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RESEARCH

Is Minimal Residual Lymph Node Disease in Papillary Thyroid Cancer of Prognostic Impact? An Analysis of The Epithelial Cell Adhesion Molecule EpCAM in Lymph Nodes of 40 pN0 Patients

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Abstract This study was aimed to assess the extend of nodal microdissemination in patients with pN0 papillary thyroid carcinoma (PTC) using immunohistochemical analysis. In early stage PTC both, systematic lymphadenectomy as well as radio iodine treatment, aimed to eliminate occult nodal tumor involvement, are under controversial debate, since little is known about the extend of lymphatic microdissemination in these patients. Formalin embedded samples of the resected lymph nodes were systematically screened for the presence of disseminated tumor cells using immunohistochemistry (monoclonal antibody Ber-EP4). Clinical and histopathological parameters as well as the post-operative course were recorded. Survival data were analysed by the Kaplan-Meier method and the log rank test. Overall 321 lymph nodes of 40 patients were screened immunohistochemically. In 12.5 % of the patients disseminated occult tumor cells were diagnosed. In addition to tumor resection 90 % of the patients underwent adjuvant radio-iodine treatment. The mean observation period in our collective was 72 months. The detection of disseminated tumor cells did not correlate with clinicopathologic risk parameters and did not have significant influence on the prognosis of these patients. Immunohistochemical analysis enables the detection of disseminated tumor cells in patients with pN0 PTC. This finding seems to support the application of adjuvant radio iodine, even in early tumor stages.

Keywords Papillary thyroid cancer · Lymphadenectomy · Radio iodine treatment · Tumor cell dissemination · Immunohistochemistry

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Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine cancer, and it usually has a favourable course with a 10-year survival exceeding 90 % [1]. However, a subset of patients develop local recurrence or distant metastases, indicating that minimal residual disease does exist in some patients. The incidence of PTC has been rising steadily over the past half century [2]. Radical resection and lymphadenectomy represent the principal treatment of PTC. Lymphatic spread is the most common form of progression of PTC [3] and the presence of lymph node involvement is associated with an increased risk of local recurrence and distant metastases [4, 5]. Therapeutic neck dissection is well accepted as part of the surgical strategy for treating macroscopic nodal metastases. However, the extent of lymph node dissection is still controversial, particularly prophylactic neck dissection for lymph node staging in the absence of macroscopically conspicuous nodes is subject to debate [6, 7]. It is alarming that even in

papillary thyroid microcarcinomas prophylactic lymph node dissection yielded metastatic lymph nodes in about 50 % of the cases [8]. On the other hand, no prognostic impact of lymph node involvement was found [9, 10].

Though the prognostic influence of prophylactic lymphadenectomy still remains unclear, lymphadenectomy enables the histopathologic determination of the individual lymph node status, which notoriously has an impact on the prescription of treatment with radioactive iodine [7]. But even therapy with radioactive iodine is not beyond dispute, since a recent systematic review of the literature could not confirm a significant and consistent benefit of radioiodine ablation [11].

However, identification of lymph node involvement is an integral component of tumor staging and represents the basis of further adjuvant strategies. Traditional histologic examination consists of single sectioning of resected lymph node samples with hematoxylin and eosin staining. By now more sensitive immunohistochemical analysis, based on the detection of epithelial cell- or tumor-associated marker proteins have been developed. Using immunohistochemistry, it has become possible to detect single tumor cells present in lymph nodes classified as tumor free by conventional histopathologic analysis [12–14]. However the clinical significance of such a detailed immunohistochemical analysis is still controversial [15], and they have not been analysed in patients with PTC.

In view of the critical role of minimal residual tumor remnants for decision making with respect to radio-iodine therapy as well as for the extent of lymphadenectomy, we re-analysed a large series of patients with histopathologically tumor free lymph nodes, using the anti-EpCAM antibody Ber EP4.

Methods

From June 1999 to July 2005, 40 patients, diagnosed as having papillary thyroid carcinoma without lymph node metastasis based on conventional histopathologic examination, were included in this study. The characteristics of the patients are presented in Table 1. Written informed consent was obtained from all patients for the surgical procedures.

Surgical Procedure 37 (92.5 %) of the patients underwent total thyreoidectomy, due to multifocal lesions or invasive tumor growth. Three patients (7.5 %) with unifocal tumors, less than 10 mm in diameter received unilateral lobectomy only.

For lymphadenectomy limited central node clearance was performed in 11 patients (27.5 %), 11 patients (27.5 %) underwent standard dissection of the central compartment, 12 patients (30 %) received modified unilateral neck dissection and in 6 patients (15 %) lymphadenectomy comprised bilateral modified neck dissection. 8 patients (20 %) had additional partial thymectomies (Table 2).

Table 1 Patient- and tumor characteristics

	n-patients	(%)
Gender		
Male	9	22.5
Female	31	77.5
Age		
≤ 45 years	20	50
> 45 years	20	50
T-stage		
T1	15	37.5
T2	13	32.5
T3	4	10
T4	8	20
Tumor diameter		
≤ 10 mm	15	37.5
> 10 mm to ≤ 25 mm	17	42.5
> 25 mm	8	20

Limited central lymph node dissection was defined as removal of certain parts of the lymph nodes in the central lymph node group, which included prelaryngeal, pretracheal and ipsilateral paratracheal lymph nodes. Conventional central lymph node dissection was performed cranially to both superior thyroid arteries, caudally to the innominate vein, laterally to the carotid sheath and dorsally to the prevertebral fascia. Modified neck dissection was defined as systematic node dissection in the central (level IV) and lateral (level II to V) compartments. The sternocleidomastoid muscle, the accessory nerve and the internal jugular vein were preserved.

Table 2 Treatment characteristics

	n patients	(%)
Thyroid resection		
Unilateral lobectomy	3	7.5
Total thyreoidectomy	37	92.5
Extend of lymph node dissection		
Limited central dissection	11	27.5
Standard central dissection	11	27.5
Modified unilateral neck dissection	12	30
Modified bilateral neck dissection	6	15
Resection margin status		
R0	33	82.5
R1	7	17.5
Radio iodine ^{131}I treatment		
Administered	36	90
Not administered	4	10

For reasons of comparability tumor stage was classified according to the 5th edition of the TNM classification of the International Union Against Cancer (UICC) [16].

Adjuvant Radio Iodine Treatment Postoperatively all patients were presented at a regular interdisciplinary endocrinological conference. Adjuvant radio iodine was administered according to the recommendation of the endocrinological board. All of the patients with microscopically positive resection margins underwent additional radio iodine ^{131}I ablation, but also 29 of the remaining patients. In summary in 36 patients (90 %) radio iodine ablation was performed. The 4 patients (10 %), who did not receive radio iodine in this series did not give consent to this treatment and all had primary tumors that were not larger than 10 mm in diameter (Table 2). The patients were ablated with ^{131}I 4–6 weeks after thyroidectomy. During this time no suppressive treatment with L-thyroxine was initiated. Patients were treated with a fixed dose of ^{131}I: 3,700 MBq ^{131}I [17]. All patients were hospitalized during treatment.

Periodic follow-up with measurement of serum thyreoglobuline (Tg) was performed regularly. In addition patients underwent diagnostic whole body scanning (WBS) with a tracing dose of ^{131}I once a year for the first 2 years and every 2–5 years thereafter.

Immunohistochemistry

The resected lymph nodes were screened for disseminated tumor cells (DTC), using immunohistochemistry and the specific monoclonal antibody (mAb) Ber EP4 (Dako, Hamburg, Germany) as previously described [18]. This mAb detects the epithelial cell adhesion molecule EpCAM, which is expressed by epithelial cells and epithelial derived tumors [19, 20].

Formalin fixed and paraffin embedded tissue blocks of the resected lymph nodes, were collected. From each sample 2–3 μm sections were cut and transferred onto glass slides. For immunohistochemistry sections were deparaffinised, rehydrated with phosphate-buffered saline (PBS) and stained using the Avidin-Biotin-Complex (ABC) technique [21]. Blocking of endogeneous peroxidase was performed by incubation in 0.3 % H_2O_2 at room temperature, followed by blocking of non specific binding using normal human serum (Vectastain, Burlingame, USA). For detection of isolated epithelial cells within the mesenchymal lymph node tissue Ber EP4 a monoclonal mouse anti-human antibody (Dako, Hamburg, Germany) in a dilution of 2.7 μg/ml in PBS was incubated for 45 min at room temperature in a humidified chamber. Then the Vectastain ABC Kit (Vectastain, Burlingame, USA) was applied, which included a biotinylated anti-mouse antibody as well as a peroxidase labeled Streptavidin complex. After each incubation the slides were rinsed in PBS. For visualisation of antibody binding, the chromogen DAB (DakoCytomation, Glostrup, Denmark) was added subsequently. Finally the sections were counterstained with Gill's hematoxylin. To exclude non-specific binding, negative controls were performed with irrelevant mouse myeloma protein MOPC 21, IgG_1 (Sigma, Deisenhofen, Germany). Corresponding papillary thyroid primary tumors served as positive control. For evaluation of the slides light microscopy at a 200× magnification was used. Evaluation was performed by two independent observers, who were blinded to the clinicopathologic data. If the observers obtained different results, the slides were re-evaluated and a consensus decision was made.

Statistical Analysis

To test the correlation between the clinico-pathological data and the detection of DTC we used the Fishers's exact test and whenever appropriate the Chi Square test. Candidate variables were evaluated, including T-stage, tumor diameter, age, status of resection margin (R-stage), administration of ^{131}I radio iodine, extend of lymph node dissection and the extend of thyroid resection. For certain parameters such as tumor diameter and age there was a wide range of values, which were assigned to different groups.

For analysis of follow up data, life table curves were calculated using the Kaplan Meier [22] method, and survival distributions were compared using the log rank test. The primary end points were disease-specific survival or cancer related death or tumor relapse, respectively. Data of patients, who were still alive and without evidence of tumor relapse at the end of the observation period, were censored. The level of significance was set at $p<0.05$. Statistical data analysis was carried out using SPSS software (SPSS Inc, Chicago, IL).

Results

The median age in our collective was 46 years (range 12–72 years). The female-to-male ratio was 3.44–1. Most patients were diagnosed at an early tumor stage. 70 % had rather small primary tumors (pT1 or pT2), whereas 30 % had locally advanced primaries (pT3 or pT4). After conventional histopathologic examination using HE-staining all patients were free of lymph node metastases (pN0). The diameter of the primary tumor was 10 mm or less in 15 patients (37.5 %: pT1a), more than 10 mm up to 25 mm in 17 patients (42.5 %) and larger than 25 mm in 8 patients (20 %). All patients showed no evidence for the presence of distant metastases. Patient and tumor characteristics are summarized in Table 1.

Treatment

The mean number of resected lymph nodes was 8.5 nodes per patients. After thyroid resection clear margins were confirmed in 82.5 % of the cases. In 7 patients (17.5 %) microscopic

tumor residues within the resection margin were found at histopathological examination. The mean duration of hospital stay was 6.5 days (range 2 – 20 days). Permanent postoperative complications such as recurrent laryngeal nerve palsy occurred in one patient. Transient postoperative hypocalcemia was observed in 11 patients (27.5 %). One patient (2.5 %) had a postoperative wound infection. None of the patients in this series had postoperative bleeding complications.

Immunohistochemical Detection of Ber EP4 Positive Cells

Primary papillary thyroid carcinomas of all patients were immunohisochemically homogenously positive for Ber EP4. All isotype controls on serial sections of all samples were consistently negative, indicating specific staining.

In total 321 lymph nodes were analyzed immunohistochemically revealing isolated Ber EP4 positive cells (Fig. 1) in 5/40 patients (12.5 %). The mean number of immunohistochemically screened lymph nodes per patient was 8. In one patient three lymph node samples were positive for Ber EP4+cells and in two patients clusters of up to five positively stained cells were detected.

At statistical analysis there was no correlation of nodular Ber EP4 detection and clinicopathologic parameters such as T-stage, tumor diameter, R-stage and age (Table 3). Surprisingly, the largest proportion of micrometastatic Ber EP4 positive cells was found in patients with papillary thyroid microcarcinomas smaller than 10 mm in diameter. In contrast none of the patients with pT3 or pT4 tumors had micrometastatic cells at all. However this difference did not reach statistical significance (Table 3).

Follow up

Follow up analysis with a mean observation period of 72 month (range 24 – 126) was available for all except of one patient.

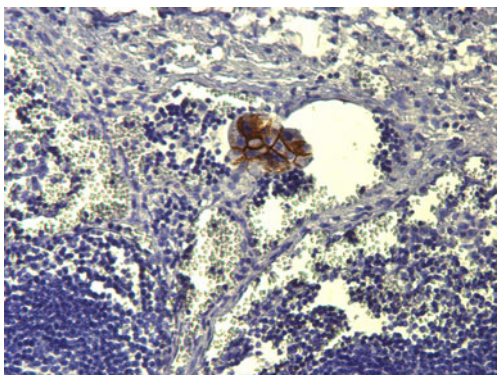

Fig. 1 Immunohistochemistry against Ber-EP4 revealing an immunoreactive tumor cell cluster of less than 0.2 mm in diameter within a peripheral sinusoid of a lymph node (reported as tumor free by analyzing Hematoxylin Eosin stained slides)

Table 3 Association between Ber-EP4+ cells and clinico-pathologic parameters

	Patients (%)	Ber EP4 + cells (%)	no Ber EP4 + cells (%)	p-value*
T-stage				
T1-2	28 (70)	5 (18)	23 (82)	
T3-4	12 (30)	0 (0)	12 (100)	0.118
Tumor diameter				
≤ 10 mm	15 (37.5)	3 (20)	12 (80)	
> 10 mm to ≤ 25 mm	17 (42.5)	1 (6)	16 (94)	
> 25 mm	8 (20)	1 (12.5)	7 (87.5)	0.484
R-stage				
R0	33 (82.5)	5 (15)	28 (85)	
R1	7 (17.5)	0 (0)	7 (100)	0.271
Age				
≤ 45 years	20 (50)	2 (10)	18 (90)	
> 45 years	20 (50)	3 (15)	17 (85)	0.633

* Chi Square

Tumor recurrence was observed in 3/39 patients (7.7 %). Locoregional relapse occurred in two patients (5.1 %) and one patient developed distant metastasis (2.6 %). Within the observation period two patients died in consequence of the underlying malignancy and one patient died without relation to the resected papillary thyroid carcinoma. The overall actuarial 5-years survival rate was calculated at 97.5 %.

Prognostic Parameters

In previous studies [23–25] clinico-pathologic parameters such as T-stage, tumor size, age, extend of lymph node dissection as well as resection margin status [26] were found to be relevant for prognosis of patients with papillary thyroid carcinoma. Furthermore we analyzed the prognostic impact of immunohistochemically detected Ber EP4+ cells. With respect to treatment characteristics we evaluated if the extent of cervical lymph node dissection as well as the administration of radio ^{131}I were prognostically relevant. However, except of the resection margin status, no significant correlations of clinicopathological parameters and prognostic data were recognized in our collective (Table 4). With respect to treatment characteristcs, neither the extent of cervical lymph node dissection nor the postoperative administration of radio ^{131}I were found to be of prognostic relevance (Table 4).

Discussion

The value of prophylactic lymph node dissection in patients with PTC and clinically inapparent lymph nodes remains

Table 4 Prognostic impact of clinico-pathologic parameters

Parameter	Actuarial overall survival (months)	p-value*
T-stage		
pT1-2	126.00	
pT3-4	108.33	0.080
Tumor diameter		
≤ 10 mm	126.00	
11 – 25 mm	114.93	
> 25 mm	107.00	0.218
R-stage		
R0	126.00	
R1	101.00	0.015
Age		
≤ 45 years	111.75	
> 45 years	126.00	0.202
Radio iodine ^{131}I treatment		
Administered	108.97	
Not adminstered	126.00	0.735
Extend of lymph node dissection		
Limited central dissection	126.00	
Standard central dissection	114.90	
Modified unilateral neck dissection	107.00	
Modified bilateral neck dissection	126.00	0.697
Detection of Ber EP4 cells		
Positive	126.00	
Negative	112.88	0.701

* Chi Square

controversial [5, 27–29] since regional lymph node involvement might increase local recurrence rates, but does not ultimately affect survival [30, 31]. However, in a more recent large population-based study an increased mortality rate with regional lymph node metastasis was observed [10].

The rationale for prophylactic clearance of the central lymph node compartment is the potential existence of occult subclinical nodal disease, being a potential source of subsequent tumor recurrence. Naturally, cervical tumor relapse is based on pre-existing residual micrometastatic tumor deposits undetectable by conventional staging methods. In a large variety of solid tumor entities immunohistochemical staining assays enabled the detection of single disseminated tumor cells in apparently tumor free lymph nodes. This finding frequently was associated with early tumor relapse and worse prognosis [32].

Actually in patients with PTC the phenomenon of immunohistochemically identifiable occult tumor cell dissemination is largely unexplored. To our knowledge there is only one report concerning the immunohistochemical analysis of patients with thyroid cancer. In this Japanese study 80 patients with pN0 staged thyroid carcinoma were analyzed and micrometastatic nodal disease was found in 53 % of the cases [33]. However, the impact of these findings on post operative survival was not evaluated, though the prognostic relevance of micrometastasis in PTC had been questioned previously [5].

Some authors [29, 34] propose that the lack of significant prognostic difference between patients, who were radically lymphadenectomized and those, who did not undergo systematic lymphadenectomy, suggested that micrometastatic tumor residues might not be relevant for the further course of the disease. Presumably, these occult cells would either be non-proliferative or easily be mopped up by radio iodine treatment. A conservative surgical approach, combined with radio iodine treatment would therefore be appropriate in the management of early stage PTC [29, 34].

In order to substantiate the ongoing debate and to elucidate the prognostic impact of occult disseminated tumor cells, we analyzed lymph nodes of patients with PTC, found to be free of lymph node metastases at routine histopathological examination. We used immunohistochemistry and the monoclonal anti-epithelial antibody Ber EP4 for visualization of disseminated tumor cells.

This approach revealed positive findings in 12.5 % of the cases. However, at follow up analysis with a mean observation period of 72 months no prognostic significance of these detected disseminated tumor cells was seen.

Since to our knowledge this is the first report on the prognostic impact of disseminated immunohistochemically detected tumor cells in PTC, our results cannot be assessed with respect to the data obtained in preceding studies. Though our collective was comparatively small, the observed lack of prognostic influence seems to support the hypothesis that the phenomenon of occult nodal tumor dissemination, indeed might not be of distinctive relevance for the further clinical course in PTC.

On the other hand the indication for adjuvant radioiodine treatment was rather liberal in our collective and most of the patients (90 %) had undergone this treatment. Therefore it is conceivable that microdisseminated tumor residues actually were eliminated by radio iodine, which might have levelled their impact on prognosis.

In fact, since disseminated tumor cells of PTC were immunohistochemically detectable, the concept of adjuvant radioiodine treatment is supported. In general, the prognostic impact of different treatments in PTC is presumably small and difficult to recognize due to the slow tumor progression and rather benign course of most patients. Therefore large multicenter trials are needed for the evaluation of radioiodine effectiveness in patients with early stage PTC.

Compared to the Japanese report the detection rate of 12.5 % of micrometastatic disease in our collective was considerably low. This discrepancy might be due to the fact that the mean number of lymph nodes analyzed in our study was 8

and thus distinctively lower than in the Japanese report, who screened a mean of 32 lymph nodes per patient. In our view the results of the Japanese report suggest that the rate of detected micrometastases might increase along with the number of lymph nodes analyzed. Thus it seems conceivable that the phenomenon of microscopic tumor dissemination is present in the majority of patients and its detection is only a matter of the number of lymph nodes screened. In order to identify relevant therapeutic targets for effective adjuvant treatment strategies the biological properties of these cells need to be further evaluated, particularly with respect to cellular proliferation, molecular pathology and ^{131}I uptake.

Conflict of Interest There is no conflict of interest that could be perceived as predjudicing the impartiality of the research reported.

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