

Lymph Node Dissection in Papillary or Follicular Thyroid Carcinoma

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Abstract. *Background: Prospective randomized studies aimed at evaluating the different therapeutic protocols for the treatment of papillary or follicular carcinoma are lacking at the moment. Although total thyroidectomy is widely accepted, indication to locoregional lymphadenectomy is strongly debated. Materials and Methods: Fifty-four patients with papillary or follicular thyroid carcinoma (45 papillary and 9 follicular) underwent functional evaluation of the gland before intervention, FNAB included. Surgical management was carried out as follows: 41 total thyroidectomy, 6 lobectomy with further totalization in 5, 6 total thyroidectomy plus central compartment lymphadenectomy and 1 left laterocervical lymphadenectomy (papillary carcinoma, treated elsewhere through total thyroidectomy plus central and right laterocervical lymphadenectomy). All operated patients were submitted to whole body scintigraphy and treated thereafter by radiometabolic therapy and chronic hormone suppressive therapy. Results: Fifty-one patients are currently alive, 3 died from non-related causes; surgical complications included 1 permanent impairment of inferior laryngeal nerve function and 1 case of hypoparathyroidism. The follow-up was from 1 to 139 months. Discussion: The optimal treatment of lymph node metastases, especially for papillary carcinomas, has not yet been defined. Two trends are evident concerning lymphadenectomy: the first one suggests routine lymphadenectomy, the second supports lymphadenectomy by necessity. In follicular carcinoma lymphadenectomy is recommended only in the presence of clinical evidence of lymph node involvement. Occult*

differentiated carcinoma does not require any further treatment of lymph nodes. Conclusion: Considering the high efficacy of radiometabolic treatment after total thyroidectomy combined with chronic TSH inhibition through L-tyrosine administration, lymphadenectomy is suggested only by necessity.

Papillary and follicular carcinomas represent the greater portion of thyroid malignant tumors; thyroid cancers are rare (about 1% of all malignant neoplasms), however an increase in their incidence has been observed during the last decade (1, 2).

A uniform therapeutic strategy is not available, due to the lack of prospective randomized studies which would allow the evaluation of different therapeutic protocols; as well, current systems of prognostic evaluation offer limited accuracy and reliability (3-8). Extension of parenchymal exeresis, lymph node clearance and radiometabolic therapy are still the object of discussion regarding their effects on cumulative survival and/or local recurrence (5-13): this is particularly true for those patients in whom a clear-cut lymph node involvement or distant metastases are not demonstrated through the preoperative diagnostic procedures (7). Total thyroidectomy followed by radiometabolic therapy is widely accepted; whereas the indication for lymphadenectomy is strongly debated (6, 7, 14-18). With regard to the latter, the available data are conflicting: significant variations are reported in the incidence of lymph node involvement and as well as in the percentage of mortality and/or recurrence in N+ cases. As a consequence, opinions about the results of routine vs by necessity lymphadenectomy and its beneficial effects in MO cases are conflicting too (6, 7, 13, 17, 18); on the other hand, trends exist for occult carcinomas and for M+ cases (5-7, 9, 19).

The aim of the present study was to evaluate whether routine lymphadenectomy offers any real advantage in terms of survival and of disease-free interval.

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Key Words: Papillary thyroid carcinoma, follicular thyroid carcinoma, lymphadenectomy.

Materials and Methods

Among all thyroid cancer patients treated in our Department from January 1989 through October 2002, 54 patients, treated by the same surgeon and followed-up by the same team, were enrolled. There were 49 females (90.8%) and 5 males (9.2%); the age ranged from 20 to 83 years (mean 47.8 years): 35 patients were under 45 years and 19 were 45 years old or more. The pathological diagnosis was: papillary carcinoma 45, follicular carcinoma 9. Preoperative study included in all patients indirect laryngoscopy, blood assay for Ca, Mg, P, FT3, FT4, PTH and FNAB. Out of 54 FNAB procedures (53 thyroid lesions, one lymph node lesion), papillary carcinoma was diagnosed in 36 instances (33 uninodular thyroid lesions, 2 multinodular thyroid lesions, 1 lymph node lesion) and follicular proliferation in 18. Recently, the FNAB retrieved material was submitted to Galectin-3 test in 3 cases (follicular carcinoma 2, papillary carcinoma 1). Surgical management consisted of the following: total thyroidectomy 41 (37 papillary, 4 follicular); lobectomy 6 (2 papillary, 4 follicular) with further totalization in 5, one patient having refused reoperation; total thyroidectomy plus central compartment lymphadenectomy 6 (4 papillary, 2 follicular); one left laterocervical lymphadenectomy (papillary carcinoma, treated elsewhere through total thyroidectomy plus central and right laterocervical lymphadenectomy).

Intraoperative microscopy was not a routine procedure; in 18 cases of uninodular pathology (52 out of 54), in which preoperative diagnosis was unclear, lobectomy was performed followed by peroperative microscopy on macroscopically normal parenchyma. The patient was advised that a total thyroidectomy would be performed in case of macro- or microfollicular hyperplasia.

Thyroid hormones and thyroglobulin were assayed 30 days p.o. All operated patients were submitted to whole body scintigraphy 45 days p.o. and thereafter treated by radiometabolic therapy and chronic TSH-suppressive therapy.

Our follow-up protocols included: cervical and whole body scintigraphy after 1, 3 and 5 years and thence for every 5 years; thyroid hormones and thyroglobulin assay every three months for the first year and successively every six months; neck ultrasonography every six months for the first year and successively every year; chest X-ray every year in case of follicular cancer.

Results

Of the 54 resected neoplastic lesions, there were 30 T1 (all papillary), 15 T2 (7 papillary, 8 follicular) and 9 T4 (7 papillary, 2 follicular). Lymphadenectomy in 8 cases resulted in 5 N1 and 3 N0 (all papillary). Surgical complications after 59 operative procedures (including 5 reoperations to complete the thyroid exeresis) included: 4 impairment of inferior laryngeal nerve function (6.8%), permanent in one case (1.7%); 2 cases of hypoparathyroidism (3.4%), permanent in one (1.7%). Fifty-two out of 54 patients (96.2%) were regularly followed-up from 1 to 139 months. Fifty patients are currently alive and free from disease: 3 died from non-related causes.

Discussion

The optimal treatment of lymph node metastases, especially for papillary carcinoma, has not yet been defined (19-22).

Papillary carcinoma. It is widely accepted that clearance of involved lymph nodes has a beneficial effect on the incidence of local recurrence (23) while doubts exist about the effect on survival; therefore it is debated whether to perform lymphadenectomy (and how extensively) (9, 24).

Papillary carcinoma is characterized by early lymph node involvement (5) in 21-80% of the patients (16,20), particularly in younger ones (25). In about 80% of the cases lymph node micrometastases may be demonstrated (5,9,26) without any agreement on their clinical significance; only 10-15% of the patients with micrometastases would develop clinically significant metastases (20,23): these would require, according to the supporters of lymphadenectomy in principle, a second operation, with enhanced morbidity (5,26). Mazzaferri and Jhiang (9) reported that lymph node involvement does not have any effect either on survival or local recurrence, provided that total thyroidectomy and radiometabolic therapy are performed. On the contrary, Dralle and Ginn (6) support the evidence that survival and local recurrence are influenced and consequently suggest, as a routine, total thyroidectomy plus central compartment lymphadenectomy (6,7). In their experience such a procedure does not imply higher morbidity, which is encountered in the case of reoperative procedures on the central lymph node compartment, causing more than 20% of inferior laryngeal nerve injury and more than 30% of permanent hypoparathyroidism (6,7,21). More aggressively, Japanese surgeons (5) suggest central and modified laterocervical lymphadenectomy, even if they do not report a significantly increased morbidity in case of reoperation for laterocervical recurrence. The same authors (27), in case of demonstrated lymph node and/or capsular involvement, suggest thyroidectomy plus radically modified regional lymphadenectomy to achieve a careful stage estimation, to reduce the incidence of local recurrence and to assure an optimal effect of radiometabolic treatment (7,27). However, it has been observed that laterocervical and central compartments are involved with similar incidence (62.1 vs 68.8%); furthermore, lymph node metastases are present in both compartments in 67% of the cases, being limited to the central one only in 20% (5).

Recently, particularly aggressive variants of papillary carcinoma have been described, in which central lymphadenectomy should be performed in principle (19,22). Thus, two trends exist in this setting: routine lymphadenectomy (with different modifications) and lymphadenectomy by necessity. Some authors perform routine clearance of the central compartment, including the anterior superior mediastinum down to the aortic arch (6,7). Others perform prophylactic lymphatic clearance of the central and lateral compartments. The extent of laterocervical dissection may be radical or modified, the latter sparing the sternocleidomastoid and digastric muscles,

the submandibular gland, the internal jugular vein and the internal accessory nerve. The modified procedure would imply reduced morbidity without any significant difference regarding local recurrence and survival (13,23,24,27). Other authors (15,18,21,28) perform lymphadenectomy only when lymph node involvement is demonstrated, relying on some studies (12,19) according to which subclinical metastases do not influence the prognosis provided surgery is followed by radiometabolic therapy. Finally, some authors (21) perform a sampling of central compartment lymph nodes, resorting to lymphadenectomy in case of positive pathological examination.

Follicular carcinoma. Lymph node involvement in follicular carcinoma is rarer than in papillary carcinoma (8-13%) (29). However it has been demonstrated that, even if a bad prognosis is mainly correlated with distant metastases, lymph node involvement indicates a more aggressive behaviour and could be correlated with a higher rate of local recurrence and reduced survival (7,8,30). Most authors suggest total thyroidectomy and regional lymphadenectomy in case of demonstrated lymph node involvement (29). Prospective studies on this topic are lacking.

Occult carcinoma. It is widely accepted that occult differentiated thyroid carcinoma does not require any further treatment of lymph nodes (7,31).

Conclusion

In conclusion, the lack of knowledge regarding the biological behaviour of the different types of differentiated cancer of the thyroid, as well as the lack of prospective randomized studies, do not allow a reliable comparison between the different therapeutic strategies found in the literature.

Two trends are evident concerning lymphadenectomy. The first one suggests routine lymphadenectomy, more or less extensively, with the aim of more radical oncologic treatment. It relies on: (a) a careful stage estimation, often not achievable preoperatively, involving however an undue overtreatment for some groups of patients; (b) the low morbidity of such a procedure, not superior to that related to simple thyroidectomy, at least with experienced surgeons, while reoperation implies higher morbidity; (c) the reduction of the amount of tissue where radioiodine may be potentially fixed, thus ameliorating the effects of radiometabolic therapy. The second trend supports lymphadenectomy only if there is clinical evidence of lymph node involvement, relying on the consideration that only clinical metastases have prognostic significance, albeit not influencing cumulative survival. It is justified by the low aggressiveness of these cancers and by the similarity in survival to patients submitted

to lymphadenectomy. Moreover, radical lymphadenectomy, even if modified, implies some morbidity, consequently doubts exist about its routine use. There is no evidence about the advantages of clearing lymph nodes without clinical metastatic involvement; control of subclinical metastases may be obtained in 80% of the cases through radiometabolic therapy. The latter is strongly recommended, both in patients submitted to lymphadenectomy and in those submitted only to thyroidectomy. As well there is complete agreement about the lifelong administration of hormone-suppressive drugs to prevent any TSH-dependent proliferation.

Our protocol in follicular or papillary thyroid cancer implies total thyroidectomy, lymphadenectomy only by necessity, post-operative radiometabolic treatment and chronic TSH inhibition through L-tyrosine administration.

References

- 1 Greco L, Gentile A and Testini M: I carcinomi della tiroide. Criteri di scelta del trattamento chirurgico. *Ann Ital Chir* LXIII 3: 339-342, 1992.
- 2 Roy B, Bruce J and Davidson J: Thyroid cancer. *Med Clin N Am* May 77 (3): 517-535, 1993.
- 3 Lemma F, De Francesco F and Marullo M: Epidemiologia del carcinoma della tiroide: nostra esperienza. *Osp Ital Chir* 5: 438-442, 1999.
- 4 Bartolazzi A, Gasbarri A, Papotti M, Bussolati G, Teresina L, Khan A, Inohara H, Marandino F, Orlandi F, Nardi F, Vecchione A, Tecce R, Larsson O and the Thyroid Cancer Study Group: Application of an immunodiagnostic method for improving preoperative diagnosis of nodular thyroid lesions. *The Lancet* 357: 1644-1650, 2001.
- 5 Noguchi M, Katev N and Mijozaki I: Controversies in the surgical management of differentiated thyroid carcinoma. *Int Surg* 81: 163-167, 1996.
- 6 Dralle H and Ginn O: Lymphadenektomie beim schilddruesen carcinom. *Chirurg* 67: 788-806, 1996.
- 7 Mann B and Buhr HJ: Lymphnode dissection in patients with differentiated thyroid carcinoma-who benefits? *Langenbeck's Arch Surg* 383: 355-358, 1998.
- 8 Rao RS, Parikk HK, Destimane VH and Havaladar R: Prognostic factors in follicular carcinoma of the thyroid: a study of 198 cases. *Head Neck* 18: 118-126, 1996.
- 9 Wu Y-J, Wu H-S, Yen R-F, Shen Y-Y and Kao C-H: Detecting metastatic neck lymph nodes in papillary thyroid carcinoma by 18F-2-deoxyglucose positron emission tomography and Tc-99m tetrofosmin single photon emission computed tomography. *Anticancer Res* 23: 2973-2976, 2003.
- 10 Biesterfeld S, Rickert D, Eichler S, Fürste K, Mrusek S and Alfer J: TV-image analysis based quantification of the proliferative activity and the apoptotic rate in thyroid tumors and thyroiditis. *Anticancer Res* 23: 4269-4276, 2003.
- 11 Pisani T, Bononi M, Nagar C, Angelini M, Bezzi M and Vecchione A: Fine needle aspiration and core needle biopsy techniques in the diagnosis of nodular thyroid pathologies. *Anticancer Res* 20: 3843-3848, 2000.

- 12 Mazzaferri EL and Jhiang SM: Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 97: 418-428, 1994.
- 13 Attie JN: Modified neck dissection in treatment of thyroid cancer. A safe procedure. *Eur J Cancer Clin Oncol* 24: 315 1988
- 14 Ley PB, Roberts JW, Symands RE and Hendricks JL: Safety and efficacy of total thyroidectomy for differentiated thyroid carcinoma: a 20 year review. *American Surgeon* 59(2): 110-114, 1993.
- 15 Cady B: Surgery of thyroid cancer. *World J Surg* 5: 3-14, 1981.
- 16 Clark OH: Total thyroidectomy. The treatment of choice for patients with differentiated cancer. *Am Surgery* 196: 361, 1982.
- 17 Bononi M, De Cesare A, Cangemi V, Fiori E, Galati G, Giovagnoli MR, Izzo L, Cimitan A, Meucci M and Cavallaro A: Hurtle cell tumors of the thyroid gland: personal experience of literature. *Anticancer Res* 22: 1-4, 2002.
- 18 Mc Unatney WN, Hay ID and Wallner LB: Papillary thyroid cancer treated at the Mayo Clinic 1946 through 1970: initial manifestation, pathological findings, therapy and outcome. *Mayo Clinic Proc* 61: 978-996, 1986.
- 19 Marchesi M, Biffoni M, Tartaglia F and Nobili Benedetti R: La linfectomia nei tumori della tiroide: nostra esperienza 1987-1998. *Osp Ital Chir* 5: 473-478, 1999.
- 20 Brierley JD, Pantarella T and Tsang RW: A comparison of different staging system predictability of patients outcome-thyroid carcinoma as an example. *Cancer* 79: 2414, 1997.
- 21 Corbellini L, Bove A and Bigonzoni G: Metodologia della conservazione delle paratiroidi durante tiroidectomia totale per cancro e per patologia benigna. *Osp Ital Chir* 5: 507-511, 1999.
- 22 Brattarola P, Petronio R and Martignoni G: Microcarcinoma ben differenziato della tiroide con aspetti aggressivi. *Osp Ital Chir* 5: 463-466, 1999.
- 23 Romano G and Toscano F: La chirurgia nel carcinoma differenziato della tiroide. *Medicina* 16-30, 1998.
- 24 D'Annibale M, Piovanello P and Appetecchia M: Carcinoma della tiroide: valutazione dei fattori prognostici. *Chir Ital* 51(1): 59-54, 1999.
- 25 Cady B: Presidential address: beyond risk group a new look at differentiated thyroid cancer. *Surgery* 124(6): 947-957, 1998.
- 26 Kelemen PR, Van Herle AJ and Giuliano AE: Sentinel lymphadenectomy in thyroid malignant neoplasism. *Arch Surg Ma* 133: 288-292 1998.
- 27 Noguchi S, Murakani N and Yamashita H: Papillary thyroid carcinoma. Modified radical neck dissection improves prognosis. *Arch Surg* 133: 276-280 1998.
- 28 Wanebo HJ, Andrews W and Kaiser DC: Thyroid cancer: some basic considerations. *Am J Surg* 142: 474-479 1981.
- 29 Block BL, Spiegel JL and Chami RG: The treatment of papillary and follicular carcinoma of the thyroid. *Ot Clin N Am* 23(3): 403-411, 1990.
- 30 Seagal K, Arad A, Lubin E, Shpitzer T and Hadar T: Follicular carcinoma of the thyroid. *Head Neck* 16: 533-538 1994.
- 31 Azadian A, Rosen IB, Walfish PG and Asa SL: Management consideration in Hurtle cell carcinoma. *Surgery* 108: 711-715, 1995.

Received December 11, 2003

Revised February 18, 2004

Accepted April 2, 2004