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Medullary Carcinoma of the Breast, Prognostic Importance of Characteristic Histopathological Features Evaluated in a Multivariate Cox Analysis

L. Pedersen, S. Holck, T. Schiødt, K. Zedeler and H.T. Mouridsen

In this study of 136 breast cancers with medullary features (MC), registered in the Danish Breast Cancer Cooperative Group (DBCG) from 1982 to 1987, we confirmed the prognostic importance of a new definition of medullary carcinoma of the breast (MC newdef) which was recently proposed by us, deduced from a previous study of a corresponding tumour material (DBCG 77-82). However, the individual histological criteria did not have the same prognostic importance as in our previous study, although prognostic trends were the same. To further improve and validate the diagnostic criteria, we combined the two populations and performed a multivariate Cox regression analysis. In the final Cox model, four histological parameters retained positive prognostic importance: (1) predominantly syncytial growth pattern, (2) no tubular component, (3) diffuse stromal infiltration with mononuclear cells and (4) sparse necrosis. We propose that these criteria are emphasized in the histological diagnosis of medullary carcinoma of the breast.

Key words: medullary breast cancer, breast cancer, histopathology, prognosis
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INTRODUCTION

MEDULLARY CARCINOMA of the breast (MC) is generally regarded as having a better than average prognosis for breast cancer. However, unanimity as to the frequency and prognosis of MC has been lacking in the literature [1]. This may be because the histopathological definition of MC has varied with time [1], but diagnostic variability also seems to pose a problem [2]. The most commonly used definitions of MC among pathologists today are those of Fisher and colleagues [3, 4] and Ridolfi and colleagues [5], which are almost concordant, from 1975 and 1977, respectively. A histological diagnosis must, in order to render some assistance in the clinical decision, be reproducible and carry consistent prognostic information. In an earlier study [2], concerning the diagnosis of MC as defined by Fisher [3] and Ridolfi [5], we found a considerable inter- and intraobserver variability with significant impact on survival. As an extension of that study, we examined the same tumour population for 11 histopathological parameters with regard to prognostic observations and observations on inter- and intraobserver variability [6]. Retaining reproducible, prognostically significant criteria (predominantly syncytial growth pattern, and diffuse, moderate or marked mononuclear stromal infiltration), we proposed a new simplified histopathological definition of MC (MC newdef). The main aim of the present paper is (1) to estimate the prognostic importance of MC newdef in another tumour population, and (2) to further improve and validate the diagnostic criteria by enlarging the primary population and carrying out a multivariate regression analysis.

MATERIALS AND METHODS

Histopathological material and evaluation

From November 1982 until January 1987, 147 patients with the diagnosis medullary carcinoma of the breast were registered in protocols of the DBCG programme (Danish Breast Cancer Cooperative Group).

When the histological records of these patients were reviewed, six tumours were found to have been wrongly diagnosed. Another five tumours could not be procured. From the remaining 136 tumours, paraffin-embedded histological material was retrieved from 26 Departments of Pathology, representing all parts of Denmark. Four-micron-thick sections, obtained from two to six paraffin blocks from each tumour, were stained with haematoxylin/eosin and van Gieson. As in the previous studies [2, 6, 7], each set of slides was assessed by the same two senior pathologists, both specialists in breast pathology. The slides were evaluated for the same 11 histopathological features (Table 1), which were previously evaluated in a corresponding tumour material, registered in the DBCG from 1977 to 1982 [6]. Regarding syncytial growth, the definition was based on the one used by Ridolfi and colleagues [5], "broad, interanastomosing sheets of tumour cells", characterised as predominantly syncytial when > 75% of the tumour grew in this way. Mitoses were

Correspondence to L. Pedersen at the Department of Oncology R, Herlev Hospital/University of Copenhagen, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
S. Holck is at the Department of Pathology, Frederiksborg Amts Centralsygehus, Hillerød; T. Schiødt is at the Department of Pathology, Rigshospitalet, Copenhagen; K. Zedeler is at the Secretariate of the Danish Breast Cancer Cooperative Group, Rigshospitalet, Copenhagen; and T. Mouridsen is at the Department of Oncology, Rigshospitalet, Copenhagen, Denmark.
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Table 1. Histopathological characteristics analysed

1.	Growth pattern	Predominantly syncytial (> 75%) Non-syncytial
2.	Circumscription	Completely circumscribed Monofocal infiltration Multifocal infiltration
3.	Stromal component	Sparse Moderate Marked
4.	Grade of mononuclear infiltrate	Sparse Moderate Marked
5.	Distribution of mononuclear infiltrate	Diffuse Focal Limited to borders only
6.	Intraductal component	Present Absent
7.	Tubular component	Present Absent
8.	Mitoses	< 2 per high power field 2–3 per high power field > 3 per high power field
9.	Nuclear pleomorphism	Slight Moderate Marked
10.	Histological grade	Grade I Grade II Grade III
11.	Necrosis	Sparse Moderate Marked

evaluated in ten high power fields (× 400). Mononuclear cells comprised lymphocytes and plasma cells. Necrosis was graded as sparse, moderate or marked; sparse when comprising 0–25% of the tumour area, moderate 25–50% and marked > 50%. Regarding histological malignancy grading, we were guided by the recommendations of the WHO [8]. After the histopathological evaluation, the specimens were subdiagnosed, according to Ridolfi [5], as TMC (typical MC), AMC (atypical MC) and NMC (non-MC), and according to the new simplified definition [6] as MC newdef or NMC. MC newdef was defined by predominantly syncytial growth pattern and diffuse, moderate or marked mononuclear stromal infiltration. For the Cox regression analysis, we combined the two sets of data (DBCG 77–82 and DBCG 82–87). The first population consists of 102 patients with the diagnosis of MC, registered in the DBCG from 1977 to 1982 [6]. The tumour material from DBCG 77–82 was procured, processed and evaluated in exactly the same manner as described above [6].

Statistical methods

In the first part of this study, we characterised the tumour material from DBCG 82–87. The prognostic importance as to each of the histopathological parameters plus the histopathological diagnostic subgroupings was analysed by Kaplan-Meier plots [recurrence-free survival (RFS) and overall survival (OS)] and log rank tests [9].

The diagnostic subgroups of MC newdef [6] and TMC [5] were also compared to a control group of infiltrating ductal carcinomas (IDC), not otherwise specified (NOS) and a control group of IDC with high histological grades (grades II and III), registered in protocols of the DBCG during the same period. The latter control group was chosen because none of the tumours in the MC newdef or TMC groups were grade I. The results from the two different populations, DBCG 77–82 and DBCG 82–87, have been compared. The two materials were then combined, and histological parameters and diagnostic subgroupings were again tested for prognostic importance in a univariate analysis (Kaplan-Meier plots plus log rank). Histological features with prognostic information in the univariate analysis plus diagnostic subgroupings were then evaluated in a multivariate Cox regression analysis [9–11], together with the most important "clinical" prognostic parameter: lymph node status. Median times of follow-up in the two patient groups (DBCG 77–82 and DBCG 82–87) are 135 and 85 months, respectively, at the time of analysis.

RESULTS

Breast cancers with medullary features registered in protocols of the DBCG from 1982 to 1987 (n = 136)

The prognostic importance of the two different diagnostic subgroupings is shown in Table 2. Concerning our own recently proposed simplified definition of MC [6], a marginally significant better OS was observed for MC newdef than for the complementary NMC group ($P = 0.048$), whereas no prognostic information could be obtained regarding RFS, as opposed to the results from DBCG 77–82 [6]. The definition of Ridolfi [5] yielded no significant prognostic information in this population. Comparing MC newdef and TMC to the control groups of IDC_{NOS} and to the control group of IDC with high grades of anaplasia (II + III), registered in the DBCG in the same period, we found that MC newdef had a significantly better OS and RFS than IDC grades II and III ($P_{OS} = 0.006$ and $P_{RFS} = 0.049$) as well as a trend for a better survival than all IDC ($P = 0.07$). As to TMC, we also found a significantly better survival than for IDC grades II + III, but no other significant differences were found.

We could thus confirm the prognostic value of MC newdef previously observed in the material from DBCG 77–82 [6]. The prognostic importance of the histopathological characteristics is given in Table 3. Syncytial growth pattern carried positive prognostic information concerning RFS and OS, which was also true for the DBCG 77–82 population [6]. Necrosis carried significant prognostic information for OS; sparse necrosis indicating the better prognosis. Tubular component presented a significant P value as regards OS; no tubular component indicating the better prognosis. These trends were also found in

Table 2. P values for prognostic importance of diagnostic subgroupings in 136 breast carcinomas with medullary features

Diagnostic subgrouping	P values RFS	OS
MC newdef	NS	0.05
Ridolfi	NS	NS
TMC versus NMC	NS	0.07
TMC versus AMC + NMC	NS	NS

RFS, recurrence-free survival; OS, overall survival; MC, medullary carcinoma; TMC, typical MC; NMC, non-MC; AMC, atypical MC. Non-significant (NS): $P \geq 0.15$.

Table 3. P values for prognostic observations on 11 histopathological characteristics in 136 breast carcinomas with medullary features

Histopathological parameter	P values RFS	OS
Growth pattern	0.01	0.03
Circumscription	NS	NS
Stroma	NS	NS
Grade of mononuclear infiltration*	NS	NS
Distribution of mononuclear infiltration*	NS	NS
Intraductal component	NS	NS
Tubular component	0.14	0.02
Mitoses	NS	NS
Nuclear pleomorphism	NS	0.04
Histological grade	NS	NS
Necrosis*	NS	0.02

See Table 2 for abbreviations. NS: $P \geq 0.15$. * As to grade of mononuclear infiltration and necrosis, marked and moderate were combined and tested against sparse. As to distribution of mononuclear infiltration, focal and limited to borders only were combined and tested against diffuse.

the previous study [6]. Nuclear pleomorphism presented a marginally significant P value as to OS; the highest grade indicating the best prognosis. As opposed to the previous results, grade and distribution of mononuclear infiltration implied no significant prognostic information in this study. Despite the described differences in the two tumour populations, all prognostic trends were similar. The two populations were, therefore, combined in order to perform a Cox multivariate regression analysis. It should be mentioned that no significant difference between the two populations was found concerning the most important clinical prognostic factor: nodal status.

Breast cancers with medullary features registered in protocols of the DBCG from 1977 to 1987 (n = 238)

Univariate analysis of the relevant histopathological parameters in the combined population (Table 4) showed a significant

Table 4. P values for prognostic observations on histopathological characteristics plus diagnostic subgroupings in 238 breast carcinomas with medullary features

Histopathological parameter	P values RFS	OS
Growth pattern	0.01	0.07
Circumscription	0.11	NS
Grade of mononuclear infiltration*	NS	NS
Distribution of mononuclear infiltration*	0.004	0.001
Tubular component	0.11	0.048
Nuclear pleomorphism	NS	NS
Histological grade	NS	NS
Necrosis*	0.03	0.005
Diagnostic subgrouping according to Ridolfi	NS	NS
TMC versus NMC	0.07	NS
TMC versus AMC + NMC	NS	NS
Diagnostic subgrouping according to MC newdef	0.03	0.006

See Table 2 for abbreviations. NS: $P \leq 0.15$. *As to grade of mononuclear infiltration and necrosis, marked and moderate were combined and tested against sparse. As to distribution of mononuclear infiltration, focal and limited to borders only were combined and tested against diffuse.

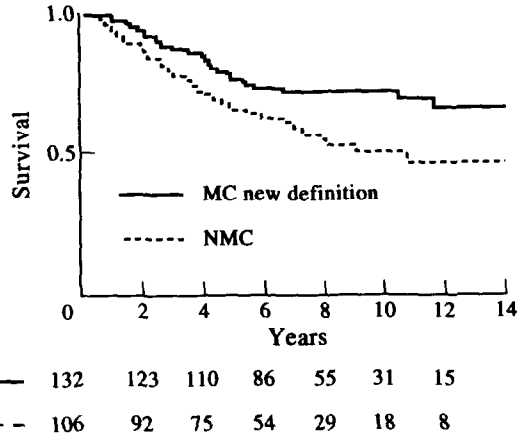

Figure 1. Kaplan–Meier plots of overall survival (OS) for 238 patients with breast cancers with medullary features in the Danish Breast Cancer Cooperative Group (DBCG) from 1977 to 1987, and evaluated as medullary carcinoma according to the new definition. The number of patients at risk is indicated under the abscissa. $P = 0.006$.

prognostic importance ($P < 0.05$) of growth pattern (syncytial growth pattern implying the better prognosis), distribution of mononuclear cells (diffuse stromal infiltration implying the better prognosis), tubular component (no tubular component indicating the better prognosis), necrosis (sparse necrosis indicating the better prognosis) and diagnostic subgrouping according to the new definition [6]. Furthermore, MC newdef showed a highly significant better RFS and OS when compared to IDC grades II + III ($P = 0.002$ and 0.0001), and also a significantly better RFS and OS when compared to all IDC ($P = 0.04$ and $P = 0.003$). Survival curves are shown in Figures 1 and 2.

The diagnostic subgrouping according to Ridolfi [5] also contained significant prognostic information in this combined population as regards TMC compared to IDC grades II and III ($P = 0.01$, $P = 0.006$), and also when compared to all IDC with regard to OS ($P = 0.04$), but not with regard to RFS ($P = 0.08$). It should be noted that the group of MC newdef comprised 132 patients, whereas the group of TMC comprised only 63 patients.

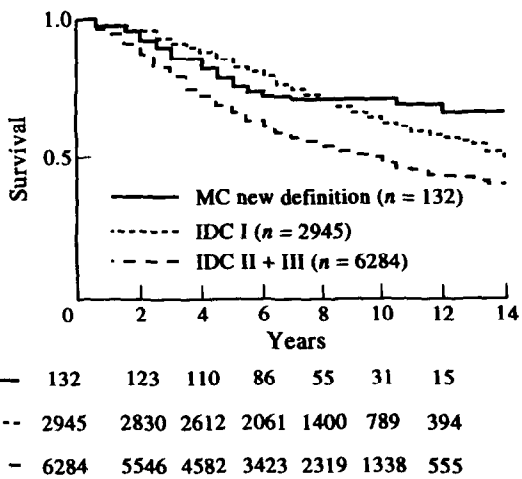

Figure 2. Kaplan–Meier plots of OS. All patients were consecutively enrolled in the DBCG from 1977 to 1987. The number of patients at risk is indicated under the abcissa. $P_{MC/IDC\ II+III} + 0.0001$; $P_{MC/IDC\ I} = 0.60$.

Table 5. Final Cox model for recurrence-free survival

Variable	β	exp β (95% C.I.)	*P* value
Growth pattern	−0.49	0.61 (0.20–1.85)	0.38
Tubular component	−0.94	0.39 (0.19–0.78)	0.008
Growth × tubular	1.44	4.22 (1.24–14.38)	0.02
Distribution of mononuclear infiltration	0.60	1.82 (1.15–2.85)	0.009
Necrosis	0.65	1.92 (1.23–2.99)	0.004

Table 6. Final Cox model for overall survival

Variable	β	exp β (95% C.I.)	*P* value
Growth pattern	−0.87	0.42 (0.12–1.41)	0.16
Tubular component	−1.32	0.27 (0.13–0.57)	0.006
Growth × tubular	1.80	6.03 (1.56–23.31)	0.009
Distribution of mononuclear infiltration	0.69	2.00 (1.23–3.26)	0.005
Necrosis	0.88	2.41 (1.47–3.95)	0.0005

When testing these prognostic parameters (including diagnostic subgroupings) in a Cox model [10], growth pattern, distribution of mononuclear cells, necrosis and tubular component remained prognostically important in the final model. This applied to RFS (Table 5) and to OS as well (Table 6). Interaction between growth pattern and tubular component is further illustrated in Tables 7 and 8. Tumours with syncytial growth pattern have a better outcome when the tubular component is absent, whereas the opposite is the case for tumours with non-syncytial growth pattern. Distribution of these prognostically important histological features is shown in Table 9. These four parameters also retained significant prognostic importance when the single most prognostically important clinical parameter was included in the model: lymph node status. Goodness of fit of Cox's regression model has been tested graphically [9], and the relevant death intensities have been found to be proportional.

Table 7. Interaction between growth pattern and tubular component in the Cox analysis

Growth pattern		Tubular component: Present β	Present (exp β)	Absent β	Absent (exp β)
Syncytial	RFS	0	(1)	−0.94	(0.39)
	OS	0	(1)	−1.32	(0.27)
Non-syncytial	RFS	−0.49	(0.61)	0.01	(1.01)
	OS	−0.87	(0.42)	−0.39	(0.68)

See Table 2 for abbreviations.

Table 8. Distribution of growth pattern and tubular component in relation to each other

Growth pattern	Tubular component: Present (*n*)	Absent (*n*)
Syncytial	14	177
Non-syncytial	12	35

DISCUSSION

In this study of consecutive material, we confirmed the prognostic importance of a new simplified histopathological definition of medullary carcinoma of the breast, MC new def, found in the earlier deductive study [6]. The prognostic impact of MC newdef is greater than that of the commonly accepted definition of Ridolfi [5]. However, when testing the individual histological parameters in the histological definition, only syncytial growth pattern was found to have a significantly positive prognostic impact (on both RFS and OS). The other two histological parameters (grade and distribution of mononuclear cells) showed no significant prognostic impact, although prognostic trends were the same in this population from DBCG 82–87 and in the previously examined corresponding tumour population from DBCG 77–82. We, therefore, combined the two consecutive tumour populations which enabled us to perform a Cox regression analysis on possible prognostically important histopathological parameters (including diagnostic subgroupings).

In the Cox analysis, the prognostic significance of the new simplified histological definition of MC [6] was not retained, so although of some prognostic importance, this definition cannot be regarded as optima. Diagnostic subgroupings, according to Ridolfi [5], yielded no significant prognostic information in the univariate statistical evaluations, although TMC conveyed some prognostic information when compared to IDC. This definition by Ridolfi was originally proposed by Fisher in 1975 [3] and evaluated by Ridolfi in 1977, who found a significantly better survival for TMC than for NMC. That TMC has a remarkably good prognosis has been observed by others [12–14], but the patient numbers in these studies were rather small (24, 26 and 27 TMC). Rapin and colleagues [13] concluded that the prognosis for TMC is so good that treatment can be less radical than for breast cancers in general. In our opinion, there is no basis for such a conclusion. In his recent paper on node-negative breast cancers [15], Fisher states that TMC follows an

Table 9. Distribution of histological parameters with significant prognostic impact in the combined population of breast carcinomas with medullary features, DBCG 77–87

Histopathological parameter	Frequency	(%)
Growth pattern		
Syncytial	189	(80.4)
Non-syncytial	46	(19.6)
Distribution of mononuclear cells		
Diffuse	193	(82.1)
Focal or borders only	42	(17.9)
Necrosis		
Sparse	182	(77.4)
Moderate and marked	53	(22.6)
Tubular component		
Present	24	(10.2)
Absent	211	(89.8)

intermediate survival, between NOS plus AMC and mucinous, tubular plus papillary forms; the latter having the best prognosis. Parallel to this, Fisher and colleagues in their recent study on MC [4], describing prognostic observations on 198 TMC and 149 AMC, found a significantly better prognosis for TMC than for IDC, not otherwise specified (NOS), in the node-negative untreated group, but found no statistically significant differences in the node-positive group. They concluded, with regard to TMC, that "although better than that of NOS form, the overall cumulative odds in negative and positive node patients are not great and may not be clinically important".

Fisher also stated that the description of a particular lesion should comply with the original description by those responsible for its identification [4]. To a clinician, a histological subgrouping of breast cancer is of value only if the specific histological characteristics offer the patient a different prognosis than the average one. It is important that the histological diagnosis is reproducible and that it is of consistent prognostic importance. If this is not the case, a remodelling of the diagnostic criteria should be performed until they meet these requirements. Neither the diagnostic criteria by Ridolfi [5] nor those by us [6] do so, but by performing the Cox analysis on the combined larger population we anticipated a better result.

Four parameters yielded significant prognostic information in the final Cox model: (1) predominantly syncytial growth pattern, (2) diffuse stromal infiltration with mononuclear cells (lymphocytes and plasma cells), (3) sparse necrosis (< 25%), and (4) no tubular component. As to syncytial growth, this particular growth pattern has been emphasized as being one of the major histopathological characteristics of MC since its definition by Foote and Stewart [16] and Moore and Foote [17] in the late 1940s [1, 7]. Inter- and intraobserver reproducibility concerning this parameter has been shown to be moderate to substantial [6, 7].

Regarding stromal infiltration with mononuclear cells, we found no significant prognostic information in the grade of infiltration; this is in agreement with the recent studies by Fisher [4] and Mitze [18], but in contrast to Ridolfi [5] and Wargotz and Silverberg [12]. However, a better prognosis with diffuse stromal mononuclear infiltration was demonstrated. To our knowledge, this observation has not been reported before. Inter- and intraobserver variability concerning the distribution of mononuclear infiltration has been reported to be fair to substantial [6].

As to the positive prognostic impact of sparse necrosis, this observation has not previously been reported in relation to MC. Fisher and colleagues [4] (in a Cox regression analysis after stratifying for the effect of nodes and protocol) and Mitze and associates [18] (in a univariate analysis on 55 patients) failed to reveal that the extent of necrosis influenced survival in MC. However, a negative prognostic impact of marked necrosis has been reported in relation to breast cancer generally [3, 15, 19]. A contrasting observation has also been reported [20]. Marked necrosis has been correlated with severe stromal cell reaction [3, 19], which was not correlated with a good prognosis. This is in agreement with our observation that distribution rather than grade of mononuclear stromal infiltration is correlated with prognosis; diffuse infiltration being correlated with the better prognosis. This observation may indicate that only tumour-associated mononuclear cells have a favourable impact on the outcome, whereas stromal mononuclear infiltration, triggered off by some local event in the tumour (e.g. necrosis), seems to be unimportant. In a previous study [6], evaluating the reproducibility of various morphological parameters, the reproducibility of the extent of necrosis was shown to be one of the best [6].

Concerning the fourth parameter retained in the Cox regression analysis, tubular component, we found that this was of least prognostic importance in the univariate analysis. In the Cox analysis, however, an interaction between growth pattern and tubular component was found. Syncytial growth pattern and no tubular component indicated the best prognosis. However, in the complementary group, in the tumours with non-syncytial growth pattern, the presence of a tubular component seemed to indicate the better prognosis. This is in concordance with the fact that IDC, featuring a high grade of tubular component, indicates a high grade of histological differentiation, which indicates a better prognosis. In the definition of Ridolfi and colleagues [5], the absence of microglandular features is part of the definition of TMC, but it seems that the authors did not analyse the prognostic importance of this parameter. In their studies, Rapin and colleagues [13] and Wargotz and Silverberg [12] adhered to the criteria of Ridolfi, and they also found a very good prognosis for TMC.

The described interaction of growth pattern and tubule component indicates that syncytial growth pattern as well as no tubular component should be included among the histopathological diagnostic criteria for MC. Neither circumscription, extension of stromal component, nuclear pleomorphism nor histological grade provided prognostic information. As to the latter two, these are important prognostic markers of breast cancer, generally, although other authors have also found no prognostic importance of these parameters in MC [18, 20, 21]. However, by definition, most MCs are histological or nuclear grade III [20, 21], and the remainder are grade II. Many previous studies have emphasized circumscription as one of the morphological markers of MC [3, 5, 22, 23], but its prognostic importance in MC has, to our knowledge, not been studied before. A sparse stromal component was stressed by Fisher and colleagues [3, 15], but again prognostic importance of extent of the stromal component in MC has, to our knowledge, not been studied before. We propose that (1) predominantly syncytial growth pattern, (2) no tubular component, (3) diffuse stromal infiltration with mononuclear cells and (4) sparse necrosis are emphasized in the histological diagnosis of MC.

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Histological Grade, Perineural Infiltration, Tumour-infiltrating Lymphocytes and Apoptosis as Determinants of Long-term Prognosis in Prostatic Adenocarcinoma

S. Vesalainen, P. Lipponen, M. Talja and K. Syrjänen

A series of 325 prostatic adenocarcinomas with a long-term clinical follow-up were subjected to light microscopic analysis of histological prognostic factors, including three grading systems (Gleason score, WHO grade, nuclear grade), perineural infiltration of the tumour (PNI), tumour infiltrating lymphocytes (TIL) and the presence of apoptotic cells (APO). All three histological classifications correlated significantly with the prognosis, but in multivariate analysis, the Gleason score was superior to the WHO grading or nuclear grading in predicting patient survival. PNI was significantly related to poor differentiation of the tumour, its progression and ominous disease outcome, particularly in T1–2MO tumours. The density of TIL was independent of the tumour differentiation, and absent or weak TIL were signs of a high risk of tumour progression and of a fatal disease. Apoptotic cells were commonly detected in poorly differentiated tumours and apoptosis was related to disease progression and low survival probability. The results suggest that the Gleason score, PNI and the density of TIL should be included in routine pathology reports, to be used by clinicians while making therapeutic decisions in prostatic cancer.

Key words: prostatic adenocarcinoma, Gleason score, WHO grade, nuclear grade, perineural infiltration, apoptosis, tumour infiltrating lymphocyte, progression, survival
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INTRODUCTION

PROSTATIC ADENOCARCINOMA is a clinically and biologically heterogeneous disease [1–6]. A proportion of tumours run an unfavourable course, while the majority of the tumours do not lead to death [6]. A number of histological grading systems have been introduced in prostatic adenocarcinoma to predict the disease outcome and to assist in selecting the proper therapy [1, 7, 8]. However, opinions differ as to which of the grading systems gives the best prognostic estimates. The Gleason score is based on histological architectural features alone [1], while the WHO grading system divides tumours into three malignancy grades on the basis of architectural and cellular features [7].