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Clinical Course of Metastatic Parathyroid Cancer

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Abstract: In a retrospective study the clinical course of 40 patients with symptomatic persistent or recurrent parathyroid cancer was analyzed in order to assess the value of aggressive surgical intervention. Recurrence was diagnosed after a median period of 33 months (1–228 months). Twenty-two patients had locoregional disease, whereas 14 patients had both local and distant spread. The remaining four patients had distant spread. Patients with just locoregional disease were subject to one to nine reoperative procedures. The median survival time from the last operation was 39 months (1–204 months). Eight patients then had no evidence of disease, three were hypercalemic and 9 of 11 had died of parathyroid cancer. Distant spread was demonstrated in 17 of 40 patients. Pulmonary metastases predominated (14 of 17). Surgical excision was performed in 9 of 14 cases. Of these nine, two patients had a subsequent disease-free interval of 36+ and 72+ months, respectively. One patient was reported hypercalcemic after 84 months, whereas five patients died of cancer between 4 and 60 months after their last surgical exploration. One patient was lost to follow-up. In all, 21 patients (53%) died of parathyroid cancer. Conspicuous nuclear atypia and frequent mitoses predominated. Image cytometric DNA analysis showed high rates for all three groups (median p90 = 80%, range 21–98%).

The course of metastasic parathyroid cancer is variable, and late recurrences may occur. Concomitant distant metastases can be anticipated in patients with persistent hypercalcemia. The lung is the most frequent site. Patients may benefit from their removal.

Parathyroid cancer is only rarely suspected in patients with primary hyperparathyroidism (HPT), as the malignant form is uncommon. Local recurrence or distant metastases may represent the only basis for a diagnosis of malignancy. The clinical features of HPT are considered to be more marked with the malignant variety. Severe hypercalcemia with hypercalcemic crisis, a palpable tumor, and renal and bone manifestations usually occur more frequently in these patients. Early age of onset has been used as one index of neoplasia. It has also been reported that men are more often affected than women, in contrast to benign HPT, which occurs predominantly among postmenopausal women. Unfortunately, neither of these signs or symptoms can be regarded as highly predictive. Both the clinician and the histopathologist tend to under- and overdiagnose [1, 2].

Moreover, there is a heterogeneity in the clinical course of patients with parathyroid carcinoma, as some patients with late recurrence have a prolonged but rather indolent course, whereas others have a rapid, aggressive onset and the disease is fatal within a short time. This variability has been recognized by several authors [1, 3–11].

Factors that are of importance for the outcome are local control, resectability of metastases, and the biologic activity of the tumor. No reliable prognostic indicator of tumor aggressiveness is so far known. Several studies have used nuclear DNA content as a prognostic index and found a correlation between aberrant DNA patterns and aggressive tumors [2, 7, 12–16].

This paper summarizes the course of a large group of patients with metastatic parathyroid cancer followed for a median period of 7 years after various treatments, mainly surgical. The purposes have been to evaluate the possible benefits of an active surgical strategy and to identify any variables in the course of the disease that can be of value in the management of patients with metastatic spread.

Patients and Methods

The patient population consists of 40 patients drawn from a retrospectively collected series of parathyroid cancer previously published [2]. Thirty-seven international surgical centers contributed 95 cases operated on during the years of 1968–1990. At follow-up, 40 of 95 patients had unequivocal signs of residual disease proved by symptoms and local or distant spread (or both). The female-male ratio of these 40 patients was 0.58, and the age distribution at the time of initial diagnosis ranged from 23 to 83 years. Median age for women was 52 years and for men 45 years. Details about the nonsurgical treatment as well as the current biochemical and physical state of all patients were incomplete for analysis and have therefore been omitted. Life-table analysis according to Kaplan Meier was performed [17].

All available tumor specimens were evaluated for their representativity and examined by two endocrine pathologists as described elsewhere [2, 18]. Hematoxylin and eosin staining was performed routinely on 4 μm thick sections. The microscopic examination included a two-step procedure where the first evaluation was performed blindly, and only tumors with obvious infiltrative or metastatic growth were considered as carcinomas [2]. For the second evaluation, histologic features

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Table 1. Types of initial procedure.

Surgical procedure	No. of cases	%
Tumor resection	28	70
Tumor resection + hemi or total thyroidectomy	8	20
Tumor resection + thyroidectomy + neck disection	1	3
Unknown	3	8

such as fibrosis, cellular growth pattern, areas of necrosis, nuclear atypia, and mitotic activity were more specifically assessed [18].

DNA cytometry was performed by means of image cytometry on Feulgen-stained sections [18]. For the interpretation of the histograms, p90 values were used, that is, the values that correspond to the percentage of tumor cell nuclei exceeding the 90th percentile of the internal standards (mainly fibroblasts and endothelial cells). p90 values > 60% have been used to denote nondiploid tumors (e.g., thyroid and endometrial cancers) [19, 20]. High rates indicate aggressive tumor behavior.

Results

Half the patients were initially treated for what was considered benign HPT. One patient was thought to have a thyroid cancer, whereas 19 patients were correctly diagnosed as having parathyroid cancer at their first operation. Most patients (70%) were treated with tumor resection only (Table 1). There was no significant association between the type of initial procedure and outcome (i.e., death from parathyroid cancer). One patient, who did not become eucalcemic postoperatively, was later found to have concomitant bone metastases. Another patient was submitted to four cervicotomies for recurrent HPT before malignant cells were clearly evident. Recurrences occurred within a wide time period, 1 to 222 months. The median time to recurrence (i.e., either clinically discovered or by any noninvasive or invasive localization modality) was 33 months. Cervical tumors were most common. In 22 patients (55%) no other site of metastatic growth was reported. Both local and distant recurrences occurred in 13 patients (33%). In all cases local recurrences preceded the distant growth. Five patients had signs only of distant spread (three pulmonary, two bone). Metastatic calcification, in addition to local and distant metastases, was described in the autopsy reports of two patients. The lung was by far the most common site for distant metastases (14 patients). Bone metastases were found in three patients, a single liver metastasis in one patient, and metastases in the spinal cord in one patient. Fifty percent of the patients were still alive after 5 years and 35% after 8 years (Fig. 1).

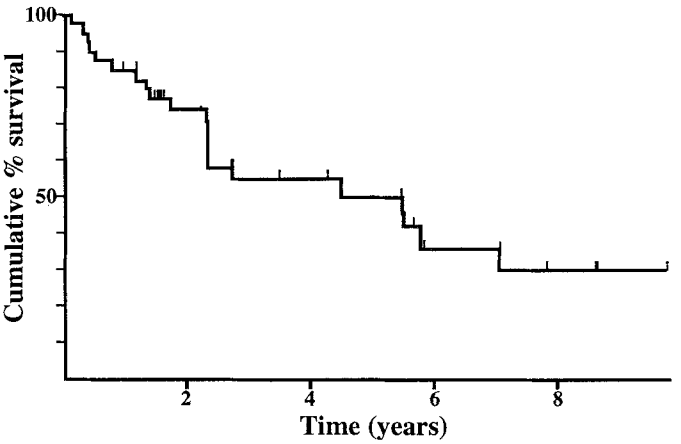

Fig. 1. Kaplan-Meier plot of actuarial survival of 40 patients with metastatic parathyroid cancer.

Surgical Treatment

Local recurrences were treated aggressively by repeated neck explorations. The number of cervicotomies including sternotomies in each patient ranged from one to nine, and recurrences appeared after a median period of 39 months (range 2–168). The median follow-up time from first recurrence among the 22 patients with only local disease was 48 months (range 0–228). Death from parathyroid cancer was reported in 9 of 22 patients (41%).

Pulmonary metastases were treated surgically in 9 of 14 patients. The course of these patients is described in Table 2. The discovery of and operation for pulmonary metastases occurred over a median period of 38 months (range 2–228). Four patients were operated on three times, four patients twice, and two patients underwent one pulmonary resection. The median follow-up time the first recurrence (local or distant) was 62 months (range 0–108), whereas the median follow-up of the patients with surgically treated pulmonary metastases was 72 months (range 4–300). Four patients were reported alive at follow-up. One patient (no. 78) was put on antihypercalcemic treatment because of symptomatic hypercalcemia, two patients (nos. 3 and 19) have had no treatment. However, in one case serum calcium levels have become elevated after 7 years (N. Thompson, personal communication). The last patient (no. 40) was lost to follow-up after 48 months. Ten patients died of their disease after a median survival of 62 months following the first documented recurrence. In only one case was the cause of death unrelated to parathyroid cancer.

Only one of three patients in whom *bone metastases* were demonstrated underwent surgical excision of the lesions. This operation led to symptomatic relief and recovery for 6 months when residual tumor was discovered. Another patient had a surgical biopsy performed, but no curative surgery was undertaken.

DNA Cytometry

The DNA distribution pattern in 35 analyzed tumors showed high rates with a median value of 80% (range 20–98%). When subdivided, patients with pulmonary metastases had a median p90 value of 53% (range 30–98%), whereas patients with only local recurrences had a median value of 75% (range 21–98%).

Histopathologic Features

The morphologic and cytologic findings are summarized in Table 3. Infiltrative growth was seen in 25 cases. A predominantly solid growth pattern was the most common finding, and

Table 2. Clinical course of 14 patients with lung metastases.

Case no.[a]	Sex	Age (years)	Site of recurrence	Time of first neck recurrence (months)	Time of first pulmonary recurrence (months)	No. of thoracotomies	Survival after first recurrence (months)	Follow-up (months)	Current state
3	F	46	Neck, lung	36	46	2	74	120	AWD
17	M	45	Neck, lung	6	12	0	6	12	DWD
19	M	60	Lung		13	0	0	13	DWD
25	F	54	Lung		228	3	72	300	AWD
30	F	74	Neck, lung	8	78	0	76	84	DWD
40	M	24	Neck, lung	24	24	1	48	48	Lost to follow up
55	M	45	Neck, lung, bone	108	120	2	108	216	DWD
64	M	25	Neck, lung	84	168	0	84	168	DWD
74	F	63	Lung		72	2	97	169	DWD
77	M	74	Lung	7	8	0	3	10	DWD
78	F	26	Neck, lung	14	14	3	34	48	AWD
80	M	59	Neck, lung	4	2	1	2	4	DWD
85	F	33	Neck, lung	5	30	1	66	71	DWD
87	M	37	Neck, lung	14	60	1	58	72	DWD

AWD: alive with disease; DWD: dead with disease.
[a]Case no. corresponds to those in Sandelin et al [2].

Table 3. Morphologic and cytologic features present in 40 cases.

Microscopic findings	No. of cases	%
Trabecular growth pattern	8	20
Fibrosis	29	73
Necrosis	17	43
Infiltrative growth	25	63
Chief cell predominance	37	93
Oxyphil cell predominance	3	8
Cellular atypia	26	65
Mitotic figures[a]	31	86

[a]Evaluated in only 36 tumors.

only in 20% was trabecular growth clearly encountered. Fibrosis was present in nearly 75% of the tumors. Chief cells dominated, and only three tumors were of the oxyphilic type. Severe nuclear atypia was present in 65% of the tumors, and mitoses were present in 80%. Focal areas of necrosis was demonstrated in nearly 50% of the tumors.

Discussion

Several aspects on the course and management of parathyroid cancer, including an evaluation of nuclear DNA cytometry for diagnostic and prognostic purposes have been published [16, 21–23]. One of the key issues relates to the diagnosis. In a publication of nine cases of parathyroid cancer from one institution, the clinical impression at the initial neck exploration in three of nine patients was of a benign lesion, but the histopathology suggested cancer and these patients all had recurrence or clinical evidence of disease [23]. In the present material of metastatic parathyroid cancer, half the tumors were not correctly diagnosed—by the surgeon or by the pathologist at the initial operation. Reasons for this underdiagnosis may be several. When asked about macroscopic infiltration of the tumor 12 of 32 surgeons stated that the tumor did infiltrate into adjacent structures. Macroscopic and microscopic infiltration did not correlate when compared in all 95 submitted cases of parathyroid cancer [2]. Adhesion to surrounding structures does not necessarily imply malignancy in HPT. Limited experience from either the clinician or the histopathologist is also a factor that is of importance. A close collaboration between the two is important for the management of each case and especially those cases that are equivocal.

After a thorough reexamination of the 56 cases (i.e., from the original series of 95) in which the diagnosis of parathyroid cancer was either confirmed by histopathology (i.e., microscopic infiltration) or by recurrent disease, certain histologic and cytologic features were identified [18]. The so-called criteria of malignancy defined by Castleman and Roth [24] and Schantz and Castleman [25] could not be confirmed or regarded as constant findings. Most tumors had a solid growth pattern, and a trabecular growth pattern was seen in only 20%. Extensive fibrosis was more common among the cancers than in the equivocal cases. The cytologic findings were more conspicuous than usually seen in benign tumors. Severe nuclear atypia with variably sized nuclei and macronucleoli were also a common finding. Finally, mitotic activity, as a general finding and in frequent numbers (> 5 per high power field), was often found among the carcinomas. When tumors that recurred either locally or with distant metastases were compared with tumors that were considered locally invasive, macronucleoli and frequent mitotic figures were encountered significantly more often. However, no mitotic figures could be demonstrated in 11%. That study also demonstrated the need of careful histologic examination and full representativity of the tumor specimens.

This study confirmed that pulmonary metastases is the most common manifestation of distant metastatic parathyroid cancer. Recurrences occurred both as an early manifestation and after a long disease-free interval. The patients did not have a worse prognosis than those with only local spread. Repeated thoracotomies were often necessary. No particular subgroup of patients in whom active surgical or medical treatment would be of special benefit could be identified. However, 50% of all deaths occurred among patients with lung metastases. Obara and coworkers presented data on seven patients with pulmonary metastases each treated by aggressive surgery at several occasions. Half of the patients responded well to aggressive

surgical therapy and are alive and well, whereas two patients died after less than 4 years despite surgery, chemotherapy, bisphosphonates, and irradiation therapy [16]. The authors concluded from literature studies that nearly 50% of patients with spread disease to the lung are alleviated by repeated thoracotomies. Early recurrences indicated a poor prognosis, and thoracotomies were hardly beneficial, which is confirmed in the present series.

The use of antihypercalcemic drugs (e.g., bisphosphonates) in preparation for surgery has proved to be of some value [16, 26]. Long-term bisphosphonates were used in one study with moderate effect [16]. August and coworkers treated four patients with radiotherapy after neck dissection for local recurrence or bone metastases and reported a local effect in two [23]. Other compounds such as chemotherapeutic agents or gallium nitrate have been documented to have some effect [27–32].

There is no controversy about the surgical strategy and the need of being radical, especially at the initial neck exploration. Nevertheless, there is still debate about the extent of surgery and the indication for a central neck dissection when a parathyroid cancer is diagnosed [5]. Lymph node metastases occur infrequently, but the tumor often invades contiguous structures such as the thyroid, the strap muscles, and the recurrent laryngeal nerve, which motivates extensive operations. Distant metastases in parathyroid cancer are best controlled by surgical excision when feasible. This treatment causes palliation of the hypercalcemic symptoms from which the patients suffer.

An aberrant nuclear DNA pattern with high exceeding rates (80%) predominated in this series. These figures can be compared with the 23% p90 level of those 39 tumors that were considered equivocal where the diagnosis of parathyroid cancer never has been established after clinical and morphologic examination. The median follow-up was more than 6 years in this group [18]. Our findings are thus in accordance with those of other groups [7, 12, 14–16, 23]. Various methods of cytometric analyses and interpretation models have been used, although most investigators have used flow cytometry. Because the modified Adams technique (image cytometry) was used in this material, an S-phase fraction could not be assessed. An argument against the use of DNA as a prognostic index is the finding of aneuploid benign parathyroid tumors [13, 33–36]. Our own published and unpublished data of more than 100 analyzed parathyroid glands with either single or multiple gland disease show approximately 10% nondiploid tumors. However, there is a clear difference in appearance between the so-called aneuploid or nondiploid malignant tumors, where the nuclear DNA content is scattered [30]. With the rapid development in molecular technique, diagnostic and prognostic markers may help to diagnose and to prognosticate this rare disease.

It can be concluded that the diagnosis of parathyroid cancer is difficult and must be based on solid criteria. The histopathologic features mentioned in combination with clinical and biochemical signs of HPT are usually sufficient for a definitive diagnosis. Equivocal cases should be followed closely in order to detect recurrences that may present late. This study supports the recommendations of active treatment of both local and distant recurrences, especially pulmonary, as no other pharamacologic or radiologic treatment had any substantial or lasting effect. Even if metastases occur at other locations (e.g., bone or liver), the patients' well-being is most likely enhanced by their removal.

Résumé

Dans une étude rétrospective, l'évolution clinique de 40 patients, ayant un cancer de la parathyroïde symptomatique persistant ou récidivant, a été analysée pour évaluer la valeur d'une attitude chirurgicale agressive. La récidive a été mise en évidence après une médiane de 33 (1-228) mois. Vingt-et-un patients avaient une maladie locorégionale alors que 14 avaient à la fois une extension locale et à distance. Les quatre autres patients avaient des métastases à distance. Les patients avec une extension locorégionale ont eu entre 1 et 9 réinterventions. La médiane de survie à partir de la dernière intervention était de 39 (1-204) mois. Huit patients n'avaient aucune évidence de maladie, trois étaient hypercalcémiques, et 9/11 avaient un cancer de la parathyroïde. Une extension à distance a été retrouvée chez 17 des 40 patients, essentiellement pulmonaires (14/17). Une exérèse chirurgicale a été réalisée dans 9/14 cas. Parmi ceux-là, deux patients ont eu un intervalle libre de maladie respectivement de 36 et 72 mois. Un patient était hypercalcémique après 84 mois alors que cinq patients sont décédés de leur cancer entre 4 et 60 mois après leur dernière intervention chirurgicale. Un patient a été perdu de vue. En tout, 21 patients (53%) sont décédés d'un cancer de la parathyroïde. Des atypies nucléaires et des mitoses fréquentes prédominaient. L'analyse d'ADN par cytométrie de flux a montré un taux élevé pour les trois groupes (médiane p 90 = 80%) (extrêmes: 21-98%). L'évolution de cancer parathyroïde métastatique est variable, et la récidive tardive peut toujours se voir. Des métastases à distance concomitantes peuvent être anticipées en cas d'hypercalcémie persistente. Le poumon est la localisation la plus fréquente, et la métastasectomie est généralement faisable.

Resumen

En un estudio retrospectivo se analizó la evolución clínica de 40 pacientes con cáncer paratiroideo sintomáticamente persistente o recidivante, con el propósito de definir el valor de la intervención quirúrgica agresiva. La recidiva fue diagnosticada luego de un intervalo de tiempo promedio de 33 meses (1-228).

Veintidos pacientes presentaban enfermedad local-regional y 14 presentaban tanto enfermedad local como extensión a distancia; los 4 pacientes restantes presentaban extensión a distancia. Los pacientes que sólo tenían enfermedad local-regional fueron sometidos a 1-9 procedimientos reoperatorios. El tiempo promedio de sobrevida desde la última operación fue 39 meses (1-204). Para entonces ocho pacientes se hallaban libres de enfermedad, tres aparecían hipercalcémicos y 9–11 habían muerto por cáncer paratiroideo; en 17/40 se demostró extensión a distancia, con predominio de las metástasis pulmonares (14/17). Se practicó resección quirúrgica en 9/14 casos, de los cuales dos tuvieron un ulterior intervalo libre de enfermedad de 36+ y 72+ meses, respectivamente. Un paciente fue hallado hipercalcémico luego de 84 meses y cinco habían muerto por cáncer a los 4-60 meses luego de su última exploración quirúrgica; se perdió un paciente para seguimiento. En total, 21 pacientes (53%) murieron por cáncer paratiroideo. Se registró

predominio de conspicua atipía nuclear y de mitosis frecuentes. El análisis citométrico de ADN mostró altas tasas para los tres grupos (media p90 = 80%, rango 21-98).

La evolución del cáncer paratiroideo metastásico es variable, y se puede presentar la recidivia tardía. En los pacientes con hipercalamia persistente se puede predecir la existencia de metástasis a distancia, con el pulmón como el lugar de más frecuente ubicación. Su resección puede significar beneficio para los pacientes que las albergan.

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