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"Occult" Papillary Carcinoma of the Thyroid: a Questionable Entity

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A series of 72 cases of "occult" thyroid papillary cancer, i.e. tumours of less than 1.5 cm in diameter, was analysed. The patients—26 males and 46 females—were treated surgically, 25 by lobectomy and isthmusectomy and 47 by total thyroidectomy. In 51 cases nodal neck dissection was performed, bilateral in 2 cases. 9 thyroidectomised patients received radiometabolic therapy. Hormone therapy (T_4) was continuously administered to 57 patients. The median duration of follow-up was 99 months (60–189). All the patients were alive (except one who died from other causes) and free of disease at last control. No relapses in the thyroid were observed in the conservatively treated patients. 2 patients of the 47 radically operated upon subsequently presented nodal metastasis and underwent neck dissection. The so-called "occult" thyroid papillary cancer does not differ from other papillary cancers with respect to morphological, clinical and prognostic factors—it differs only in size. Considering occult papillary tumours as an entity is questioned in this paper.
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INTRODUCTION

THE TERM occult papillary thyroid carcinoma (OPTC) has been used for thyroid tumours not exceeding 1.5 cm in size [1–7]. This term has been questioned, in that it should be used to define those tumours undetectable by clinical examination or imaging techniques and indirectly suspected because of overt cervical nodal metastases and finally found at surgery. However, clinically evident papillary tumours have also been defined as occult purely because of their size. The WHO has proposed a major diameter of 1 cm for occult papillary carcinoma and the term microcarcinoma has been introduced for these tumours [8].

A conservative treatment, less than total thyroidectomy, has been indicated for these tumours [9–11]. A series of 72 papillary cancers ≤ than 1.5 cm in major diameter has been analysed, with the purpose of evaluating whether OPTC is still to be considered as an entity.

PATIENTS AND METHODS

72 patients with OPTC less than 1.5 cm in size who were observed and treated at the National Cancer Institute, Milan, from 1975 to 1985, were considered. There were 26 males and 46 females; patients' age ranged from 6 to 58 years for males (mean 37.6) and from 9 to 72 years for females (mean 34). These tumours of small size accounted for 19% of 380 thyroid papillary carcinomas observed in the same period. 2 patients had previously received radiation therapy on cervical region and mediastinum, for tonsillar hypertrophy and Hodgkin's disease lymphoma, respectively.

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Clinical presentation

21 patients presented with a palpable nodule in the thyroid. In 14 cases both a thyroid nodule and ipsilateral regional nodes were revealed by clinical examination. In 35 patients the primary tumour was clinically occult in that the tumour was not palpable. In these cases, the thyroid tumours had been suspected from the presence of palpable suspicious regional nodes, and detected at ^{131}I scintigraphy and/or ultrasound scan, except in 3 patients, whose tumours, a few millimetres in diameter, were only found at surgery. In 2 additional cases, a thyroid papillary carcinoma was a fortuitous finding during operations performed for parathyroid adenomas. In conclusion, should we consider as occult all the tumours of less than 1.5 cm in major diameter, all the 72 cases would be occult. However, when considering the detectability of these lesions at clinical examination, only 35 cases would be defined as occult. With regard to the use of the imaging technique, the number of occult tumours would be three. Regional enlarged lymph nodes were evident at clinical examination in 49 patients (68.1%): in 35 of them, enlarged cervical nodes were the first and only sign of disease. Metastatic involvement was demonstrated by fine needle biopsy in 31 cases and confirmed in frozen sections in 14 cases. Metastatic lymph nodes were ipsilateral, except in 2 patients with bilateral cervical nodes.

Treatment

All the patients underwent surgery. Frozen sections provided the diagnosis of papillary thyroid carcinoma (PTC) in all cases. 25 patients, under 40 years of age, received conservative surgery, i.e. lobectomy and isthmusectomy, whereas 47 were traditionally operated upon by total thyroidectomy. In all cases the laryngeal nerve was dissected and recurrent nodes removed. Nodal neck dissection was performed, because of involved cervical nodes, in 51 patients; in 2 of them metastatic nodes undetected at clinical examination were only found at surgery. Neck dissection—bilateral in 2 cases— was of the conservative type in 48 cases (subcutaneous mastoideus muscle, spinal nerve and jugular vein were preserved); in 3 patients nodal dissection was of the

traditional radical type. This kind of operation performed on 3 patients was practically abandoned after 1976 for thyroid papillary cancer. Out of 51 neck dissections, 8 were associated with lobectomy, whereas in 43 cases they were performed together with total thyroidectomy.

Following surgery, the 47 patients who had been radically operated on (total thyroidectomy), received a ^{131}I scan, revealing residues of thyroid gland left behind in 28 cases. Only 9 of them with residues exceeding 10% of the administered activity were treated by radiometabolic ^{131}I therapy. Hormone therapy (T_4) was continuously administered to 47 patients treated by total thyroidectomy and to 10 of the 25 patients who had received lobectomy and isthmusectomy (suppresive treatment).

Pathology

Pathological examination of the 72 surgical specimens provided the following information: in all cases a PTC was found, the size of which ranged from 0.2 to 1.5 cm (mean 8.3 mm). In no case was the tumour capsulated. According to sub-types, the distribution of tumours was as follows: 17 follicular variant, seven tall cell and five columnar cell variant and 43 not otherwise specified (NOS), in 16 of which a marked desmoplasia was present. The thyroid capsule was microscopically involved by the tumour in 11 cases (15.3%).

Multicentricity, i.e. microfoci of papillary cancer, was identified in 17 cases (23.6%). In about 50% of these cases (9 patients treated by total thyroidectomy) microfoci were observed in the opposite lobe of the gland.

Nodal metastases were pathologically observed in 51 cases (70.8%): metastatic regional nodes were ipsilateral in 49 patients and bilateral in 2 patients. The nodes sited along the laryngeal nerve were involved in only 2 cases. The mean number of nodes involved was eight (range two to 41).

Follow-up

No patients were lost to follow-up, the median duration of which was 99 months (range 60–189). All of them had a thorough clinical examination every 6 months, annual chest X-rays and whole body ^{131}I scans (exceptions were made for the 25 patients treated by lobectomy). In patients treated by conservative surgery (lobectomy), ultrasound scans on the residual gland were also performed. f T_3, f T_4 and thyroid stimulating hormone (TSH) were assessed for all patients. Thyroglobulin was measured annually for thyroidectomised patients.

RESULTS

71 patients were alive and free of disease at last control (1 patient had died from acute pancreatitis at 153 months from surgery). No relapses in the opposite lobe were observed in any of the 25 lobectomies. Nodal relapse occurred in 2 of the patients previously treated by total thyroidectomy, at 118 and 147 months from surgery; they received second surgery (conservative neck dissection). No distant lesions have been recorded so far.

Out of 47 patients treated by total thyroidectomy, 12 experienced hypoparathyroidism (25.5%) which was permanent in 4 cases. Permanent lesion of the laryngeal nerve was recorded in 1 patient treated by lobectomy.

DISCUSSION

The term occult is rather confusing. Occult thyroid papillary cancers have also been defined in other terms, such as small, minute, tiny or micro-carcinomas [9, 12, 13]. All these definitions consider small sizes (less than 1–1.5 cm in major diameter) as the common denominator of these lesions, independently of clinical detectability. The review of the literature on the subject does not allow the definition of the actual prevalence of OPTC: according to the few surgical reports available, occult tumours account for 6 to 35% of all papillary cancers observed in the same period [1–3].

In our series, they represent 19% of 380 papillary cancers treated between 1975 and 1985. Autopsy studies do not provide significant information: it is well known that papillary cancers of the thyroid, clinically unexpressed, have been found on autopsy in 5–36% of cases, cases aged over 20 years with no significant differences between the two sexes [2, 3]. Females seem to be more frequently affected when clinically detectable cancers of this type are considered. Kasai and Sakamoto [13] reported a female:male (F/M) ratio of 9 for their series of 66 cases. The F/M ratio was 4.6 in the series reported by Pelizzo *et al.* [11], 3 in Schroder's report [14] and 1.8 in our series. No particular age is affected. In our series of patients, ages ranged from 6 to 72 years, and the same wide range was reported by Hubert [9], Pelizzo *et al.* [11] and Schroder [14].

With regard to pathological patterns, the so-called occult carcinoma does not differ from larger papillary carcinomas, apart from the frequent presence of desmoplasia and the superficial location of the tumour close to the capsule of the gland. In accordance with this last feature, thyroidal capsular invasion is not unusual. In fact, in our cases series, capsular invasion was observed in 15.2% of the patients and histological variants, not related to unfavourable prognosis, such as tall and columnar cell papillary carcinomas were also observed in 12 cases. These variants seem to have a more aggressive clinical course [15, 16], but this has not been the case for our patients so far.

The risk of distant spread is certainly less for small tumours, but sporadic cases of occult tumours with distant metastases have been reported [12, 17, 18].

Regional lymph nodes are frequently affected, in spite of small tumour size. Nodal involvement was recorded in 70.8% of our cases. Hubert [9] reported 40% of nodal metastasis, a rate very close to the 42% of Kasai's [13] series. When looking at the literature, it is evident that a high rate of nodal involvement has been reported, up to 50% [6, 17, 19–23], even for larger papillary tumours. In other words, lymphotropic regional spread is characteristic of papillary thyroid tumours in general; it is not specific for occult tumours, and we do not think that our figure of 70.8% (the highest rate reported in the literature) is convincing evidence to the contrary. Moreover, it is well known that nodal regional involvement does not affect survival [14, 17, 22].

The so-called multicentricity of papillary carcinoma, better defined as intrathyroidal lymphatic spread, has been frequently referred to by those who advocate total thyroidectomy. The presence of multicentricity cannot be excluded for occult tumours. Microfoci of papillary cancer were identified in 17 (23.6%) cases of our series; in 50% of these cases, microfoci were observed in the opposite loci of the gland.

Finally, when considering treatment, occult papillary tumours have been considered as susceptible to conservative measures, even by authors who usually support total thyroidectomy for papillary cancers [6, 11, 24]. It is well-known that two opposing attitudes divide surgeons on surgical procedures for papillary thyroid cancer. Many authors [25–29] state that total thyroidectomy should be always indicated. As many authors claim that lobectomy and isthmusectomy should be the procedure of choice for unilateral tumours [14, 17, 20, 22, 24, 29–38]. Only for the

so-called occult tumours does conservative surgery seem to be generally accepted.

Since there is no report in the literature stating that total thyroidectomy significantly affects overall survival, but only disease-free survival, the main reason that total thyroidectomy has been advocated lies in the possibility of better monitoring of treated patients by scintigraphic scan and thyroglobulin measurements. Why should occult papillary tumours escape this opportunity? Because of their size? Obviously, we agree on the indication of lobectomy and isthmusectomy for unilateral papillary cancers under 3 cm in size in patients with good prognostic factors. The indication should not be restricted to the so-called occult papillary cancers [21, 32, 34, 36, 39]. These tumours only differ from other papillary tumours in their size, arbitrarily identified as less than 1–1.5 cm, and it is not surprising that small tumours bear a better prognosis than larger ones. Many prognostic factors have been studied and used to identify low risk patients [40] susceptible to conservative procedures, and the discriminant size for this possible indication is well over 1 cm. Christiansen [41] stated that occult tumours ($\leq$ 1.5 cm) and intrathyroidal cancers larger than 1.5 cm which do not penetrate the capsule, had cumulated survival rates which were not significantly different.

In a series of 380 OPTC studied at the National Cancer Institute, Milan, with the purpose of evaluating prognostic factors, the unfavourable events rate was practically the same for tumours $\leq$ 1.5 cm and $\leq$ 3 cm (unpublished data). The 25 patients of our series treated by lobectomy did not experience local or nodal recurrences, whereas nodal metastases occurred in 2 patients, initially N_0, treated by total thyroidectomy. No deaths from the disease have been recorded so far for the entire series. Median follow-up, 99 months, could be considered as short, but the great majority of relapses usually occur within 10 years of primary treatment [21].

In conclusion, we do think that the so-called occult tumour should not be considered as a separate entity. In fact, these tumours show no differences when compared to other unilateral papillary cancers, except in their size, discretionally established as < 1–1.5 cm. They are not different from other unilateral papillary tumours under 3–4 cm of size as far as sex, patients' age, pathological patterns, risk of regional and distant spread, prognosis and treatment are concerned. Moreover, thanks to the progress of diagnostic tools, it is likely that an increasing number of clinically occult cancers will be detected and treated. Consequently, the term occult should be abandoned. Microcarcinoma could be accepted, although its use should be restricted to defining very small lesions of a few millimeters in diameter.

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Expression of Sialyl-Tn Antigen is Correlated with Survival Time of Patients with Gastric Carcinomas

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Expression of sialyl-Tn antigen (STN) was examined by an immunohistochemical method in 85 primary gastric carcinomas. The STN expression occurred in 53 (62.4%) cancers, and the positive staining was correlated with degree of gastric wall and lymph vessel invasion, lymph node metastasis, and stage of tumour. Five-year survival rates of patients with STN-positive cancers (47.2%) were significantly lower than those with STN-negative cancers (84.4%) ($P < 0.01$), and patients with STN-positive cancers at stage III and stage IV had a worse prognosis. In the cancers with serosal invasion, patients with STN-positive cancers disclosed a significantly poorer prognosis than those with STN-negative cancers ($P < 0.01$). Therefore, it is suggested that a careful follow-up study and intensive postoperative therapy are needed for patients with advanced gastric cancers with positive STN expression.
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INTRODUCTION

NEOPLASTIC TRANSFORMATION is often associated with changes in glycosylation of glycolipids or glycoproteins in cell membranes. Recently, a novel monoclonal antibody recognising a core structure of mucin-type carbohydrate chain has been made by Kjeldsen *et al.* [1]. This antibody (TKH2) directed to the tumour-associated *O*-linked sialyl Tn 2-6-α-*N*-acetylgalactosaminyl [sialyl-Tn(STN)] epitope was made by immunisation with ovine submaxillary mucin. Immunohistochemical studies have demonstrated that STN is expressed in human bladder cancer [2], ovarian cancer [3], and gastrointestinal cancer cells [4–6], whereas its expression in normal adult tissues is highly restricted [1, 4, 6, 7]. In this study, we examined the expression of STN in gastric cancers of different stages, and determined whether the STN expression might influence the prognosis of patients with gastric carcinomas.

MATERIALS AND METHODS

Patients and pathological studies

85 patients with primary gastric cancers were selected. The patients had undergone gastrectomy in the Department of Surgery, Shiga University of Medical Science Hospital, from 1981 to 1986. Tissue from the resected stomachs were fixed in formalin and embedded in paraffin. Serial paraffin sections of 5 microns were cut, and they were stained by routine histopathological techniques. Histological classification was made according to the criteria of the WHO International Histological Classification of Tumours [8] and stages of cancers were determined according to the Japanese Research Society for Gastric Cancer [9], and TNM classification was also recorded (stage I: T1,2, 3N0M0, stage II: T1,2,3N1M0, stage III: T1,2,3N2M0, stage IV: T1,2,3,4N3,4M1).

Immunoperoxidase staining

The expression and localisation of STN in tissues was determined immunohistochemically by the avidin–biotin–peroxidase complex (ABC) method using 10% formalin-fixed and paraffin-embedded sections [10]. All steps were conducted at room temperature. After deparaffinisation, sections were rehydrated, incubated with freshly prepared 3% hydrogen peroxide in methanol for 30 min, and then washed three times with phosphate-buffered saline (PBS). Then, 10% normal horse serum in PBS was applied to the sections for 30 min. The primary monoclonal antibody TKH2 (Otsuka Assay Labs, Tokushima, Japan) was applied to the sections at a dilution of 1:10 in PBS for 2 h. After rinsing in PBS, the sections were incubated for 30 min with biotin-labelled horse anti-mouse IgG (Vector Labs.). The sections were then treated with avidin–biotin com-

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