

The Prognostic Factors of Thyroid Medullary Carcinoma-Clinical Analysis of 73 cases

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Abstract **Propose** To explore the prognostic factors of medullary thyroid carcinoma (MTC). **Methods** The current study was designed to collect and analysis the information about the clinical and follow-up of 73 cases of MTC treated in our hospital. **Results** It was showed that 51% of cases (37/73) occurred in 3 to 4 decades, it is more common in female than in male, 83.6% of these cases were regarded as II to III clinical stage. After treatment, the survival rate for 5 years were 100%, 41.5% and 0 in the group of clinical I, III and IV stage respectively, none of 8 cases in which the tumors were removed incompletely surgically combined with the postoperative radiotherapy survived up to 5 years. **Conclusions** The clinical stage, the thoroughness of the remove of MTC and the metastatic lymph nodes were the significant prognostic factors of MTC. It should be recognized that in most cases of MTC, the mass could be removed completely, though it was huge, because of its thin capsule. Although a little cancerous tissue left after operation, the good prognosis will be obtained after the post-operative radiotherapy. So, the surgical remove of the cancerous mass should not be given up without being thought carefully.

Key Words medullary thyroid carcinoma; diagnosis; treatment; prognosis

Medullary thyroid carcinoma (MTC) is a neoplasm of the calcitonin-secreting parafollicular C cells of the thyroid gland. It is relatively rare in clinic whose occurrence is about of 5%~10% of total thyroid carcinoma^[1]. Therefore, the clinical report about this tumor is infrequent. The information of the clinical diagnosis, treatment and follow-up information about 73 cases of MTC which possess 5.0% (73/1327) of all the thyroid carcinoma cases treated in our department from 1954 to 1989 were collected and analyzed in order to explore the essential prognostic factors of this tumor.

MATERIAL AND METHODS

Clinical materials

Seventy-three patients, ages ranged from 14 to 76 (medium 37.4) years old, of which 37 cases were 30 to 40 years old. They were treated with surgical operation or combined the surgery and postoperative radiotherapy. Among them, 24 cases of male and 49 cases of female, the sex rate was 1:2.1. Among of them, The courses of disease were

various from one month to 28 years, there were two occurrence peaks were found, one was less than one year (24/73, 57.6%), the other was three to five years (23/73, 31.5%). The most common clinical appearance was the slowly growing neck mass without any symptom in spite of 6 cases had hoarse, 11 cases had diarrhea which was various from three to ten times per day, but most was three to five times per day, 3 cases had the symptoms of dysphagia, dyspnea and drinking cough caused by the huge neck mass. Among these 73 cases, 67 cases were sporadic and 6 cases were familiar which all were included in 24 cases (32.9%, 24/73) with bilateral diseases. On the examination, the mass varies from 1cm~2cm to near to 20 cm in size. And their hardness were medium or hard without a clear border mostly which less movable even unmovable caused by the adhesion to its surrounding organ and structures such as muscle, trachea, esophagus. The huge mass could depress these organs to induce narrow and dislocation. The lymphadenopathy were found in 26 cases on neck, 9 cases in the mediastinum, one case in subaxillary. One case had the pulmonary metastasis. The tongue lymphohemangioma were found in 2 cases, the pheochromocytoma in two cases, and multiple neuromas of lingual mucosa in 2 cases.

In total 73 cases, the serum calcitonin levels

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were variously elevated in 54 cases (74.0%).

The clinical stages were recognized as 1 stage 6 cases, 2 stage 20 cases, 3 stage 41 cases and 4 stage 6 cases.

Surgical Treatment

The mass extensive dissection —i.e. the lobectomy and the dissection of the ipsilateral strap muscle, the connective tissue and lymph node within the triangle formed by the trachea and esophagus medially, the carotid lateral were performed simultaneously or combined radical operation of thyroid carcinoma were performed respectively according to the cancerous metastatic neck lymphadenopathy.

In the cases of bilateral thyroid carcinoma, with proved or suspected one side neck metastasis, when the combined radical operation on the same side the most of the opposite thyroid gland and cancerous mass were dissected simultaneously, but the superior or inferior part of the gland and the posterior capsule of thyroid gland should be left. However, if the bilateral lymph node metastasis were suspected even proved, the combined radical operation should be performed separately. In such case, it must be paid attention to leave the posterior capsule of the thyroid gland in order to avoid the serious postoperative complication-hypothyroidism. When the vessels in the root of neck and the upper mediastinum, were involved, the huge mass of tumor and metastatic lymph nodes were removed radically after evaluating the patients' general condition, radiographic appearances carefully. In case the mass was too huge or the patients' general condition was too poor to the surgical radical operation, the debulken operation was performed which was in 8 cases. In spite of one patient whose trachea involved was dissected partly and the dermato-trachea fistulization was made, the masses were dissected from the involved trachea and esophagus successfully in 17 cases, the left defect of esophagus could be sutured directly or repaired with tissue flap. Before the operation, the pheochromocytomas were surgically removed in 2 cases. All these wounds got healing smoothly despite that 2 cases had the post-operative hand-foot convulsion, which were controlled after given calcium for one to two weeks.

Post-operative radiotherapy

In the cases of huge mass, the post-operative radiotherapy (40Gy) was given after four to six

weeks. If the dissection was unsatisfactory, the radiotherapy dosage should be up to 60Gy.

Following-up

All these patients were followed-up continuously, the medium following-up time was 17 years, the longest was 26 years. Statistics method The X^2 test was used.

RESULTS

Survival rate

The survival rates of 73 patients were determined with life-span table. It was showed that three-year survival rate was 78.4%, five-year survival rate was 67.3%, the ten-year and longer survival rate was 52.9%.

The relationship between cervical lymph node metastasis and survival rate.

The total metastasis rate of cervical lymph nodes in 73 cases was 67.1% (49/73), the rate of both side of neck was 21.9% (16/73). In the group without palpable neck lymphadenopathy before the operation and 31.9% (15/47) of cases were proved the cervical lymph nodes metastasis by the postoperative histopathological examination, The survival rates of 3 year, 5 year, 10 year and longer of 38 patients who had the neck lymphadenopathy before operation were 69.4% (27/38), 52.6% (20/38) and 34.4% (13/38) separately, and in the 35 patients neck lymphadenopathy before operation they were 87.4% (31/35), 82.0% (29/35) and 71.4% (25/35) respectively. The significant differences were found between these two groups ($p < 0.05$, $p < 0.01$).

The relationship between the clinical stage and survival rate.

The survival rates of 3 years in the groups of 1, 2, 3 and 4 stages were 100% (6/6), 100% (20/20), 70.73% (29/41) and 0 respectively. The 5 years survival rates of above groups were 100% (6/6), 85.0% (17/20), 41.46% (4/6) and 0. The 10 years and longer survival rates of these groups were 66.67% (4/6), 70.0% (14/20), 29.27% (12/41) and 0. The statistical analysis showed the significant differences in the 5 years, 10 years and longer survival rates between the 1-2 stage groups and 3-4 stage groups ($p < 0.05$, $p < 0.01$).

The relationship between the pre-operative diar-

rhea and survival rate.

The survival rate of 3-year, 5-year, 10-year and longer in the diarrhea group (11 cases) and without diarrhea group (62 cases) were 70.7% (8/11), 63.6% (7/11), 45.5% (5/11); 83.9% (52/62), 71.7% (44/61) and 61.2% (38/62) respectively. There was no statistical significant difference between these two groups.

The relationship between the post-operative recurrence and survival rate.

18 cases of total 73 cases of MTC had post-operative recurrence, the earliest recurrence occurred on the 3rd month post-operatively and the latest case occurred in 11th year post-operatively. There were 13 cases occurred by 4 to 5 years post-operatively. The survival rates of 3-year, 5-year, 10-year and longer in the recurrent group were 83.0% , 50.0% and 33.3%; and these survival rates in the non-recurrent group were 85.5%, 80.0% and 72.2% respectively. The significant differences of the survival rates were found between these two groups ($p < 0.01$).

The blood vessels metastasis.

During the follow-up period, 9 cases (13.3%) had blood metastasis, among of them, 7 cases metastasize to lung (one case had bilateral pulmonary metastasis), 1 case to liver, 1 case to rib and 1 case to thymus.

DISCUSSION

The grade of malignancy of MTC is between those of papillary thyroid carcinoma and undifferentiated thyroid carcinoma, which belongs to the medium malignant thyroid carcinoma. The incidence of MTC is more in female than that in male, the female-male ratio of 2.1 to 1 in our groups is similar to that report of modigliani E. et al. In which the rates was 1.35:1^[2]. Eighty percent of the patients with MTC were sporadic cases, whereas the remaining 20 percent have the disease in the inherited form^[3]. Only 6 cases (8.6%) with the familiar history were found in our groups. In general, MTC appeared as slowly growing lateral neck mass, and the bilateral occurrence is rare. The masses are usually hard solid, less movable even unmovable, sometimes with the neck lymph nodes metastasis. They varied from less than 1cm to more than 20 cm in size. The patients have no tenderness and

other symptom until the mass has been large enough to cause the disturbance of breath and swallowing, dyspnea or dysphagia, or invades the recurrent nerve to cause hoarse, so MTC is not noticed at early stage. In this study, 83.6% (61/73) of patients was 2 or 3 stage. The longest course of disease was 28 years, the course of 31 case were more than one year. The familiar MTC occurs earlier than the sporadic cases and often bilaterally, all the 6 cases of the former were younger than 30 years old and occurred bilaterally in our groups. Because the C cells secrete multiple amines and small peptide hormones such as calcitonin(CT) that cause diarrhea, osteodynia, flushing face, especially the diarrhea is the characteristic symptom of some MTC, but there were only 15.1% (11/73) patients had this appearance though the higher occurrence of diarrhea was reported. The MTC diagnosis should be considered if the patient with thyroid mass and diarrhea. CT value is regarded as the mark of the diagnosis of MTC, it should be routinely measured for the patient suspected to be with this tumor and the members of the family with MTC in order to discover MTC early. Otherwise, the CT value should be measured during the following-up period so that the recurrence was found earlier. In our groups, 74% (54/74) cases had various elevation of CT values. It was reported that RET gene mutation, serum carcinoma-embryonic antigen (CEA) value and somatostatin analogs value tests are of some diagnostic value of sporadic MTC, the values of two latter may elevated in MTC patients, which may be correlated to the patients' prognosis^[4]. Being different from other differentiated thyroid carcinoma, about one third cases of MTC may have bilateral diseases which was 32.9% (24/73) cases in our groups, it should be paid much attention to. The major treatment method of MTC is radical surgical remove of the primary mass and the metastatic cervical lymph nodes, the extensive lobectomy or combined radical operation may be performed according to the patient' condition. In the case of bilateral disease, the upper or inferior one third of one thyroid lobe and the posterior capsule of the thyroid gland should be kept so that the postoperative hypoparathyroidism could be avoided effectively. Although some huge masses could involved both neck even extended into upper mediastinum, most of them have a thin and complete capsule to separate the masses from the surrounding organs and structures. Sometimes, they ad-

here even invade to the surface of trachea and esophagus, but grew into these tubular organs rarely. It is not proper to abandon the surgical treatment of these cases only according to their image examination results only.

The MTC patients especial those with the familiar history should be proceeded the abdominal ultrasonic and image examination before the operation in order to determine if the pheochromocytoma co-exists. In such case, the pheochromocytoma should be surgically removed before the operation of MTC to avoid the dangerous accident caused by too much catecholamine into blood during the neck operation. In our study, among these 6 cases with the familiar history, 2 cases had the co-existed pheochromocytoma, their MTC surgical treatment were performed safely after the pheochromocytoma was dissected.

There is persistent controversy about the prognostic factors of MTC, It was reported that the prognosis of the inherited MTC especial MEN2A was much better than that of the sporadic MTC. Other prognostic factors have been reported such as the tumor invasiveness, the neck lymph node metastasis clinical stage, the size of the mass, the differentiation of MTC cells, the thoroughness of the surgical dissection and so on [5-7]. As only 6 cases had the familiar history in our groups, the inheritance effect was not discussed. From our results, the clinical stage and the thoroughness of the surgical dissection of MTC may be the major prognostic factors. The survival rate for 5 years was 100% in the 1 stage group, but only 41.5% in 3 stage group, even no patient could survived up to three years in 4 stage group. On the other hand, 8 cases whose primary masses and cervical metastatic lymphnodes were removed incompletely, despite the post-operative radiotherapy were performed, only 2 patients survived up to three years, no patient survived to five years. No relationship was found be-

tween the pre-operative diarrhea and the patient's prognosis.

MTC is different from other differentiated thyroid carcinoma, no inhibitory effect on the recurrence and growth of tumor through the post-operative usage of thyroid hormone. It is crucial, therefore, to remove the primary and metastatic lesions of MTC operatively. In case of huge mass, extensive invasion, or the mass adhered to the large neck vessels, invaded to the trachea and esophagus even extended into the mediastinum, so long as the patient's general condition is permissible, the surgical treatment should not be abandoned. The good result may be obtained if the post-operative radiotherapy was given then.

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