Leading article

Lymph node dissection and medullary thyroid carcinoma

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Medullary thyroid carcinoma (MTC) differs fundamentally from thyrocyte carcinomas, not only in embryology and microscopic anatomy, but also in function, tumour biology, pathogenesis and genetics. Importantly, in contrast to thyrocyte carcinomas, MTC can be diagnosed at a preclinical stage by a specific secretory product, calcitonin. Furthermore, again in contrast to thyrocyte carcinomas, the hereditary variant of MTC can be identified unequivocally in about 95 per cent of patients; the *RET* proto-oncogene was identified by Mulligan and by Donis-Keller in 1993 as the susceptibility gene for hereditary MTC. A major disadvantage compared with differentiated thyroid carcinomas is the inability to treat MTC with radio-iodine. In addition, no multimodal treatment protocol has been proven effective in advanced and/or metastasizing MTC. Taken together, there is no currently available alternative to surgical treatment for both curative and palliative situations.

Total thyroidectomy

While some groups perform lobectomy in selected patients with genetically proven sporadic MTC[1], total thyroidectomy is generally accepted as the single essential element of primary surgical treatment for all forms and stages of MTC. The reasons are as follows. First, intraglandular lymphatic spread occurs in 10–20 per cent of patients with sporadic MTC. Second, the hereditary background is often unknown at the time of primary operation and may not even be detected in the case of rare mutations of the *RET* proto-oncogene. Third, radio-iodine treatment for microscopic intraglandular deposits is not effective in MTC. Despite the above, it must be conceded that there are no prospective studies of sporadic MTC that prove the outcome is better after total thyroidectomy than after unilateral lobectomy. On the other hand, no histological, biochemical or molecular markers currently exist to indicate those occasional patients who may benefit from non-total thyroidectomy. In hereditary MTC, because of the genetic alteration of the whole C-cell system, there can be no place for any resection less than total thyroidectomy.

Compartment-oriented microdissection

Compartment-oriented microdissection depends on certain features of lymph node colonization, which typically occurs in anatomically defined 'compartments' before the borders to the next lymph node compartment are crossed. This phenomenon occurs in several human cancers and is also evident in thyroid carcinoma, especially of the papillary and medullary types. Four locoregional lymph node compartments can be differentiated[2]: the central (first), ipsilateral–cervicolateral (second), contralateral–cervicolateral (third) and upper mediastinal (fourth) (*Fig. 1*). The definitive proof that these four compartments are really locoregional comes from the observation that not only papillary but also medullary carcinomas with metastases within these compartments are potentially curable. The superiority of this compartment classification compared with the Robbins and Union Internacional Contra la Cancrum (UICC) classifications of cervical lymph node groups has been proven by several international multicentre studies[3,4]. First, it reflects the biological principle of compartmental colonization within anatomically defined

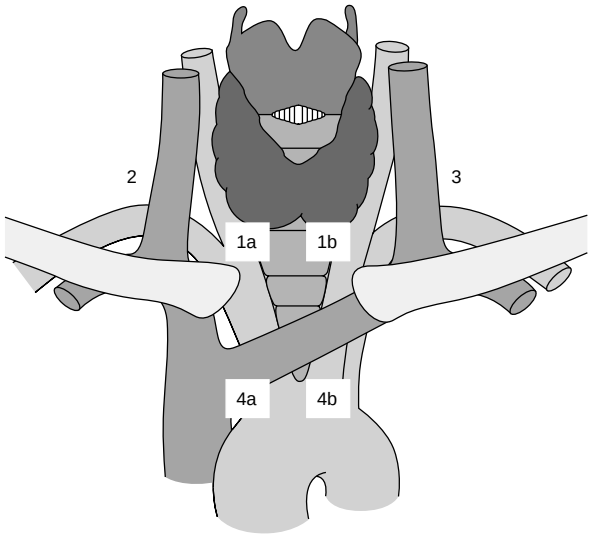

Fig. 1 Compartment classification: 1a, right cervicocentral; 1b, left cervicocentral; 2, right cervicolateral; 3, left cervicolateral; 4a, right upper mediastinal; 4b, left upper mediastinal

borders; second, it can be easily applied by different centres; third, it clearly differentiates the side of the neck; and fourth, it includes the infrabrachiocephalic upper mediastinum within the locoregional lymph node system.

Thyroid cancer needs its own lymph node staging system because tumour biology and locoregional metastatic routes differ completely from those of aerodigestive tumours of the neck. From pathoanatomical and pathohistological studies it can be concluded that lymph node metastases occur much more frequently in MTC than in papillary cancer (65 *versus* 47 per cent respectively). Moreover, compartmental tumour involvement of lymph nodes is greater in MTC than in papillary cancer. This means that in most cases of MTC more than one lymph node, or group of lymph nodes, is involved microscopically or even macroscopically.

The introduction of meticulous, compartment-oriented microdissection not only for primary but also for reoperative MTC surgery has been a great leap forward. It has resulted in a significantly improved rate of biochemical cure (normalization of stimulated calcitonin levels), from 30–50 per cent previously to 60–80 per cent for primary operation, and from 0–20 to 30–40 per cent for reoperation[2,7–9]. However, certain questions arise. How many compartments should be dissected in different tumour stages? How does compartmentectomy influence recurrence and survival in patients with local disease, with or without systemic disease?

Extent of lymph node dissection

There is ongoing controversy about what constitutes an adequate extent of node dissection for this rare tumour. This is complicated not only by problems arising from the tumour itself (often a chronic disease, even in the case of distant metastases), but also by the concept of 'the surgeon as a risk factor'; the latter is a training and experience issue. The central compartment is the first lymph node station in the overwhelming majority of thyroid cancers, including MTC. From local data on 339 patients with MTC treated from 1995 to 2001, it appears that only 15 per cent of node-positive MTC skips the central compartment and metastasizes directly to the ipsilateral cervicolateral nodes. However, at reoperation persistent lymph node metastases are often found in the central compartment (65 per cent of patients undergoing reoperation locally). The ipsilateral cervicolateral compartment is primarily involved as frequently as the central compartment (about 35 per cent for all tumour stages). Nevertheless, in reoperative cases persistent lymph node metastases are frequently found in the ipsilateral cervicolateral compartment (approximately 50 per cent of cases locally). The contralateral cervicolateral compartment is involved primarily in about 20 per cent of all patients with MTC; in the reoperative situation this value is only slightly higher than in the primary situation. The infrabrachiocephalic upper mediastinal compartment is involved in approximately 15–20 per cent of all patients with MTC, but in about half of those with pathological tumour (pT) stage 4 tumours (*Table 1*).

The chance of biochemical cure has been reported as correlating with the number of compartments and the number of lymph nodes involved; in one study no biochemical cure was associated with three or more involved compartments and ten or more involved lymph nodes[10]. To answer the question about which type of

Table 1 Locoregional lymph node involvement in medullary thyroid carcinoma

		No. of positive compartments resected*			
		Cervicocentral	Cervicolateral		Mediastinal
pT status	*n*		Ipsilateral	Contralateral	
Primary MTC					
pT1	35	5	4	0	0
pT2	16	5	6	3	2
pT3	3	0	0	0	0
pT4	14	12	13	8	7
Total	68	23 (34)	23 (34)	11 (16)	9 (13)
Reoperative MTC					
pT1	16	9	8	3	0
pT2	59	36	29	11	11
pT3	7	5	3	2	2
pT4	11	10	6	4	5
Total†	93	60 (65)	46 (49)	20 (22)	18 (19)

Values in parentheses are percentages. *Number per pathological tumour (pT) category by the respective pT population. †Excluding one pTx carcinoma. MTC, medullary thyroid carcinoma. Data from Machens *et al.*[6], with permission

Table 2 Surgical strategy for patients with medullary thyroid carcinoma

	Primary operation	Reoperation
No evidence or suspicion of distant metastases	TT, C1–3, C4 only in the case of nodal involvement	Completion operation according to extent recommended for primary operation
Distant micrometastases	TT, C1 + 2 or 3 (according to site of primary tumour), contralateral–cervicolateral and/or upper mediastinal compartmentectomy only in the case of nodal involvement	Completion operation according to extent recommended for primary operation
Distant macrometastases	TT plus selective removal of symptomatic lymph node metastases	Selective removal of symptomatic lymph node metastases

TT, total thyroidectomy; C1–4, compartments according to the compartment classification[2]

operation fits the majority of patients with MTC (those with an intrathyroidal MTC without distant macrometastases), the present author, like others[9], recommends total thyroidectomy with three-compartment lymphadenectomy (central plus bilateral cervicolateral) in primary as well as completion surgery (*Table 2*). Most difficult is the decision regarding the extent of operation in patients with locoregional and distant disease (proven or suspected). In the case of symptomatic locoregional disease and the presence or suspicion of distant micrometastases, the local pathology often plays the role of 'pacemaker' of the disease. For this reason the author recommends local tumour control by microdissection of the affected compartments. Only in the case of proven distant macrometastases would the extent of cervical reoperation be confined to the removal of symptomatic cervical nodes. Mediastinal lymph node dissection has a place only in curative interventions directed at proven metastases. Although this locoregional strategy should go along with an increased chance of biochemical cure, further long-term studies are necessary to establish its superiority in terms of disease-free survival.

The main problem today is to identify correctly patients with micrometastases by modern imaging techniques (or bone marrow analysis) and to differentiate between patients with progressive and those with stable disease. Ongoing research in this regard holds out hope of being able to modify the present concept of radical locoregional lymph node surgery in MTC. At present, the best way to cure the patient is early diagnosis in sporadic MTC, and prophylactic thyroidectomy in gene carriers of hereditary MTC[11].

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