

Effective Long-term Palliation of Symptomatic, Incurable Metastatic Medullary Thyroid Cancer by Operative Resection

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Objective

To evaluate the short- and long-term consequences of palliative resection of specific symptomatic lesions in patients with widely disseminated (incurable) medullary thyroid cancer (MTC).

Summary Background Data

Although reoperative neck microdissections can normalize calcitonin levels in patients with metastatic MTC confined to regional lymph nodes, there is no curative therapy for widely metastatic disease. However, these patients frequently have prolonged survival, but often with debilitating symptoms.

Methods

Between October 1981 and January 1997, 16 patients (mean age, 46 ± 3 years; 10/16 female) underwent 21 palliative reoperations for unresectable MTC at the Johns Hopkins Hospital. All patients had significant symptom(s) or impending compromise of vital structures by a discrete lesion and had unequivocal *preoperative* evidence of a total disease burden that was unresectable.

Results

The mean interval from initial thyroidectomy to palliative surgery was 5.8 ± 1.5 years. All patients had significant tumor

burdens as evidenced by preoperative calcitonin values ranging from 900 to 222,500 pg/mL ($nL \leq 17$ pg/mL). The palliative operations consisted of reoperative neck dissection/mass excision (11), mediastinal mass resection (4), esophagectomy (1), liver trisegmentectomy (1), sigmoidectomy (1), bilateral simple mastectomies (1), pituitary resection (1), and subcutaneous mass excisions (1). All but two of the operative specimens contained MTC. There was no perioperative mortality. The long-term morbidity rate was limited to one recurrent laryngeal nerve injury. All patients had initial relief of the index symptom(s) after the palliative surgery, followed by a median actuarial *symptom-free* survival rate of 8.2 years.

Conclusions

Patients with widely metastatic MTC often live for years, but many develop symptoms secondary to tumor persistence or progression. Judicious palliative, reoperative resection of discrete, symptomatic lesions can provide significant long-term relief of symptoms with minimal operative mortality and morbidity. In selected patients with metastatic MTC lesions causing significant symptoms or physical compromise, palliative reoperative resection should be considered despite the presence of widespread incurable metastatic disease.

Medullary thyroid cancer (MTC) is an uncommon neuroendocrine tumor derived from the calcitonin-producing

thyroid C-cells and accounts for 3% to 5% of cases of thyroid cancer.¹ Complete surgical resection (total thyroidectomy, usually with a modified lymph node dissection) at a relatively early stage of the disease remains the only reliable cure for MTC.² However, despite initial thyroidectomy, more than 50% of patients with MTC will have persistent disease, manifested as elevated, postoperative serum calcitonin levels.^{3,4} Although reoperative neck micro-

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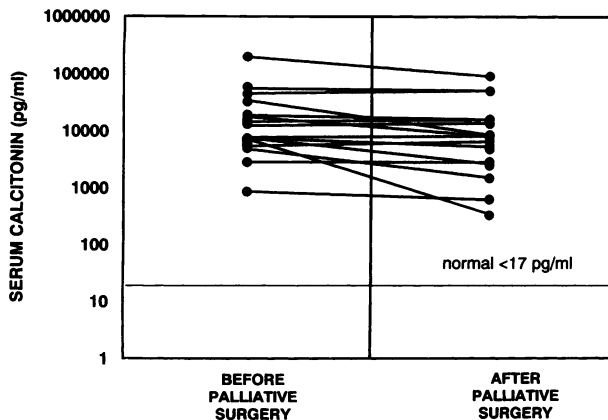


Figure 1. Serum calcitonin levels before and after palliative surgery. All patients had highly elevated calcitonin levels both pre- and postoperatively, suggesting incurable metastatic disease. Normal values are <17 pg/mL (line under "normal <17 pg/ml") by the standard Nichols assay. This emphasizes that the primary benefit of these resections performed for symptomatic palliation lies in the removal of a specific lesion rather than in a debulking of a substantial proportion of the total tumor burden.

dissections can normalize calcitonin levels in some patients with metastatic disease confined to regional lymph nodes⁴⁻⁶, there is no curative therapy for patients with widely metastatic disease. However, these patients frequently have prolonged survival rates,^{3,7,8} but often with debilitating symptoms. Despite a few, uncontrolled reports to the contrary,^{9,10} MTC has proven to be particularly unresponsive to radiotherapeutic and chemotherapeutic approaches that can be helpful for the palliation of other symptomatic disseminated solid malignancies.^{1,11} Moreover, there is no effective alternative approach to treat many of the debilitating symptoms, including airway obstruction, diarrhea (which is unresponsive to octreotide¹), and flushing. Although several studies have addressed the results of reoperation in patients with resectable disease for curative intent,^{3-8,12} the effect of reoperation for palliation of symptoms in patients with disease that is recognized preoperatively to be incompletely resectable has not been formally documented. Therefore, we evaluated the long-term effectiveness of reoperation for palliation of symptomatic, incurable metastatic MTC.

METHODS

Fifty-one patients who had surgery for MTC at the Johns Hopkins Hospital between October 1981 and January 1997 were identified from the Johns Hopkins Hospital pathology database. To determine the role for palliative reoperation for symptomatic metastatic disease, patients with unresectable MTC recurrences were identified. Of the 51 patients, 16 subsequently had undergone 21 palliative reoperations in the face of unresectable disseminated MTC and form the basis for this report.

All patients had previously undergone thyroidectomy and subsequently developed recurrent disease. All patients had

significant symptoms or impending compromise of vital structures by a distinct lesion that was judged to be resectable, but had a total disease burden that was recognized *preoperatively* as unequivocally incompletely resectable (incurable). (Although it is difficult to quantify this retrospectively, we estimate that we operated upon fewer than half of the patients in this category initially referred for consideration of resection). Medical records were reviewed and patients and relatives were interviewed to assess symptomatic improvement after reoperation. Projected symptom-free survival after each procedure was estimated by Kaplan-Meier analysis (SPSS software, SPSS).

RESULTS

Patient Demographics

The mean age of patients at the time of initial thyroidectomy was 46 ± 3 years. The mean age at the time of palliative surgery was 52 ± 3 years. Of the 16 patients, 10 were women and 6 were men. Nine patients had MTC that was not associated with any inherited genetic defect (sporadic MTC), whereas six had multiple endocrine neoplasia (MEN) type 2A and one had familial MTC.

Tumor Burden and Symptoms

All patients had had previous total thyroidectomies for treatment of their primary tumors. All 16 patients had had advanced MTC at the time of initial diagnosis, as demonstrated by the clinical stage at initial thyroidectomy (Table 1). No patient had stage I or II disease at that point. The mean interval from initial thyroidectomy to the palliative surgical procedure was 5.8 ± 1.5 years.

At the time of palliative resection, all 16 patients had metastatic disease that was clearly recognized *preoperatively* to be incurable (multiple metastases in the neck or mediastinum that were not totally resectable, liver metastases, lung metastases, disseminated disease, or diffuse, un-

Table 1. MTC TUMOR STAGE* AT INITIAL RESECTION

Stage	Description	No. of patients
I	C-cell hyperplasia	0
II	Tumor <1 cm and negative cervical lymph nodes	0
III	Tumor ≥ 1 cm, or any size with positive cervical lymph nodes	9
IV	Any size with metastases outside the neck or with extrathyroidal extension	7

* Clinical staging of medullary thyroid cancer, National Thyroid Cancer Treatment Cooperative Study.

MTC = Medullary thyroid cancer.

Table 2. PALLIATIVE OPERATIONS FOR MTC NECK MASS RESECTIONS OR DISSECTIONS

No.	Preoperative Symptoms	Operation	Viability	Symptom Status	F/U* (yrs)
1	Airway compromise	Tracheal mass resection	Dead	(SF)†	3.2
2	Dyspnea	Tracheal mass resection	Alive	SF	8.3
3	Airway compromise	Neck mass resection	Alive	recurrence	1.0
4	Airway compromise	Right MRND	Dead	SF	1.7
5	Airway compromise	Neck mass resection	Dead	SF	4.5
6	Dyspnea, dysphagia	Neck mass resection	Dead	SF	1.6
7	SVC syndrome	Left MRND	Alive	SF	2.1
8	SVC syndrome	Redo bilateral MRND	Alive	SF	0.9
9	Tracheocutaneous fistula	Neck dissection, fistula removal	Alive	SF	3.2
10	Arm pain	Left neck/brachial plexus mass excision	Alive	recurrence	0.3
11	Arm pain	Left brachial plexus mass excision	Dead	recurrence	0.9

SF, symptom-free; MRND, modified radical neck dissection; SVC, superior vena cava.

* F/U indicates the total number of years of follow-up of the symptom-free patients, or the time to recurrence of the symptom(s); therefore in both cases the figure in this column represents the (minimum) symptom-free postoperative interval.

† Until death.

localized regional disease). All patients also had substantial total tumor burdens, as evidenced by preoperative serum calcitonin values ranging from 900 pg/mL to 222,500 pg/mL (normal range ≤ 17 pg/mL) (Figure 1).

Surgical Management

Tables 2 through 4 summarize the experience with the 21 palliative operations. Ten patients underwent 11 operations for symptoms due to tumor recurrence in the neck area (Table 2). Seven of these 10 patients had resection of one or more neck masses. Figure 2 depicts a three-dimensional reconstruction of a computerized tomographic scan of the neck of one of these patients before palliative surgery. Three of 10 patients required formal modified radical neck redisections to remove symptomatic tumor. Two patients had resection of tumors compressing the brachial plexus causing arm pain. One patient had a resection of a tracheocutaneous fistula. Metastatic MTC was found in all resected specimens from these 11 surgeries, except in the latter case where the tracheocutaneous fistula was found to be free of histologic evidence of tumor.

Four patients underwent mediastinal dissections to remove MTC metastatic to mediastinal lymph nodes (Table

3). In one patient, four masses were resected. Figure 3 illustrates the standard (extensive) mediastinal dissection we usually perform in these patients. All resected specimens from these four operations contained metastatic MTC. Six other operations were performed for palliation of metastatic MTC (Table 4). Metastatic MTC was found in all of these cases as well, except for one patient with a colon mass that proved to be an obstructing villous adenoma (not MTC) upon histologic examination.

After 21 operations in these 16 patients, there was no operative mortality. Morbidity was limited to one patient with recurrent laryngeal nerve injury after redo bilateral modified radical neck dissections for massive neck recurrence and consequent superior vena caval syndrome, one patient with a transient Horner's syndrome after neck dissection, and one patient with transient postoperative atrial fibrillation after mediastinal mass resection. Therefore, the long-term morbidity rate was 5%.

Patient Outcomes

No patients were lost to follow-up. Follow-up from the time of palliative surgery until death or the latest review

Table 3. PALLIATIVE OPERATIONS FOR MTC—MEDIASTINAL DISSECTIONS

No.	Preoperative Symptoms	Operation	Viability	Symptom Status	F/U (yrs)
1	Dyspnea	Mediastinal mass resection (x4)	Alive	Recurrence	1
2	Dyspnea	Mediastinal mass resection	Alive	SF	7.4
3	Dyspnea	Mediastinal mass resection	Alive	SF	11
4	Dyspnea, innominate vein compression	Mediastinal mass resection	Alive	SF	5.6

SF, symptom-free; F/U, time of last follow-up or of recurrence of symptoms.

Table 4. PALLIATIVE OPERATIONS FOR MTC—OTHER RESECTIONS

No. (yrs)	Preoperative Symptoms	Operation	Viability	Symptom Status	F/U
1	Cachexia, diarrhea	Hepatic trisegmentectomy	Dead	SF	1.9
2	Dysphagia	Esophagectomy	Alive	SF	5.5
3	Diarrhea	Subcutaneous mass excisions	Alive	SF	0.9
4	Visual field defects	Pituitary resection	Alive	SF	0.7
5	Breast pain, ulceration	Bilateral simple mastectomies	Dead	SF	0.1
6	Colonic mass	Sigmoid colectomy	Dead	SF	8.2

SF, symptom-free; F/U, time of last follow-up as of recurrence of symptoms.

(October, 1997) ranged from 0.1 to 11 years. All patients had a significant quantitative burden of residual, metastatic MTC remaining after palliative surgery, as evidenced by persistently elevated postoperative calcitonin levels (Figure 1). Clearly, the operative resection had little effect on the

overall tumor burden in all but one patient. All patients had initial relief of the symptom(s) for which the palliative operation had been undertaken. Of the 16 patients, 6 subsequently died of disease, whereas 10 lived with the disease. Therefore, the median survival rate for this group has not been reached yet. Of the six patients who died, five remained free of their palliated symptom(s) until their death. Of the 10 patients who were alive as of this writing, 9 have remained free of their palliated symptom(s). Actuarial symptom-free survival is depicted in Figure 4. Patients who underwent palliative surgery for metastatic MTC were projected to have a median symptom-free survival of 8.2 years after the palliative operation. Their actual median symptom-free survival has not been reached after a median actuarial follow-up of 3.2 years.

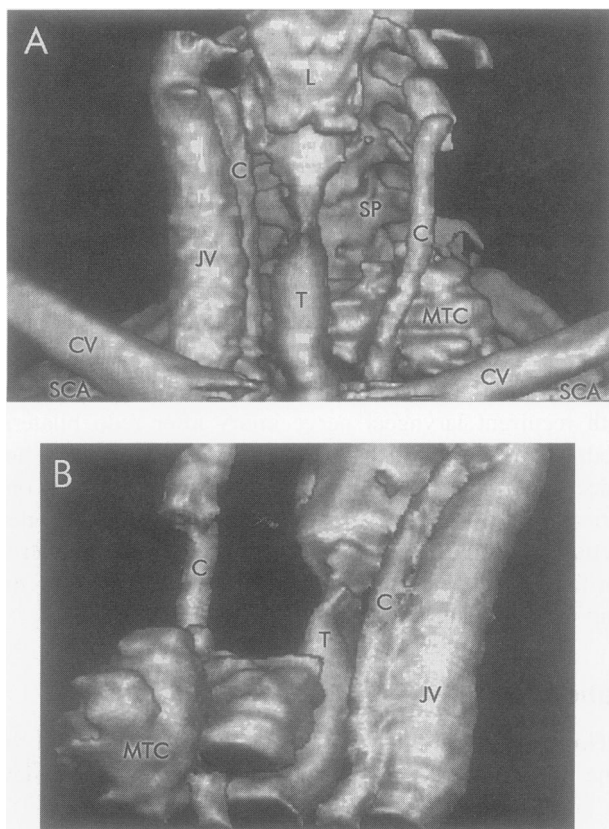


Figure 2. Three-dimensional reconstruction of neck/chest computerized tomographic images of a patient with a metastatic MTC mass at the junction of the left subclavian and carotid arteries, causing pain, left arm edema, and some dyspnea. These symptoms were relieved after excision.

A. Anterior view.

B. Oblique, posterolateral view.

JV=jugular vein; C=carotid artery; SCA = subclavian artery; MTC = metastatic medullary thyroid carcinoma (mass); T = trachea; L = larynx; CV = clavicle; SP = spine. (Three-dimensional reconstructions of computerized tomographic data courtesy of S. James Zinreich, MD, Neuroradiology, Johns Hopkins.)

Neck Mass Resections and Dissections

Ten patients underwent 11 palliative neck operations for MTC (Table 2). Eight of the 11 neck resections/dissections were for airway compromise or superior vena cava syndrome. Only one of the eight patients subsequently developed recurrent symptoms, which appeared 1 year after palliative surgery. The other patients remained asymptomatic until their most recent follow-up or until their death (follow-up range, 0.9–8.3 years). Two of the 11 neck operations were for arm pain caused by brachial plexus involvement. Recurrent arm pain soon developed in both patients, at 0.3 years and 0.9 years after palliative surgery, respectively.

Mediastinal Dissections

Four patients had resection of one or more mediastinal masses for symptoms of dyspnea or airway compromise (Table 3). One of these patients developed recurrence of these symptoms at 1 year, but the remaining three patients were alive and symptom-free after 5.6, 7.4, and 11 years of follow-up.

Other Palliative Operations

Six patients had other palliative operations for metastatic MTC (Table 4). One patient had MTC that invaded the esophagus and larynx, and underwent a laryngectomy and

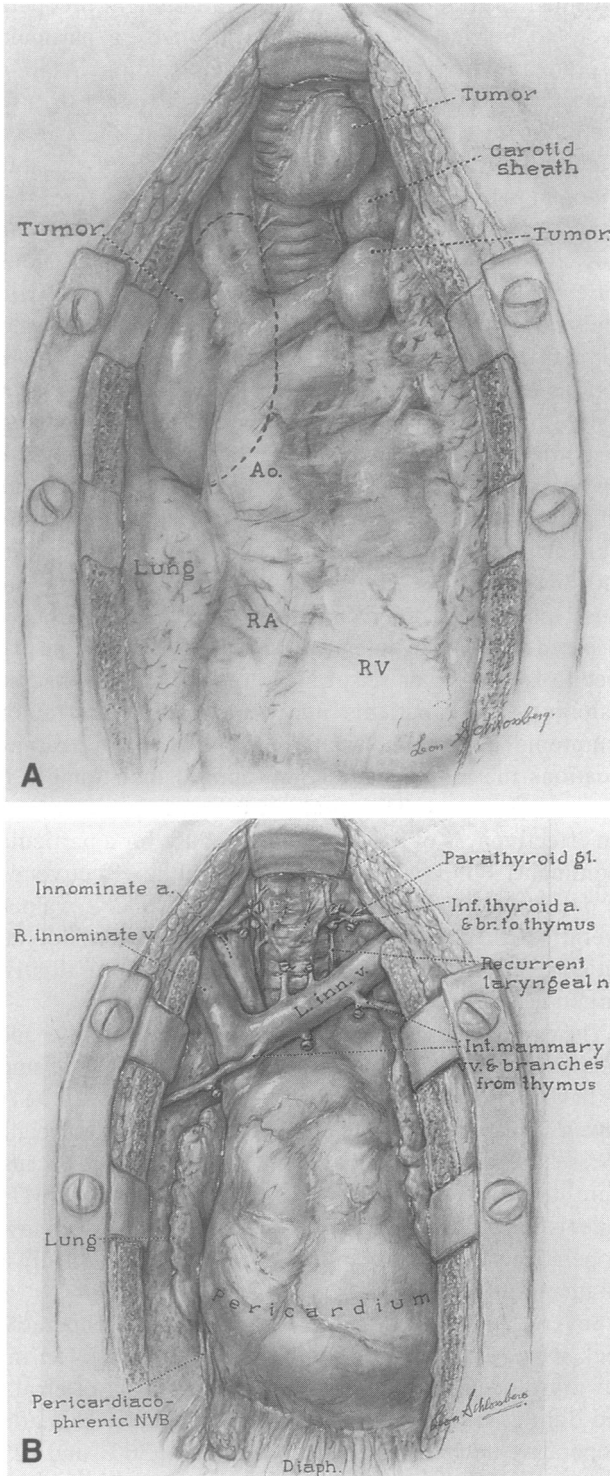


Figure 3. Technique of mediastinal dissection to remove metastatic MTC masses.

A. Patient with two large, discrete masses of MTC in what were once lymph nodes within the anterior mediastinum, producing substernal discomfort (“pressure”) and dyspnea. Note also the local recurrence of MTC adjacent to the trachea in the old left thyroid lobe “bed.” In this case, this reflects an inadequate *initial* “total” thyroidectomy and is possibly the source of the subsequent recurrent metastases.

B. The mediastinum as it appears after complete dissection (exenteration). Regardless of the extent of metastatic disease that is encountered at the time of median sternotomy, we believe that usually, the entire anterior mediastinum should be resected *en bloc* (i.e., mediastinal exenteration) just as is done for myasthenia gravis (Modified from Bulkley, et al., *Ann Surg*, 226:324–335, 1997).¹⁹

carcinomatosis almost 2 years later. One patient had moderate diarrhea from metastatic MTC that subsided after resection of multiple subcutaneous MTC nodules. One woman had visual field defects that were relieved by transphenoidal resection of a pituitary gland containing an MTC metastasis. Another woman underwent bilateral simple

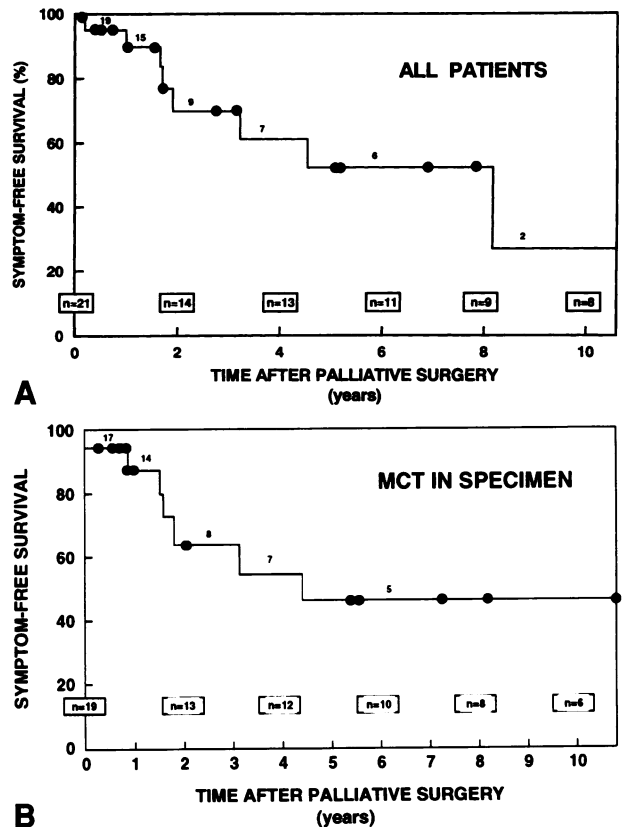


Figure 4. Kaplan-Meier curve illustrating the (actuarial) symptom-free survival of the patients who underwent palliative reoperation for metastatic MTC. The numbers on the curve represent the number of patients remaining palliated of their symptom(s) at the time. The corresponding numbers along the abscissa indicate the number of patients eligible for follow-up at that time.

A. All 21 operations in 16 patients.

B. Results for just those 19 operations for which metastatic MTC was documented histologically in the resection specimen.

esophagectomy, and reconstruction with a gastric pull-up, and esophagogastronomy. She remained asymptomatic 5.5 years later. Another patient had severe, progressive cachexia associated with severe diarrhea and external compression of the stomach by a massively enlarged, tumor-laden liver (Figure 5). The patient underwent an uneventful hepatic trisegmentectomy and was able to eat and gain substantial weight postoperatively, ultimately dying from

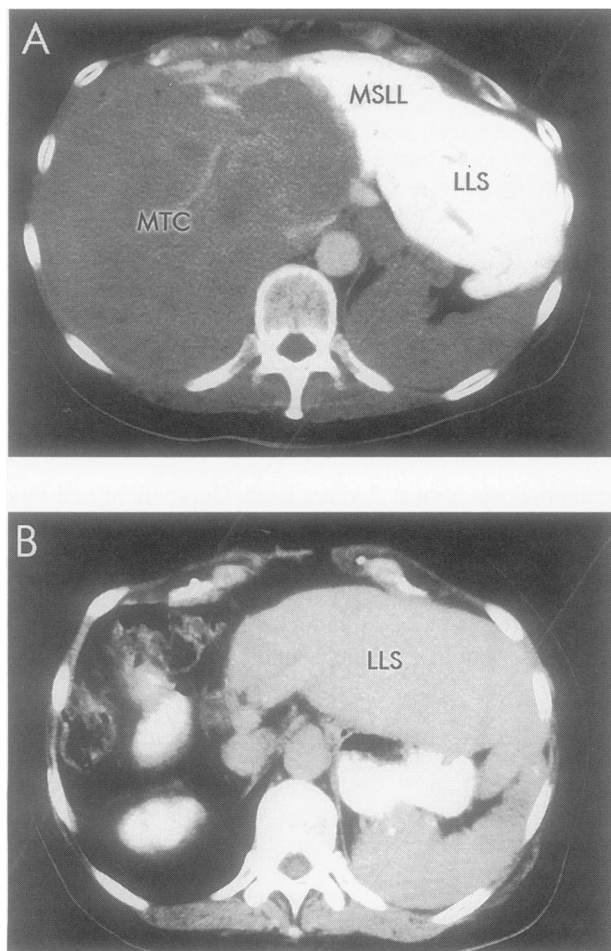


Figure 5. Abdominal computerized tomographic scan of a patient who had cachexia due to MTC metastatic to the liver, causing massive hepatomegaly and consequent extrinsic gastric compression. Following hepatic trisegmentectomy, the patient was able to resume eating, gained 20 pounds, and remained palliated until death, 1.9 years later, from disseminated disease.

A. Preoperative abdominal computerized tomographic scan, showing massive hepatic metastasis involving the (R) hepatic lobe and encroaching upon the medial segment of the left hepatic lobe.

B. Postoperative abdominal computerized tomographic scan. Note regenerative hypertrophy of the left lateral segment, without evidence of recurrent disease. The patient died 23 months after surgery from diffuse carcinomatosis.

MTC = medullary thyroid carcinoma (metastases); LLS = left lateral hepatic segment; MSLL = medial segment, left hepatic lobe.

mastectomies to palliate bilateral breast infiltration by MTC, causing severe pain and skin ulcerations. Although this was effective initially, she died a month later of disseminated disease.

DISCUSSION

Despite these apparently encouraging results with reoperative resection for palliation of symptoms in patients with metastatic MTC, this study has some important limitations. First, each patient was selected carefully to

have had specific symptoms that were thought preoperatively to be due to anatomic intrusion by a particular discrete tumor mass. The basis for resection in all of these cases was to treat specific symptoms rather than for debulking of the total tumor mass. Indeed, the ineffectiveness of this approach for the debulking of the total tumor masses is illustrated in Figure 1. Therefore, it is important to emphasize that the results of this study are only applicable to a similar group of carefully selected patients. Secondly, there were no control patients with equivalent symptoms that were treated by other means, or not at all. However, to date, no other effective treatment options exist, to the authors' knowledge, and the preoperative persistence of the symptoms to be palliated suggests that no treatment at all would not have resulted in (spontaneous) palliation in these long-surviving patients. Thirdly, the patients in this study have not yet reached their median survival. Thus, the follow-up time is limited, but it is substantially longer (up to 11 years) than those reported in other (smaller) series.^{2,4,13} Finally, we assessed the improvement after palliative resection of a specific symptom or set of symptoms related to discrete lesion(s). These patients may have had other (minor) symptoms due to metastatic MTC in other anatomic locations that could have compromised their quality of life in other ways. This study is focused specifically on the effectiveness of a palliative procedure for a particular (dominant) symptom and does measure the effectiveness of palliation as so defined. It did not formally evaluate overall quality of life, except that we noted all of our patients returned to full functional status after palliative surgery.

The prolonged, indolent course of MTC, even after metastases have appeared, is well-described.^{14,15} Several studies have shown that patients with persistent metastatic MTC have a 5-year survival rate of more than 90%,^{7,8} especially in cases of well-differentiated tumors.¹⁶ However, because more than 50% (as high as 80% in some series) of MTC patients have persistent disease after initial thyroidectomy,³ reoperative surgery is often traditionally considered only as an attempt to cure the patient.

Several authors have addressed the role of reoperative neck surgery for persistent hypercalcitoninemia after initial thyroidectomy.^{4-6,12} Moley et al.,^{4,12} Tissel et al.,⁵ and Buhr et al.⁶ reported normalization of calcitonin after reoperative neck microdissections in 38%, 36%, and 17% of patients, respectively, with relatively short follow-up. However, the long-term complication rates in these series averaged 15%. Conversely, other authors have reported far lower success rates in normalizing calcitonin levels in such patients.^{7,8,17} By combining these latter three series, only 1 of 42 patients had normalization of their calcitonin levels after surgery. Thus, the role and long-term benefit of reoperation for cure (e.g., excision of all residual neoplastic tissue) remains somewhat controversial.

The role of reoperative surgery for palliation in pa-

tients with widely metastatic disease has been less widely reported. In a recent report from Moley et al., seven patients underwent palliative debulking/excision of peritracheal tumors, and five remained asymptomatic at 6, 17, 24, and 25 months, respectively.⁴ They concluded that "it is our belief that even in the presence of distal metastases, local control by operative removal of tumor in the neck will result in improved survival and quality of life." Two additional individual cases of palliative surgery for MTC also have been reported. One patient with severe diarrhea responded to tumor debulking,² whereas another patient with cholestasis and hypercoagulability responded to surgical debulking of the MTC tumor mass in the neck.¹³

In this study, we report a larger experience with palliative surgery for symptoms in patients with metastatic, incurable MTC, with a follow-up of up to 11 years. Our strategy is to palliate specific symptoms that are based on anatomic invasion or compression by a particular, discrete lesion. These palliative reoperations are not an attempt to debulk a certain percentage of the tumor nor (necessarily) an effort to prolong survival. All of the patients had initial relief of symptoms after surgery with a projected, actuarial median symptom-free survival of 8.2 years. Almost all patients who had palliative neck or mediastinal surgery for symptoms of airway or vascular compromise had long-term palliation. In other cases, reoperation was successful in treating symptoms of cachexia (because of gastric compression), diarrhea, visual field defects, and breast pain. However, reoperative surgery for brachial plexus pain provided only short-term palliation, with recurrence in both patients within 9 months.

A major impetus for the consideration of palliative surgical excision for symptomatic MTC is the relative ineffectiveness of alternative forms of therapy. Radioactive iodine, although effective in treating well-differentiated thyroid cancer, has been found to be of no benefit.¹⁸ External beam radiation has limited use, and in a study of 202 unrandomized patients who had either radiotherapy *versus* no therapy for MTC, the group of patients receiving radiotherapy actually had a poorer outcome.¹¹ We have found radiotherapy to be useful only occasionally and in highly selected situations, such as in patients with pain from discrete bony metastases. Chemotherapy has been used with mixed reports of response, but we have found it to be rarely helpful.² Octreotide has been anecdotally reported to improve some symptoms such as flushing, but it clearly has little effect, or even exacerbates, other symptoms. Indeed, the diarrhea associated with disseminated MTC is remarkably refractory to octreotide, in our experience, and as reported in the literature.¹

Patients with widely metastatic MTC often live for years, but many experience symptoms secondary to tumor progression that compromise their quality of life. Palliative reoperative resection can often provide significant long-term relief of specific symptoms due to a particular discrete lesion, with minimal operative mortality or morbidity. In

selected patients with discrete lesions, causing specific symptoms or physical compromise, palliative resection should be considered, despite the presence of widespread incurable metastatic disease.

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