บทความพิเศษ

Current management of thyroid cancer.

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วิธีรักษามะเร็งของต่อมธัยรอยด์ชนิด well differentiated ที่ใช้กันมากที่สุดในปัจจุบัน ได้แก่การผ่าตัดทำ near total thyroidectomy และทำ radio-iodine ablation หลังผ่าตัดประมาณ 4-6 สัปดาห์ และตามด้วยการใช้ฮอร์โมนของธัยรอยด์ (T4 หรือ T3) เชื่อกันว่าวิธีนี้จะทำให้มี local recurrence น้อยที่สุด และมี survival ดีที่สุด

อย่างไรก็ตามยังไม่มีข้อยุติ โดยเฉพาะในการรักษา papillary cancer ที่อยู่ด้านเดียวของต่อมธัยรอยด์ ว่าวิธีดังกล่าวจะดีที่สุดหรือเหมาะสมที่สุดเสมอไป ทั้งนี้เพราะมะเร็งชนิดนี้มีการดำเนินโรคที่ยาวนานมาก อาจต้องใช้เวลา 20 ปีขึ้นไป เพื่อให้เห็นผลของการรักษาที่ต่างวิธีกัน และยังไม่เคยมี prospective controlled trial เพื่อเปรียบเทียบผลการรักษาด้วยวิธีต่าง ๆ เลย

การประเมินความรุนแรงของมะเร็ง โดยอาศัยเกณฑ์ต่าง ๆ เช่น อายุ (Age) การมี distant Metastasis ขนาดของก้อน (Size) การลุกลามของก้อนออกนอกต่อมธัยรอยด์ (Extent) และลักษณะทางพยาธิของชิ้นเนื้อ (histologic Grading) โดยนำแต่ละเกณฑ์เหล่านี้มาให้คะแนนตามระดับความรุนแรง และนำคะแนนทั้งหมดมารวมกัน (AGES score, AMES score) ซึ่งเริ่มมีการทดลองปฏิบัติมาใน 5-10 ปีนั้น ทำให้เห็นว่ามะเร็งชนิดนี้ส่วนใหญ่เป็นชนิด low risk ซึ่งมีการพยากรณ์โรคดีมากไม่ว่าจะรักษาด้วยวิธีใด ดังนั้นจึงเป็นไปได้ว่าแนวโน้มการรักษามะเร็งชนิดนี้จะเป็นแบบ selective มากขึ้น เช่น บางรายอาจจำเป็นทำแค่ unilateral lobectomy หรือบางรายอาจไม่จำเป็นต้องทำ radio-iodine ablation ทันทีหลังผ่าตัดเสมอไป เป็นต้น

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Thyroid cancer is increasingly encountered in hospital practice partly due to heightened awareness by the general public and partly to the increased use of fine needle aspiration cytology in the evaluation of relatively common thyroid nodules. As a result thyroid cancer are being discovered at the more favourable stage where disagreement in their treatment exists. The great majority of thyroid cancer is the well differentiated type which runs a long clinical course with good prognosis. Therefore any meaningful assessment of the treatment efficacy necessarily requires a large number of patients and a long period of follow-up, probably 20 years or more. As there are no prospective randomized studies comparing various surgical techniques matched for age, sex and definite histology with adequate follow-up it appears that the disagreement in the treatment will continue for some time. Errors in histologic classification of the tumour, differing surgical skills and lack of reliable method to quantitate biologic aggressiveness of the cancer all help to sustain the controversy.[1]

Pre-operative diagnosis

Malignant thyroid tumours may be clinically obvious at presentation as hard and irregular nodules associated with rapid growth, hoarseness or neck node enlargement. More commonly they present as single nodules which are firm, well circumscribed and mobile in euthyroid patients. The use of fine needle aspiration cytology allows rapid diagnosis of such nodules. Its use has replaced scanning, ultrasonography or a trial of TSH suppression with exogenous thyroid hormone as the primary investigation. Surgery is indicated when the results of FNA-cytology are positive or suspicious. Negative cytology results should be repeated at intervals as false negative results may occur through sampling error. In the group with negative results the need to perform surgery should be evaluated together with the recognized risk factors such as history of neck radiation in childhood,[2] age (over 40 years) and family history of medullary carcinoma. History such as rapid growth, continuing enlargement inspite of hormone therapy or large size would also favour surgical intervention in those with negative FNA results.

It is agreed that the best initial approach to suspicious or malignant thyroid nodule after FNA-cytology is total (or as near total as possible) lobectomy with isthmusectomy. This allows proper histological examination to be carried out. Should the nodule prove to be carcinoma then there is no need to re-operate on this side which would expose the recurrent nerve and parathyroids to greater risk of injury. What to do with the contralateral lobe is a matter of controversy.

Papillary Carcinoma

This is the most common thyroid cancer accounting for 60-70% of all cases. Included here are tumours with mixed papillary and follicular pattern which are known to behave like papillary cancer. Papillary cancer is a disease of the young

with peak incidence in the third decade. The female to male ratio is about 3 or 4 to 1. It is rarely encapsulated and can arise within cysts. The tumour shows evidence of multicentricity in about 30% of cases.[3] The spread is mainly to the regional lymph nodes. Blood borne metastases are rare and mainly to the lungs.

Papillary cancer is classified clinically according to the extent of its local invasion. When the tumour is confined within the thyroid capsule it is known as intrathyroidal. When the tumour erodes through the thyroid capsule it is termed extrathyroidal. These terms do not refer to lymphatic or blood borne spread and intrathyroidal tumours are often accompanied by metastatic cervical lymph nodes. Small intrathyroidal tumours (less than 1 or 1.5 cm in diameter) which are not palpable are known as occult or minimal cancer. These tumours may present with enlarged cervical nodes.

Openions differ regarding the optimal extent of surgery for unilateral papillary cancer. In general there are 3 approaches which have equally good data from the literature to support.

1. **Total thyroidectomy** The arguments for this procedure are as follow.[4]

a. The procedure is safe in expert hands
b. Clinical recurrence in the opposite lobe is about 5% after lobectomy alone.[5]
c. There are known instances of anaplastic cancer arising in a long-standing occult differentiated carcinoma. Total thyroidectomy would prevent such development.[6]
d. Total thyroidectomy facilitates the use of radioactive iodine in detection and treatment of recurrent disease or metastasis.
e. Total thyroidectomy increases the sensitivity of thyroglobulin measurement which may be useful in detecting recurrent disease.[7]

2. **Near total or subtotal thyroidectomy** This procedure includes total lobectomy on the side of lesion, isthmusectomy and subtotal or near total lobectomy on the contralateral side leaving about 1-2 grams of thyroid tissue on its posterior surface to protect the parathyroids and the recurrent nerve. Its proponents,[3,8] claim that this procedure has all the advantages of total thyroidectomy and is much safer. Should remaining thyroid tissue needs to be destroyed it can be easily accomplished with radioactive iodine.

3. **Unilateral lobectomy** The tumour bearing lobe is completely removed together with the isthmus. The procedure is based upon the following arguments.

a. The microscopic foci of carcinoma which might be left behind in the other lobe is rarely a source of recurrence or metastasis.
b. Anaplastic transformation of the multicentric occult foci is very rare.[9]
c. The remaining lobe can be removed in case of recurrence with little risk.

d. There are no proven survival benefit with more extensive procedure.[10]

Near total (subtotal) thyroidectomy is emerging as the most acceptable procedure to most surgeons when the diagnosis is established at the time of primary operation.[11-13] It is the procedure that carries very little risk of permanent hypoparathyroidism and its survival benefit is as good as total thyroidectomy. For low risk patients, i.e. under 40 with small intrathyroidal tumour which represent the majority of papillary cancer patients, near total thyroidectomy gives no survival benefit over unilateral lobectomy but it is associated with much less local recurrence, 4% vs 14% in 30 years.[14]

During thyroidectomy node bearing soft tissues in the pre and paratracheal area are removed with the specimen. This will prevent difficult dissection in this area later should the nodes become involved subsequently. Occult node metastasis may occue in 20-80% of the patients but their significance is unknown.

Management of neck nodes There is a general agreement that cervical nodes should not be removed unless they are clinically involved.[8] Enlarged or suspicious nodes should be biopsied. Most surgeons advocate modified radical neck dissection for extensive involvement of nodes preserving sternomastoid, spinal accessory nerve and internal jegular vein. Limited or local excision of the nodes is satisfactory with lesser degree of node involvement. Formal radical neck dissection is indicated in rare instance when the metastatic nodes become fixed and the cancer has eroded the node capsules into the adjoining soft tissue.

Management of locally invasive cancer Direct local invasion of the trachea is a bad sign and when possible should be removed. Defect in the trachea if not too extensive may be left for insertion of tracheostomy tube at the end of the operation. When the invasion is extensive the trachea needs to be resected. Up to 4-6 cm of trachea can be resected and an end-to-end anastomosis can be performed after mobilization of trachea.[15] The benefit of more extensive surgical procedure for aggressive local disease is not clear.

Post operative management After surgery all patients with papillary cancer should be given thyroid hormone indefinitely to suppress TSH secretion because papillary cancer is TSH dependent.[5] The dose required may be estimated accurately by serial estimation of serum TSH levels.[16] Clinically the dose of thyroxin given daily varies between 200-300 microgram depending on build and age of the patients.

The use of radioactive iodine Radioiodine is useful in the management of residual disease and metastasis that take up iodine. However, its routine use following adequate removal of primary tumour by total (or near total) thyroidectomy in order to search and control subclinical metastasis is still debatable. In some centres it is performed only in high risk cases without apparent survival advantage.[5,17,18] In spite of the controversy many

centres adopt radio-iodine therapy as a matter of routine following surgery.[14] Thyroid hormone replacement is withheld for 4 weeks and whole body scan with ^{131}I is performed (1-5 mci). The scan is repeated 6 months later and functioning metastasis are ablated. The procedures is repeated at 6 monthly intervals until all metastasis are completely destroyed. Follow up scan is performed at 3 or 5 yearly intervals. Serum thyroglobulin estimation may be used in place of thyroid scan in the follow up (see later) after complete ablation of all metastasis. For metastases which do not take up radio-iodine multiple chemotherapy may be tried. Radiotherapy is usually reserved for local recurrence.[19]

The use of thyroglobulin If facilities for estimation of serum thyroglobulin exist then it should be done at 6 or 12 monthly intervals to monitor the progress of treatment. Following total thyroidectomy or ablation of thyroid remnant with radio-iodine the thyroglobulin levels should be undetectable or very low (below 10 ng/ml). Higher levels would indicate persistent or recurrent disease. The patient should be taken off thyroid hormone replacement for 4 weeks before its estimation as the level is sensitive to TSH stimulation.[7] An elevated thyroglobulin level requires confirmation of functioning metastasis with radioactive iodine scan. An elevated thyroglobulin level and a normal ^{131}I scan should raise suspicion of nonfunctioning metastasis which should be searched carefully with conventional radiologic methods.

Prognosis Papillary cancer generally has good prognosis. Overall 10 year survival after treatment is about 95%.[3,20] The prognosis is determined mainly by the age of the patients and the extent of primary lesion. Ten year survival is significanly reduced 72% vs 95%, in those over the age of 40 and in those with extra thyroidal disease, 60% vs 95%.[8] Distant metastasis is also a bad sign when present in adults but not necessarily so in children.[7]

Follicular Carcinoma

This is the second commonest thyroid cancer accounting for 15-20% of thyroid cancer cases. It usually presents as a single nodule and occurs mainly in women over 40 years of age. The tumour is well encapsulated and its malignant nature is based upon identification of capsular or vascular invasion. Multicentricity occurs in about 15% cases.[22] Metastasis occurs primarily by hematogenous route to the bone, lung and brain which are not uncommonly the main presentation of the disease. Two types of follicular cancer are recognised. The minimally invasive cancer shows only microscopic invasion of the thyroid capsule or capsular venous sinus. These lesions are rarely multicentric and rarely metastasize and are associated with excellent prognosis. The second type is the widely invasive cancer which shows invasion into the extracapsular vasculature. This is an aggressive tumour which accounts for most of the morbidity and mortality associated with follicular carcinoma. On the

whole follicular cancer are more virulent than papillary cancer. Ten year survival for minimally invasive cancer is about 85% whereas for widely invasive type is about 40%.

Surgical treatment of follicular cancer. The range of surgical procedures for follicular cancer localised to one lobe is the same as for papillary cancer. Likewise there are no prospective controlled trial to indicate the merits of one procedure over the rest. However, total (or near total) thyroidectomy appears to be the procedure of choice for most surgeons.[23] This is because of the more aggressive nature of the follicular cancer which gives rise to metastatic disease more frequently than papillary cancer. Total (or near total) thyroidectomy facilitates subsequent scanning with ^{131}I in search of metastasis. If extrathyroidal infiltration is present then it is resected widely as for papillary cancer. The rare metastatic nodes, if present, are similarly removed. Total thyroidectomy is indicated in the Hurthle cell carcinoma which is a rare variant of follicular carcinoma because the tumour is unresponsive to radio-iodine or external radiation.[24]

Six to eight weeks following surgery, total body scan should be performed and remaining thyroid remnant is ablated. Subsequent scanning schedule is the same as in papillary cancer. Metastasis which do not take up radio-iodine and do not respond to radio-iodine therapy are treated by external radiation and chemotherapy but the results are disappointing. All patients should be put on thyroid hormone indefinitely.

Prognosis Minimally invasive follicular carcinoma carries the best prognosis. Factors known to be associated with poor prognosis are:[20,25]

1. Age over 40
2. Extra capsular angio-invasion
3. Extension beyond thyroid capsule
4. Presence of distant metastasis
5. Large size
6. Poor histologic grade

Medullary Carcinoma

This is not a common cancer and arises from parafollicular c-cell. The tumour produces calcitonin which can be used for diagnosis and for follow-up. Other hormone secretions are ACTH and prostaglandin, the latter probably accounting for the symptoms of watery diarrhoea seen in about one-third of patients with medullaly carcinoma. Microscopically it consists of sheets or clusters of round or polyhedral cells separated by areas of collagen and amyloid. Clinically the tumour usually presents as a hard, well circumscribed nodule which appears pale grey when cut. The spread is first to the cervical nodes and later to distant sites such as lung, liver and bone. The tumours do not take up iodine and is not responsive to TSH. Clinically there are 2 types.

1. Sporadic type. The patient is older and often presents with single nodule.

2. Familial type. The tumour is almost always bilateral. The patients are younger and the prognosis is better. There is also an association

with other endocrine neoplasia such as pheochromocytoma, hyperparathyroidism and neuromata of mucuous membrane.

Treatment Medullary cancer is treated by total thyroidectomy because of its multicentricity. Metastatic nodes are treated by modified or radical neck dissection. It is important to look for pheochromocytoma and hyperparathyroidism in these patients. Pheochromocytoma should be operated on before thyroidectomy. Bilateral adrenalectomy may be required because of multi centricity and bilaterality of the lesion. Parathyroidectomy can be performed at the same time as thyroidectomy.

Prognosis Five year survival is approximately 90% in patients with neagative nodes and 65% with positive nodes. At ten years the figures are 85% and 40% respectively.[1] Survival is worse with the sporadic type.

Anaplastic Carcinoma

This is one of the most aggressive cancer known and accounts for 5-10% of thyroid cancer. Histologically the tumour is composed of spindle cells with high mitotic activity, pleomorphic multinucleated giant cells, extensive necrosis and inflammation, hemorrhagic space and tumour invasion into vessels. It affects patients over the age of 60 years. The usual presentation is that of a rapidly growing mass causing dyspnoea, neck pain, dysphagia and hoarsness. Many already have bone or lung metastasis at the time of presentation. Survival after treatment beyond 6-12 months is highly unusual.

Treatment If the tumour still confines within the thyroid capsule it is appropriate to do total thyroidectomy. When the tumour has broken out of thyroid capsule and deeply invades soft tissue of the neck, then palliative debulking should be attempted and tracheostomy performed to avoid subsequent air way obstruction. After the operation external radiation to the neck is given often with temporary response. Multiple chemotherapy may also be tried also with variable response.[26,27]

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