complications in case of TT

**Keywords:** Total thyroidectomy, Near total thyroidectomy, Radioactive iodine, Recurrent laryngeal nerve.

### INTRODUCTION

There is a considerable controversy concerning the most appropriate surgical treatment of patients with differentiated thyroid carcinoma. This concerns the extent of thyroid resection. Such controversy still exists despite critical analysis of operative results for many years. Surgeons are divided into two camps: those advocating routine less than total thyroidectomy "consisting of at least removal of one entire lobe and isthmus, to include a portion of all gross tumor."<sup>(1-3)</sup> And those advocating routine total thyroidectomy.<sup>(4-8)</sup> Many have reported minimal morbidity following (TT) and recommended its use for all thyroid cancers. Others recommended less than total thyroidectomy which is associated with fewer complications, because only one RLN is at risk and it is virtually impossible to injure all the parathyroid glands.<sup>(9)</sup>

The high risk of local recurrence after less than total thyroidectomy has been amply demonstrated.<sup>(10-12)</sup>

Recurrence in the opposite lobe after a variable interval has been frequently noted due to high incidence of multicentric foci in all types of differentiated thyroid carcinoma.<sup>(12)</sup>

Whether or not total thyroid resection can be accomplished, has been questioned.<sup>(13-15)</sup> Several series have reported that there were large areas of post operative uptake of RAI 131 after TT.<sup>(13,17, 29)</sup>

The current study aims at reevaluating our experience with TT versus (NTT) in treatment of differentiated thyroid carcinoma.

## PATIENTS AND METHODS

Thirty-two Patients aged, 15-60 years with F:M incidence of 2:1, having differentiated thyroid carcinoma (21 papillary and 11 follicular) diagnosed by preoperative clinical examination, thyroid scan, neck US, FNAB and intraoperative frozen section histodiagnosis with extensive capsular sampling in order to increase the diagnostic yield of follicular carcinoma. Such patients were designated to receive either (TT) or (NTT) from 1994 through 1997 "in the way that if TT was performed for certain case, the next case with nearly the same histopathologic criteria should undergo NTT". This dichotomy in surgical approach has led to the formation of two comparable groups in regard to age, sex, extent (stage I = intrathyroidal, stage II = intrathyroidal with cervical nodes involved) and histopathologic type. Each group with 16 cases, TT group {11 papillary and 5 follicular & 5 stage I, 8 stage II} and NTT group (10 papillary and 6 follicular & 7 stage I and 11 stage II) Table 1. Surgery was performed by 10 different surgeons in Ain-Shams University hospitals, and in the private practice.

The operative technique of total and near total thyroidectomies have been described elsewhere.<sup>(14-20)</sup> TT involves total extrafascial resection of both thyroid lobes, the juxta thyroidal lymph nodes (pretracheal, above and below the isthmus and along the superior poles and inferior thyroid vessels), thyroid veins are ligated and removed at their junction with great venous trunks preserving RLN and inferior parathyroids. The chief requirements are time patience and care. NTT involves total ipsilateral lobectomy plus isthmectomy and partial contralateral lobectomy (removal of anterior 3/5) with removal of juxtathyroidal lymph nodes. In both surgical approaches, the lateral cervical lymph nodes along the great vessels in the neck if clinically palpable were dealt with by modified block neck dissection preserving the sternomastoid muscle, the internal jugular vein and the spinal accessory nerve.

In the TT group multiple biopsies from the thyroid bed were taken (from pretracheal region, tracheo-esophageal groove, area of ligament of Berry, suprasternal fossa and superior thyroid strumps) and the study of post operative RAI131 scan which is usually performed after one month is assessed to evaluate the thoroughness of total thyroidectomy. Also extensive histopathologic examination of the contralateral lobe by subserial sectioning was done to detect multicentric foci.

Postoperatively, patients were left without replacement therapy for one month when they become hypothyroid. Then RAI131 whole body scan is performed and both ablative dose of RAI131 (100-180 microCuri) for residual thyroid tissue and therapeutic dose (150-180 microCuri) for

extranodal metastasis and external beam radiotherapy for painful bony metastasis and cytotoxic chemotherapy for cases resistant to therapeutic RAI131, were given, also replacement therapy by oral supplementation with elemental Calcium and vit D3. or i.v calcium in severe cases of hypocalcaemia.

The whole patients (the two groups) were followed up both in the short term (early postoperative period) by laryngoscopy (to detect RLN palsy), T3, T4, TSH and in S.Ca to detect hypoparathyroidism and in the long term for a minimum of 5 years to 8 years through hospital records and direct correspondence by clinical examination, neck US, whole body scan and FNAB to detect recurrences which were defined as the discovery of thyroid carcinoma at least 6 months after thyroidectomy which was subdivided into neck (or locoregional) recurrences (i.e in the thyroid bed or nodal) and distant recurrences (bony and soft tissue beyond the neck).

Patients are then put on TSH suppressive dose of L. thyroxine and followed up regularly every 6 months for the first five years and yearly thereafter by serum thyroglobulin level (to avoid unnecessary repeat RAI131 studies) which if it is raised. the L. thyroxine is discontinued for 4 weeks and RAI131 study is done and ablative or therapeutic dose of RAI131 is given accordingly if serum thyroglobulin is not raised, RAI131 study is not done.

### Statistical methodology:

- SPSS windows version(8) and EPI info -6- were used for analysis of this data as follows:
- Description of quantitative variables in the form of mean, standard deviation, median and range.
- Description of quantitative variables in the form of frequency and percentages.
- T-student test of two independent samples used to compare each two quantitative groups.
- Chi-square test used to compare qualitative variables.
- Significance level (p) value:
  - $P > 0.05 \rightarrow$  insignificant test
  - $P < 0.05 \rightarrow$  significant test
  - $P < 0.01 \rightarrow$  highly significant test

## RESULTS

The results of this study revealed: the patients presented at a mean age of ( $35 \pm 5.5$  SD) (range, 15-60y), with female to male ratio (F:M=2:1) Table 1, the two groups of study were comparable in regard to number, age, sex, size, extent {all were stage I and II (i.e. intrathyroidal)} and histopathologic type, (TT) group with 11 papillary and 5 follicular and (NTT) with 10 papillary and 6 follicular Table 1. In the TT group, 15 of 16 cases (93.8%) showed residual uptake in the

neck and only one showed no uptake in RAI131 study done after one month postoperatively. Also multiple biopsies from the thyroid bed revealed thyroid tissue in 12 of them (75%) Table 2. And extensive histopathologic examination of the contralateral lobe revealed foci of cancer in 6 cases (37.5%) Table 2.

On follow up, 4 cases of the TT group (25%) developed permanent hypoparathyroidism and one case developed RLN palsy, on the other hand, in the NTT group only one case developed transient hypoparathyroidism and none developed RLN palsy Table 3. Of the 32 cases studied 7 patients (20.8%) developed recurrences (both locoregional, and distant).

In the TT group, 3 developed recurrences, one in the thyroid bed and 2 as boney metastasis. In the NTT group, 4 cases developed recurrences, one in the thyroid bed and

one as nodal recurrence, and 3 cases developed distant metastasis (two as boney metastasis and one as lung metastasis). On the other hand, one case in the NTT group developed both thyroid bed local recurrence and boney metastasis in the same time Table 3, 5 out of the 32 cases (15.5%) have died during the period of follow up (interval to death was, 2-5 years), 2 in the TT group (died of boney metastasis) and 3 in the NTT group (2 died of boney metastasis and one of lung metastasis). There are no statistically significant difference between the two study groups in regard to recurrences and overall survival ( $P > 0.05$ ) Table 3.

All patients died were above 50 years at operation, 4 males and one female, tumor sizes were  $> 1.5$  cm and histopathologic type of all tumors were invasive follicular carcinoma Table 4. All cases with papillary carcinoma are still alive.

**Table 1. Demographic data & histopathological and clinical characteristics of the tumor for both groups of study**

	Total thyroidectomy n=16	Near total thyroidectomy n =16	P value	Sig.
Age				
Mean $\pm$ SD	37.5 $\pm$ 6.3	35.6 $\pm$ 5.4	$> 0.05$	NS
Range	15-60	15.58		
Gender				
M	5 (31.3%)	6 (37.5%)	$>0.05$	NS
F	11 (68.8%)	10 (62.5%)		
Mean size of the tumor (cm)	1.52 $\pm$ 0.2	1.56 $\pm$ 0.3	$>0.05$	NS
Extent				
Stage - I	5 (50%)	7 (43.7%)	$>0.05$	NS
Stage - II	8 (50%)	11 (68.8%)		
Histopathological types				
Papillary	11 (68.8%)	10 (62.5%)	$>0.05$	NS
Follicular	5 (31.3%)	6 (37.5%)		

Stage I: intrathyroidal; stage II: cervical nodes involved; stage III: invasion into surrounding structures.

**Table 2. results of postop. RAI 131 study , multiple biopsies from thyroid ped and histopath. Exam. Of the contralat. Lobe after Total thyroidectomy**

Total thyroidectomy n= 16	Positive	Negative
Residual uptake in the nek	15 (93.8%)	1 (6.2%)
Biopsies from thyroid bed	12 (75%)	1 (25%)
Multicentric foci in contralat. Lobe	6 (37.5%)	10 (62.5%)

**Table 3. Postoperative complications , recurrences and mortality among the study groups**

	Total thyroidectomy n=16	Near total. Thyroidectomy n=16	P value	Significance
<b><u>Postoperative complications</u></b>				
Hypoparathyroidism	4 (25%) p.	1 (6.3%) T.	> 0.05	NS
RLN palsy *	1 (6.3%) P.	0		
<b><u>Recurrences</u></b>				
<b>Neck (locoregional)</b>				
- Thyroid bed	1 (6.3%)	1 (6.3%)	>0.05	NS
- Nodal	0	1 (6.3%)		
<b>Distant</b>				
- Boney	2 (12.5%)	2 (12.5%)	>0.05	NS
- Soft tissues	0	1 (6.3%)		
<b>Both</b>	0	1 (6.3%)		
<b><u>Mortality</u></b>	2 (12.5%)	3 (18.8%)	>0.05	NS

\* RLN recurrent laryngeal nerve palsy

P. Permanent

T. Transient

**Table (4): Characteristics of mortality cases**

Age at operation	> 50 years
Sex	4 M and 1 F
Tumor size	> 1.5 cm
Histopathologic type	All invasive follicular carc
Distant metastasis	All +ve

## DISCUSSION

In this comparative prospective therapeutic trial in patients with differentiated thyroid carcinoma it appears that there is no significant difference between(TT) and(NTT)regarding occurrence of recurrences and overall survival.

The ideal surgical treatment for differentiated thyroid carcinoma has been subject of debate for many years.

The advantage of TT over less than total thyroidectomy is based on a number of observations.

1. When distant metastasis occur in case of follicular carcinoma they can be detected and treated with RAI131, as there is no residual thyroid tissue to compete with metastasis for RAI. However, several authors, suggest that the so called TT is rarely complete and used adjunctive RAI131 to clean up residual thyroid tissue.(21,22) There are reports of occult metastasis discovered through whole body

scanning only after residual cervical thyroid tissue had been destroyed.(23)

Surgical ablations preferred however, science it will also remove multicentric tumors that might not be ablated by radio isotope.(24)

2. Multicentricity and bilaterality are frequent in differentiated thyroid carcinoma.(25)

In our study 37.5% of patients undergone TT showed mutlicentric foci on extensive histopatologic examiantion of the contralateral lobe.

3. Recurrence of thyroid carcinoma in the stump after less than total thyroidectomy has been frequently reported,(26) furthermore, residual foci of low grade thyroid carcinoma carry a risk of anaplastic transformation.(27)

4. TT allows for serum thyroglobulin to be used as a tumor

marker for recurrence after TT as any remaining thyroid tissue will decrease the diagnostic sensitivity of thyroglobulin assay.<sup>(28)</sup>

5. TT for recurrent carcinoma is at higher risk of complications than primary TT.<sup>(28)</sup>

Many surgeons claim that, it is rarely possible to completely extirpate the thyroid gland. A survey of literature reveals that in many centres post operative RAI131 studies demonstrated significant remnants of thyroid in the neck after the so called TT and ablative doses of radioisotope were given to complete thyroidectomy.<sup>(28,29)</sup>

In our study multiple biopsies from the thyroid bed taken intraoperatively after TT revealed residual thyroid tissue in 75% of patients and RAI 131 studies done after one month postoperatively revealed significant uptake in (93.8%) of cases undergone TT indicating difficulty of obtaining actual complete TT.

There are several anatomic reasons why minute fragments of functioning thyroid tissue may be left behind during attempted TT:

1. The pyramidal lobe may extend for a considerable distance superior to the operative field. Usually no attempt is made to trace it above the level of the larynx. Under normal circumstances, pyramidal lobe is not visible on preoperative scans, but when the rest of thyroid gland is removed, these traces of thyroid tissue begin to actively take up RAI131.<sup>(30)</sup>

2. The postero-medial limit of thyroid terminating in the dense ligament of Berry varies greatly. Minute nests of thyroid cells may be difficult to see grossly and may be left in situ, such nests will appear as minute foci of RAI uptake in postoperative scan.<sup>(32,33)</sup>

3. Rarely, benign functioning thyroid tissue may be sequestered from the thyroid.<sup>(31,32)</sup>

Also, some surgeons on an attempt to preserve the parathyroids and safeguard the RLN may leave behind some of thyroid tissues for safety purposes.

Surgeons advocating NTT demonstrate equal long term results, yet fewer complications,<sup>(33,34)</sup> science it is virtually impossible to injure all parathyroid glands and only one RLN is at risk.<sup>(9,10,33)</sup> Secondary operation occasionally may be needed for recurrent disease in the contralateral side, but the number of patients exposed to permanent iatrogenic morbidity is far less than if primary TT had been performed.<sup>(33)</sup> They point out that multicentric foci don't necessarily translate into clinically significant disease and that anaplastic transformation is a remote possibility.<sup>(19)</sup>

In our study, 4 of the 16 cases undergone TT showed

permanent hypoparathyroidism and only one showed permanent RLN palsy. On the other hand, none of the NTT group showed RLN palsy and only one showed transient hypoparathyroidism indicating an increased risk of complications in case of TT.

Schroder et al. (1986) in his retrospective study of 109 patients with nonmedullary thyroid cancer had found that the statistically significant factors affecting cancer mortality were age > 40 years tumor size > 1.5cm, extranodal local or distant metastasis, angioinvasion and anaplastic pathologic features. Also, found that male patients with lesions > 1.5 and patients with evidence of angioinvasion had significantly increased recurrence rate.<sup>(19)</sup>

Cady and Rossi (1988) In Lahey Clinic have developed the AMES scoring system to identify low and high risk groups in differentiated thyroid cancer, where predictors of cancer related mortality are; age, distant metastasis, tumor size and extent of spread. Such predictors can be summarized as follows; a female under 50 years or male under 40 years with tumor size < 4cm, limited to the thyroid with minimal capsular invasion and no vascular invasion or distant metastasis is defined as low risk and has excellent prognosis, while a female > 5 years or male > 40 years with tumor size > 4cm with extrathyroidal spread or major capsular invasion, and/or vascular invasion or distant metastasis is defined as high risk with poor prognosis. Because the surgeon knows patient's age, whether distant metastasis are present or not and the size and extent of tumor spread can be evaluated intraoperatively, the AMES scoring system has practical application and can be used at time of surgery to determine the extent of thyroid resection.<sup>(36)</sup>

All of our mortality cases were within the high risk group (age > 50 years, were mostly males, tumor size > 1.5cm, distant metastasis present and all were with invasive follicular carcinoma) Table 8. All patients with papillary carcinoma are still alive, owing to the indolent course of this histopathologic type.

NTT is a procedure that can be performed safely by most surgeons experienced with neck surgery, conversely TT is fraught with complications.

The goal of thyroid cancer surgery should be to maximize therapeutic effectiveness while minimizing iatrogenic morbidity. and near total thyroidectomy achieves this goal in vast majority of cases.

Total versus near-total thyroidectomy appear to bear no significant differences in regard to occurrence of recurrences and overall survival, despite an increased risk of complications in case of total thyroidectomy. So, we recommend near total thyroidectomy as the preferred treatment option for differentiated thyroid carcinoma and

total thyroidectomy is to be resorted to in case of invasive variety of follicular carcinoma (vascular and/or capsular) or gross bilobar involvement or distant metastasis provided being done by an experienced surgeon.

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