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Prognostic Importance of Various Clinicopathological Features in Papillary Thyroid Carcinoma

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The influence of various pathological features on tumour recurrences and cancer deaths has been studied in 173 consecutive cases of surgically treated papillary thyroid carcinoma recorded in 1971–1985. During the follow-up (median 7.3 years), 18.6% of the 161 radically treated patients had recurrent disease, and 8.7% died of thyroid cancer. In the univariate life-table analysis, recurrence-free survival was significantly related to age, pTNM category, tumour size, presence of certain growth patterns, tumour necrosis, tumour infiltration in surrounding thyroid tissue and thyroid gland capsule, lymph node metastases, presence of extra-nodal tumour growth and number of positive lymph nodes, whereas only tumour diameter, thyroid gland capsular infiltration and presence of extra-nodal tumour growth remained as significant prognostic factors in the multivariate analysis. Regarding thyroid cancer deaths, sex, age, pTNM category, radicality of surgical treatment, tumour diameter, macroscopic appearance, cellular atypia, tumour necrosis, thyroid gland capsular infiltration, vascular invasion, extra-thyroidal extension and lymph node metastases were all significant variables in the univariate analysis. However, only sex, age, radicality of surgical treatment and vascular invasion were found to be significant predictors of thyroid cancer deaths in the final multivariate Cox model, whereas cellular atypia and necrosis showed a borderline significance. Our study thus documents the independent importance of certain histological features for morbidity and mortality in surgically treated cases of papillary thyroid cancer.
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INTRODUCTION

THE INFLUENCE of prognostic factors such as sex, age, histological type and tumour stage on the survival of patients with thyroid cancer has previously been described in several reports [1–5], but few studies have concentrated on the possible prognostic impact of various pathological features, using multivariate survival analysis [6, 7]. Such information may improve the risk estimation for individual patients. In the present study, the relationship between various clinicopathological variables and survival has been analysed in all cases of papillary carcinoma recorded in our hospital during 1971 to 1985. Complete follow-up of all patients and information on causes of death have been available, thereby allowing for the specific analysis of thyroid cancer deaths.

PATIENTS AND METHODS

Patients

This material has been described previously [8, 9]. Briefly, all 263 patients who were surgically treated for thyroid cancer at the Department of Surgery, Haukeland Hospital, University of Bergen in the period 1971–1985 have been studied retrospectively. These cases account for 10% of 2625 thyroid carcinomas reported in Norway during 1970 to 1985, with no marked differences in sex distribution, age and histological types between the present material and all cases in the entire Norwegian population [9, 10]. However, our patients tended to be somewhat younger, and the frequency of papillary carcinoma was slightly higher. Since only surgically treated cases have been included in our series, only 2.2% of the cases had distant metastases at the time of presentation, compared to 11.3% of the national material.

After histological revision, 32 cases were excluded as benign lesions, leaving 231 malignant tumours, with a mean age of 48.7 years (176 papillary, 30 follicular, 10 medullary, 7 undifferentiated, 7 malignant lymphomas, 1 squamous cell carcinoma). For the study of pathological features and prognosis, 173 cases of papillary carcinoma were included (3 cases with lymph node presentation without detectible primary tumour in the thyroid or ectopic structures were excluded). Separate survival analyses of the other histological types were not possible due to the low number of cases and few events (tumour recurrences and thyroid cancer deaths).

Table 1 shows a female : male ratio of 3 : 1. The mean ages of females and males were 45.2 and 48.5 years, respectively (not significant). Of the papillary carcinomas, 50.3% were localised (intrathyroidal) and 55.0% were found in the pTNM-I category. All 173 patients were surgically treated in our institution, most of them with near-total/total thyroidectomy (88.4%), and 93.1% were considered to be radically treated, without macroscopically remaining tumour tissue. Pathological lymph nodes were removed mostly using a "node-picking" procedure.

17 of the cases (9.8%) were incidentally found during surgery for benign thyroid lesions and palpable tumours (1 thyreotoxicosis, 1 hyperparathyroidism, 7 colloid goitre, 8 follicular adenoma).

Variables

The following variables were studied: sex; age at the time of diagnosis: 0–29, 30–49, 50–69, 70+ years; histological type according to the WHO classification from 1988 [11]; pTNM

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Table 1. Distribution of papillary carcinomas according to sex, age, pTNM category and surgical treatment (n = 173)

Variables	*n*	%
Sex		
Male	43	24.9
Female	130	75.1
Age (years)		
0–29	36	20.8
30–49	61	35.3
50–69	57	32.9
70+	19	11.0
pTNM Category*†		
I	94	55.0
II	25	14.6
III	50	29.2
IV	2	1.2
Surgical treatment		
Unilateral lobectomy	14	8.1
Near-total/total t.e.	153	88.4
Others	6	3.5
Radicality of surgical treatment*		
Radical	161	93.1
Not radical	12	6.9

*See Patients and Methods.
†2 cases were excluded due to lack of information.

Table 2. Follow-up data with reference to age and pTNM category in patients with papillary thyroid carcinoma

		Recurrences		Deaths		
Variables	*n*	Local	Others	TC*	Others	Active disease
Age (years)						
<50	97	13	0	1	0	5
≥50	76	14	6	14	13	4
pTNM category†						
I	94	10	0	0	2	3
II	25	3	1	2	1	2
III	50	14	4	10	10	3
IV	2	0	0	1	0	1

*TC = thyroid carcinoma.
†2 cases were excluded due to lack of information.

category was defined according to the UICC criteria from 1987 [12], including patients' age in addition to the usual pTNM variables; surgical treatment: unilateral lobectomy, near-total/-total thyroidectomy (t.e.), others; radicality of surgical treatment: radical (treated for cure), not radical (i.e. macroscopically remaining tumour tissue).

In addition, several pathological features were studied, most of them being recorded as categorical and dichotomous variables (presence/absence), although subjective grading was used in some instances. A more detailed review of these features has been presented separately [9]. The following variables were included: tumour diameter, macroscopic tumour appearance (demarcated, predominantly solid tumour vs. others), presence of tumour capsule, variant growth patterns (cribriform or trabecular or solid or squamous in addition to papillary/follicular growth), variant cell types (oxyphil, clear, spindle, giant or small cells in addition to the ordinary cell type) and various nuclear types (hyperchromatic or ground glass). Furthermore, differentiation grade was recorded using the critera of Tscholl-Ducommun and Hedinger [13], and cellular atypia was graded as done by Tennvall *et al.* [6].

Secondary changes were also studied: presence/absence of cystic changes or tumour necrosis, quantity of inflammatory cells (none, few, moderate, many), and presence/absence of fibrosis and psammoma bodies.

The extent of primary tumour infiltration was examined with respect to infiltration of the tumour capsule, surrounding thyroid tissue, thyroid gland capsule, vessels and extra-thyroidal structures. Thyroid capsular invasion (TCI) was recorded as present in cases where groups of tumour cells were observed in the connective tissue of the thyroid gland capsule, including the cases where early extra-thyroidal invasion was suspected. Major extra-thyroidal invasion (pT4) was used when obvious/major extra-thyroidal tumour growth was evident, i.e. tumour infiltration of skeletal muscle, large nerves or lipomatous tissue. Vascular invasion was also recorded. The presence of multifocal or bilateral growth was determined after histological examination. Finally, the presence of lymph node metastases, number of positive lymph nodes and intra-nodal vs. extra-nodal growth of tumour tissue was recorded.

Follow-up

Data concerning locoregional tumour recurrences (local lymph node metastases or soft tissue recurrences in the thyroid bed), appearance of distant metastases and survival was achieved through examinations in our institution or by correspondence to the patients' home physicians. Recurrences or metastases within 4 months after the primary operation were referred to the time of diagnosis. For all patients who died, death certificates were examined as well as autopsy reports when available. Last date of follow-up was 1 July 1989, and the median follow-up time was 7.3 years (range 3.6–18.3 years). No patient was lost to follow-up.

Statistics

Analyses were performed by various programmes in the statistical package BMDP [14]. Associations between different variables were assessed by Pearson's χ^2 test. Age differences were tested by Students' *t*-test. All significance probabilities refer to two-sided tests. Survival analysis (life-table method) was done by BMDP-1L using the Mantel–Cox test for differences between groups, and plots for cumulative proportion surviving are given. Recurrence-free survival, i.e. the time from diagnosis until the appearance of locoregional recurrences or distant spread, and the patient survival (survival time until thyroid cancer deaths) were studied. The influence of covariates on survival was analysed by the proportional hazards method [15] with BMDP-2L, using a forward stepwise procedure. In these analyses, all variables with a *P*-value of 0.10 or less in the life-table studies were included. Estimated regression coefficients and *P*-values are given in the tables.

RESULTS

Table 2 shows that tumour recurrences during the follow-up period occurred in 18.6%. Of the 28 deaths, 53.6% were due to

Table 3. Univariate survival analysis (life-table method) of patients with papillary thyroid carcinoma according to sex, age, pTNM category and surgical treatment (the figures in parenthesis give the number of patients which were alive after 10 years and eligible for estimation of 10-year survival; the P-values correspond with a standard life-table analysis, based on all patients and observed events during the whole follow-up period)

Variables	*n**	10-year recurrence-free survival (%)	*P*†	10-year patient survival‡ (%)	*P*†
Sex			N.S.		0.0012
Males	43 (13)	70.6		82.3	
Females	130 (42)	81.8		94.0	
Age (years)			0.0068		<0.00005
0–29	36 (15)	79.8		100.0	
30–49	61 (18)	88.6		97.7	
50–69	57 (19)	76.0		89.4	
70+	19 (3)	45.5		57.2	
pTNM category			0.0016		<0.00005
I	94 (30)	89.3		100.0	
II	25 (6)	79.5		91.6	
III	50 (7)	57.4		79.2	
Surgical treatment			N.S.		N.S.§
Unilateral lobectomy	14 (4)	81.8		85.7	
Near-total/total t.e.	153 (48)	78.3		91.9	
Others	6 (3)	100.0		83.3	
Radicality of surgical treatment			—		<0.00005
Radical	161 (54)	—		94.5	
Not radical	12 (1)	—		39.0	

*Patients who were not radically treated by surgery were excluded in the analyses of recurrence-free survival ($n = 12$).
†Mantel–Cox test for difference.
‡Only deaths from thyroid cancer were considered.
§$P \leq 0.10$.

thyroid cancer. Only one death from thyroid cancer occurred among patients below the age of 50 years, whereas 43.3% of the recurrences were found in this group of patients. Follow-up data with reference to pTNM categories are also shown. The median time from diagnosis until the appearance of recurrent disease was 19.5 months, and 73.3 and 83.3% of these events occurred within 3 and 5 years, respectively. Active disease was present in 5.3% of the cases at the time of last follow-up. Regarding deaths from thyroid cancer, 53.3 and 86.7% occurred within 5 and 7 years of follow-up, respectively. All 17 cases incidentally found during surgery for benign lesions were 10 mm or less in diameter (median 6.0 mm). Five of these cases showed thyroid capsular invasion, 1 case showed major extra-thyroidal extension (pT4) and 1 case presented with regional lymph node spread. These 17 cases were included in the survival analyses. However, no recurrences or thyroid cancer deaths occurred in this group.

Univariate analysis of recurrence-free survival

Table 3 shows the influence of standard variables on recurrence-free survival in papillary carcinomas. Age and pTNM category had a significant impact on tumour recurrences. The cumulative proportion of patients in the youngest age group with recurrent disease during 10 years of follow-up was about 20%, and this proportion increased with age, especially above 50 years of age.

Tables 4 and 5 and Figs 1 and 2 summarise the prognostic influence of various pathological features on recurrence-free survival. Tumour diameter had a highly significant influence on recurrences, being evident in tumours above 30 mm in diameter (Table 4). Tumours of 30 mm in diameter or below showed a 10-year recurrence-free survival of 87.8%, compared to 48.0% in those above 30 mm ($P < 0.00005$). Presence of one or more of the variant growth patterns in addition to papillary structures indicated somewhat increased risk of recurrent disease, but the difference was rather small ($P = 0.014$) (Fig. 1). Furthermore, tumour necrosis showed a marked influence on recurrence-free survival (Table 4, Fig. 1). Regarding extent of tumour infiltration, both invasive growth in the thyroid tissue and thyroid gland capsule (TCI) were significant determinants of tumour recurrences, especially the last variable, while major extra-thyroidal invasion (pT4) and vascular invasion were not statistically significant (Table 5). Tumour spread to the regional lymph nodes showed a highly significant importance, with 10-year recurrence-free survival of 91.7 and 60.2% in the compared groups, respectively. Significant associations to number of positive lymph nodes and extra-nodal tumour growth were also present (Table 5, Fig. 2). The other variables, like cell type (oxyphilic cells, which were present in 19.7% of the cases, or clear cells, which were present in 29.5%) or the presence of psammoma bodies, were not associated with differences in recurrence-free survival.

Table 4. Univariate survival analysis (life-table method) of patients with papillary thyroid carcinoma according to important pathological features (for figures in parenthesis and P values see heading to Table 3)

Variables	n*	10-year recurrence-free survival (%)	P†	10-year patient survival‡ (%)	P†
Tumour diameter (mm)§			0.0001		0.0011
0–10	46 (17)	92.7		97.8	
11–20	53 (23)	86.7		95.2	
21–30	32 (8)	84.3		95.8	
31–40	9 (1)	42.9		86.7	
41–50	9 (1)	56.3		87.5	
51+	15 (2)	51.6		72.1	
Tumour appearance			N.S.		0.037
Demarcated, solid tumour	115 (37)	79.6		96.1	
Others	58 (18)	77.2		81.8	
Tumour capsule			N.S.		N.S.‖
Present	81 (33)	82.6		96.1	
Absent	92 (22)	75.9		86.2	
Grade of atypia			N.S.		0.0010
Slight/moderate	161 (52)	80.6		91.6	
Marked	12 (3)	45.9		82.6	
Tumour necrosis			0.004		<0.00005
Absent	162 (51)	81.4		93.4	
Present	11 (4)	35.2		58.5	

*Patients who were not radically treated by surgery were excluded in the analyses of recurrence-free survival (n = 12).
†Mantel–Cox test for difference.
‡Only deaths from thyroid cancer were considered.
§Tumour diameter could not be determined in 9 cases.
‖$P \leq 0.10$.

Univariate analysis of thyroid cancer deaths

Table 3 shows that sex and age had a clear influence on the patient survival. Males had a somewhat reduced survival compared with females, and increased occurrence of thyroid cancer deaths was observed in patients above 50 years of age. Survival was clearly reduced in patients not considered to be radically treated by surgery.

Table 4 shows that tumour diameter was significantly related to patient survival, which was somewhat reduced when the tumour diameter was greater than 30 mm. Patients with tumours 30 mm or below had a 10-year survival of 96.1%, compared with 80.1% in those with larger lesions ($P < 0.00005$). Furthermore, demarcated, solid tumours had a better survival than the others ($P = 0.037$). Of the cellular/nuclear features that were studied, only cellular atypia showed a highly significant influence on survival (Table 4, Fig. 3). Cell type (oxyphilic or clear cells) was not significantly associated with survival. Predominance of non-papillary growth (mostly follicular) did not influence patient survival ($P = 0.85$), although 5 cases with a dominant solid growth tended to have a poorer survival (not shown). Furthermore, squamous metaplasia was not associated with survival ($P = 0.26$). Tumour necrosis was a strong prognostic indicator, showing 58.5% survival for 10 years in the small group of patients with necrosis, compared with 93.4% in the other group ($P < 0.00005$) (Table 4, Fig. 3). Regarding the extent of primary tumour infiltration, thyroid capsular invasion (TCI), major extra-thyroidal invasion (pT4) and vascular invasion were all significant factors (Table 5, Fig. 3). Presence of TCI and vascular invasion were significantly correlated (Pearson's χ^2: $P = 0.002$). In patients with tumour spread to the local lymph nodes, 84.4% survived for 10 years, compared with 95.5% of those without ($P = 0.033$) (Table 5, Fig. 3). Thyroid cancer deaths were not influenced by the number of positive lymph nodes, extra-nodal tumour growth or any of the other variables included.

Multivariate analysis of recurrence-free survival

Table 6 shows the adjusted influence of the most important variables on recurrence-free survival. Of the factors with significant influence in the univariate study, only tumour diameter (TD), infiltration of the thyroid gland capsule (TCI) and presence of extra-nodal tumour growth (ENTG) in the lymph node metastases remained as independent variables, whereas age tended to have some importance. TCI was found to be the strongest prognostic factor as judged by the Cox proportional hazards method. When pT4 was included instead of TCI, only TD and ENTG remained as independent variables. When TCI and pT4 were combined, the final variable was found to be a strong predictor (regression coefficient: 1.50, $P = 0.009$) together with ENTG (regression coefficient: 1.37, $P = 0.006$). When only local recurrences were included as end-point, TCI and ENTG remained as equally strong and independent variables (not shown).

Table 5. Univariate survival analysis (life-table method) of patients with papillary thyroid carcinoma according to extent of primary tumour infiltration and nodal spread (for figures in parenthesis and P values see heading to Table 3)

Variables	n*	10-year recurrence-free survival (%)	P†	10-year patient survival‡ (%)	P†
Extent of infiltration					
Tumour capsule			N.S.		N.S.
Absent	7 (4)	100.0		100.0	
Present	166 (51)	78.1		90.6	
Thyroid parenchyma			0.0024		N.S.§
Absent	52 (26)	93.7		96.0	
Present	121 (29)	71.0		88.5	
Thyroid gland capsule			<0.00005		0.0010
Absent	87 (38)	94.9		97.7	
Present	86 (17)	57.1		83.5	
Major extra-thyroidal invasion (pT4)			N.S.§		0.029
Absent	144 (51)	80.6		92.5	
Present	29 (4)	72.9		83.6	
Vascular invasion			N.S.§		0.0003
Absent	149 (49)	80.9		94.5	
Present	24 (6)	67.1		66.6	
Local lymph nodes			<0.00005		0.033
Negative	99 (35)	91.7		95.5	
Positive	74 (20)	60.2		84.4	
Number of positive lymph nodes			<0.00005		N.S.
0	99 (35)	91.7		95.5	
1–2	28 (8)	85.5		82.9	
3–4	19 (2)	26.8		78.4	
5+	27 (10)	51.3		91.4	
Tumour growth in lymph nodes			0.022		N.S.
Intra-nodal	21 (6)	82.9		80.0	
Extra-nodal	49 (13)	46.5		85.6	

*Patients who were not radically treated by surgery were excluded in the analyses of recurrence-free survival ($n = 12$).
†Mantel–Cox test for difference.
‡Only deaths from thyroid cancer were considered.
§$P \leq 0.10$.

Multivariate analysis of thyroid cancer deaths

Table 7 shows that sex, age, radical treatment and vascular invasion had a significant and independent influence on thyroid cancer deaths, whereas necrosis and cellular atypia showed a borderline significance. The combined variable of TCI and pT4 did not enter the final regression model as a significant variable. If radicality of surgical treatment was not included, sex, age and cellular atypia ($P = 0.020$) turned out to be independent variables.

DISCUSSION

Several studies of thyroid cancer prognosis have been performed, both clinical and population-based [1–7, 16–19]. However, the results are often difficult to compare, due to significant methodological differences. In hospital series, selection of patients may vary considerably, according to referral patterns and treatment policy. In unselected, population-based studies, all cases are included, with discrepancies in sex, age and stage distribution when compared to clinical series. Histological reclassification is also considered to be of crucial importance, with exclusion of benign cases, correct typing of carcinomas and a precise postsurgical staging as major advantages. Finally, the quality of follow-up data and statistical evaluation are important. In the present series of papillary carcinomas, only surgically treated and reclassified cases have been included, and complete follow-up was obtained, with tumour recurrences and specific deaths as end-points in the univariate and multivariate survival analyses.

Various clinicopathological factors were significantly related to recurrence-free survival in the life-table analyses, but only tumour diameter, thyroid capsular invasion and lymph node spread with extra-nodal tumour infiltration persisted as independent variables in the final multivariate model. Regarding tumour size, a "break-point" of 3 cm was indicated, and patients with larger tumours were more prone to develop recurrent disease. Increasing tumour diameter was previously found to be associated with thyroid capsular invasion [9], which also showed a strong and independent influence on recurrence-free survival. The significant influence of thyroid capsular invasion, which may possibly be regarded as a marker of early extra-thyroidal

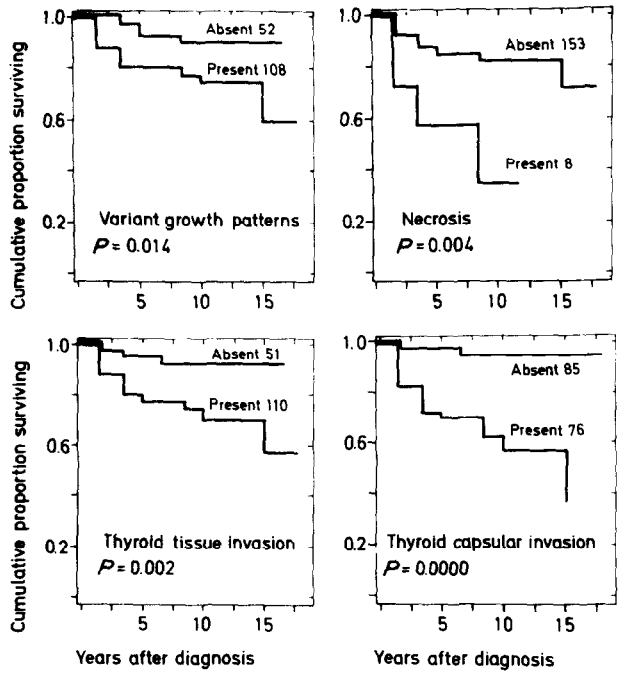

Fig. 1. Recurrence-free survival according to significant histopathological features of papillary thyroid carcinomas ($n = 161$) (where $P = 0.0000 \approx P < 0.00005$)).

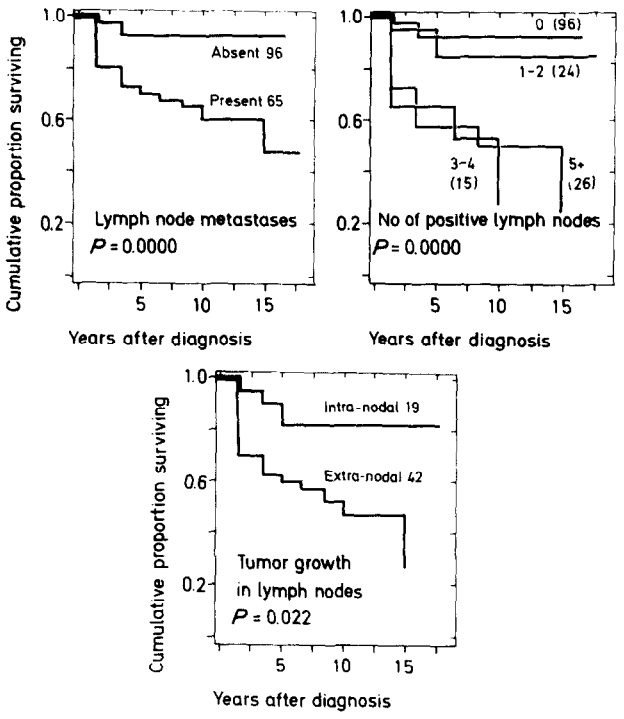

Fig. 2. Recurrence-free survival according to lymph node status at the time of diagnosis ($n = 161$) (where $P = 0.0000 \approx P < 0.00005$)).

extension, has not been focused in other multivariate studies, and this feature should therefore be reported as a prognostic factor in papillary thyroid cancer.

In accordance with other studies [2, 4], lymph node spread was found to strongly predict recurrent disease, predominantly local recurrences. However, the risk especially increased when

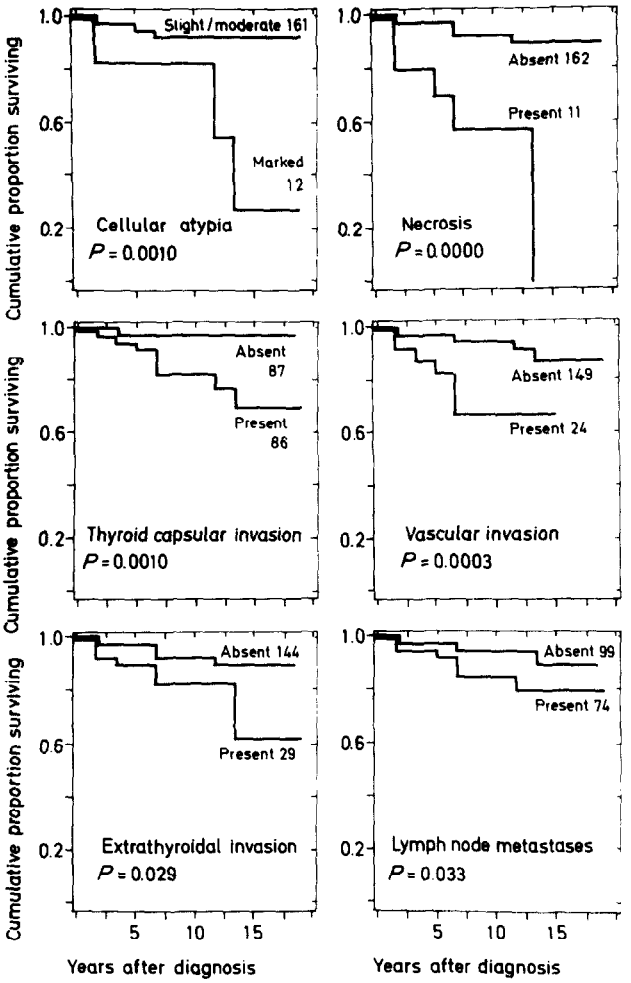

Fig. 3. Thyroid cancer deaths according to significant histopathological features of papillary thyroid carcinomas ($n = 173$) (where $P = 0.0000 \approx P < 0.00005$).

Table 6. Final multivariate model (Cox proportional hazards method) of recurrence-free survival in radically treated patients with papillary thyroid carcinoma (n = 154)*

Variables	Regression coefficient	*P*-value
Age†	(0.35	0.088)
Tumour diameter‡	0.90	0.050
Infiltration of thyroid capsule§	1.52	0.009
Extra-nodal tumour growth§	1.35	0.007

*Cases with insufficient information were excluded ($n = 7$).
†0–29, 30–49, 50–69, 70+ years.
‡> 30 mm vs. ≤ 30 mm.
§Present vs. absent.

Table 7. Final multivariate model (Cox proportional hazards method) of thyroid cancer deaths in patients with papillary thyroid carcinoma (n = 173)

Variables	Regression coefficient	*P*-value
Sex*	−1.97	0.003
Age†	1.98	0.0004
Radicality of surgical treatment‡	1.99	0.003
Vascular invasion§	1.31	0.036
Marked cellular atypia§	(1.26	0.076)
Necrosis§	(1.14	0.064)

*Females vs. males.
†0–49, 50–69, 70+ years.
‡Not radical vs. radical.
§Present vs. absent.

extra-nodal tumour infiltration was present, and this variable had an independent prognostic importance. We also suggest that this feature should be evaluated and reported. Finally, it is worth noticing that sex did not influence the occurrence of tumour recurrences, whereas age showed a borderline significance.

Most recurrences and thyroid cancer deaths occurred during the first years after diagnosis, but they also presented at later instances. This confirms the view that papillary thyroid cancer is a protracted tumour disease and also that long follow-up schedules may be necessary.

The prognostic factors of significant importance for thyroid cancer deaths were somewhat different from those predicting recurrent disease, indicating that other mechanisms may be involved. The influence of sex has been discussed in earlier reports. Recent studies have shown that sex hormone receptors are present in some thyroid carcinomas [20, 21], and this finding suggests that hormonal factors may act as growth regulators. In our present study, females showed a significant better survival than males, when other factors were adjusted for. Byar *et al.* [1] and Tubiana *et al.* [2] also found by multivariate analyses that females had a superior survival, but this has not been confirmed in other studies of reclassified papillary carcinomas [4, 6, 22, 23]. Interestingly, no significant sex difference was found in a previous Norwegian population-based study [5], but those patients were somewhat older and with more advanced disease, and they were included irrespective of surgical treatment. The inclusion of old patients with advanced disease would probably tend to mask a possible sex difference in some subgroups, due to the impact of stronger prognostic factors.

There is almost general agreement that age at the time of diagnosis is a major prognostic factor [1–5], although Schelfhout *et al.* did not confirm this [24]. In accordance with other studies, it seems that the risk increases in patients above 50 years [1, 5, 15], although some reports indicate an earlier "break-point" [1–3]. The biological basis for this strong and independent age effect is not known, although it should be mentioned that DNA aneuploidy, which has been identified as a prognostic factor in thyroid cancer [22, 23, 25, 26], increases with age in malignant thyroid tumours [23]. However, other factors may also be of importance, since age was found to persist as an independent variable when ploidy was adjusted for [22].

According to several reports, the presence of extra-thyroidal invasion is an important prognostic factor in thyroid cancer [1, 3,4]. In the univariate analysis, extra-thyroidal extension (pT4) was found to be of importance, but its significance was abolished in the final regression model. This is, however, in line with another multivariate study of reclassified papillary carcinomas [6], but contrasts to the reports of Hrafnkelsson *et al.* [22] and Joensuu *et al.* [23]. Our results may in part be explained by a highly significant association between age and extra-thyroidal tumour growth [9], although differences in tissue sampling from the surgical specimens may also in part explain the discrepancies.

In this study, a number of histopathological features of the primary tumour were examined with respect to prognostic impact. Vascular invasion was identified as an independent prognostic factor and thus confirms the results of univariate studies [17, 27]. Although found in only 14% of the cases, its presence identifies a high-risk group with respect to thyroid cancer deaths. Furthermore, the importance of cellular atypia and necrosis should not be neglected [6], although they showed only a borderline significance in the final multivariate model. It has been suggested that marked cellular atypia correlates with the presence of DNA aneuploidy [6], and the adverse prognostic influence of these variables may thus reflect a common mechanism, for instance related to genetic instability as an important factor in tumour progression.

The recent pTNM classification from UICC [12], where age at the time of diagnosis has been included in addition to the traditional pTNM-variables, was found to correlate well with the risks of recurrent disease and thyroid cancer deaths. However, the definition of various subgroups within each of the pTNM variables should be further studied in larger series and modified to achieve optimal prognostic discrimination. In addition to this general system, our present study has provided some information on specific histological features that may be added as valuable indicators.

In summary, this study of papillary thyroid carcinomas demonstrates that important prognostic information may be obtained by careful histological examination of the surgical specimens. Our results indicate that tumour diameter, thyroid capsular invasion, vascular invasion and extra-nodal tumour growth are significant prognostic parameters, in addition to the sex and age of the patients. Tumour recurrences and thyroid cancer deaths were predicted by different sets of variables. Our findings should be further validated in larger series of histologically reclassified cases.

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The Budgetary Impact of 5-HT$_3$ Receptor Antagonists in the Management of Chemotherapy-induced Emesis

Alison L. Jones, Graham J. Lee and Nick Bosanquet

The study examined the budgetary implications of using 5-hydroxytryptamine$_3$ receptor antagonists(5-HT$_3$RA), granisetron or ondansetron, in the management of chemotherapy-induced emesis (CIE). A treatment model was constructed to represent a baseline of efficacy and costs for treating a cohort of patients with conventional antiemetics. Groups of patients who would be expected to receive the most benefit from 5-HT$_3$RA were then identified and the effect upon costs of using these compounds in a consecutively larger proportion of selected patients was calculated. On the basis of illustrative costs from The Cookridge Hospital in the UK, it was concluded that the new antiemetics can be used in acute emesis with substantial clinical benefit for an increase of 3–10% to total treatment costs. However, for delayed emesis these compounds have not yet shown a clinical advantage, and the increase in total costs of 12–34% is not justified.
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INTRODUCTION

NAUSEA AND vomiting are ranked by patients as the most distressing side-effects of cancer chemotherapy [1]. Although careful use of antiemetics can control emesis in approximately 60% of patients, some conventional antiemetic regimens also cause distressing side-effects, in particular extrapyramidal reactions (EPR). Thus, chemotherapy-induced emesis (CIE) remains a significant problem, which may severely undermine quality of life of patients undergoing treatment. The 5-hydroxytryptamine$_3$ receptor antagonists (5-HT$_3$RA) are a new class of antiemetic compounds, which may represent an opportunity to improve the management of CIE, thereby enhancing quality of