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Guidelines

Prognostic Performance and Reproducibility of the 1973 and 2004/2016 World Health Organization Grading Classification Systems in Non–muscle-invasive Bladder Cancer: A European Association of Urology Non-muscle Invasive Bladder Cancer Guidelines Panel Systematic Review

Viktor Soukup [a,*], *Otakar Čapoun* [a,*], *Daniel Cohen* [b], *Virginia Hernández* [c], *Marek Babjuk* [d], *Max Burger* [e], *Eva Compérat* [f], *Paolo Gontero* [g], *Thomas Lam* [h,i], *Steven MacLennan* [h], *A. Hugh Mostafid* [j], *Joan Palou* [k], *Bas W.G. van Rhijn* [l], *Morgan Rouprêt* [m], *Shahrokh F. Shariat* [n], *Richard Sylvester* [o], *Yuhong Yuan* [p], *Richard Zigeuner* [q]

[a] *Department of Urology, General Teaching Hospital and 1st Faculty of Medicine, Charles University in Praha, Praha, Czech Republic;* [b] *Department of Urology, Royal Free London NHS Foundation Trust, London, UK;* [c] *Department of Urology, Hospital Universitario Fundación de Alcorcón, Madrid, Spain;* [d] *Hospital Motol and Second Faculty of Medicine, Charles University, Department of Urology, Prague, Czech Republic;* [e] *Department of Urology, Caritas-St. Josef Medical Center, University of Regensburg, Germany;* [f] *Department of Pathology, Hôpitaux Universitaires de l'Est-Parisien HUEP, Assistance Publique Faculty of Medicine Pierre et Marie Curie, Institut Universitaire de Cancerologie GRC5, University Paris 6, Paris, France;* [g] *Department of Surgical Sciences, Urology, University of Turin, Turin, Italy;* [h] *Academic Urology Unit, University of Aberdeen, Scotland, UK;* [i] *Department of Urology, Aberdeen Royal, 12 Infirmary, Aberdeen, Scotland;* [j] *Department of Urology, Royal Surrey County Hospital, Guildford, UK;* [k] *Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain;* [l] *Department of Urology, Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [m] *Department of Urology, Groupe Hospitalier Pitie?—Salpêtrière, Assistance Publique Hopitaux de Paris, Faculty of Medicine Pierre et Marie Curie, Institut Universitaire de Cancérologie GRC5, University Paris 6, Paris, France;* [n] *Department of Urology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria;* [o] *EAU Guidelines Office Board, European Association of Urology, The Netherlands;* [p] *Department of Medicine, Health Science Centre, McMaster University, Hamilton, Ontario, Canada;* [q] *Department of Urology, Medizinische Universität Graz, Graz, Austria*

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Abstract

Context: Tumour grade is an important prognostic indicator in non–muscle-invasive bladder cancer (NMIBC). Histopathological classifications are limited by interobserver variability (reproducibility), which may have prognostic implications. European Association of Urology NMIBC guidelines suggest concurrent use of both 1973 and 2004/2016 World Health Organization (WHO) classifications.
Objective: To compare the prognostic performance and reproducibility of the 1973 and 2004/2016 WHO grading systems for NMIBC.
Evidence acquisition: A systematic literature search was undertaken incorporating Medline, Embase, and the Cochrane Library. Studies were critically appraised for risk of bias (QUIPS). For prognosis, the primary outcome was progression to muscle-invasive or metastatic disease. Secondary outcomes were disease recurrence, and overall and cancer-specific survival. For reproducibility, the primary outcome was interobserver variability between pathologists. Secondary outcome was intraobserver variability (repeatability) by the same pathologist.

* Corresponding authors. Department of Urology, General Teaching Hospital and 1st Faculty of Medicine, Charles University in Praha, Praha, Czech Republic. Tel. +420 224967847; Fax: +420 224967102.
E-mail addresses: viktor.soukup@seznam.cz (V. Soukup), otakar.capoun@seznam.cz (O. Čapoun).

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2004/2016 World Health Organization classification
Prognosis
Recurrence
Progression
Repeatability
Reproducibility

Evidence synthesis: Of 3593 articles identified, 20 were included in the prognostic review; three were eligible for the reproducibility review. Increasing tumour grade in both classifications was associated with higher disease progression and recurrence rates. Progression rates in grade 1 patients were similar to those in low-grade patients; progression rates in grade 3 patients were higher than those in high-grade patients. Survival data were limited. Reproducibility of the 2004/2016 system was marginally better than that of the 1973 system. Two studies on repeatability showed conflicting results. Most studies had a moderate to high risk of bias.
Conclusions: Current grading classifications in NMIBC are suboptimal. The 1973 system identifies more aggressive tumours. Intra- and interobserver variability was slightly less in the 2004/2016 classification. We could not confirm that the 2004/2016 classification outperforms the 1973 classification in prediction of recurrence and progression.
Patient summary: This article summarises the utility of two different grading systems for non–muscle-invasive bladder cancer. Both systems predict progression and recurrence, although pathologists vary in their reporting; suggestions for further improvements are made.

1. Introduction

Up to 70% of patients with non–muscle-invasive bladder cancer (NMIBC) have tumour recurrence, and about 10–15% progress to muscle-invasive disease [1]. Accurate prediction of tumour recurrence and progression is important to determine appropriate therapy and follow-up. Tumour grade is an important predictor of tumour prognosis [2]. However, histopathological classifications are known to be limited by inter- and intraobserver variability, which may have profound prognostic implications [3].

Current European Association of Urology (EAU) recommendations for grading of NMIBC indicate that both the 1973 and the 2004/2016 World Health Organization (WHO) classification should be used [4]. The 1973 classification distinguishes three different grades and evaluates microscopic features related to the degree of cellular atypia, necrosis, and mitotic activity. Grade 1 (G1) carcinomas (well-differentiated) are defined as showing only mild degrees of cytological atypia and infrequent mitotic figures. Grade 3 (G3) carcinomas (poorly differentiated) are defined as showing marked nuclear pleomorphism, loss of maturation from the base to the surface, and mitotic activity. Grade 2 (G2) carcinomas (moderately differentiated) comprise all tumours between these extremes [5]. The lack of clarity between the three grades may adversely affect prognostic prediction due to high intra- and interobserver variability. Furthermore, there is a tendency to classify the majority of tumours in the middle group (G2) [6].

In an attempt to reduce variability and increase reproducibility, a new grading system based on more detailed histological criteria has been promoted since 1998 by the International Society of Urological Pathology (ISUP) and was subsequently adopted by the WHO in 2004. The main aim was to standardise the classification and grading of urothelial neoplasms, creating a uniform terminology for use by pathologists and urologists [7,8]. Under the 2004 system, some G1 lesions are classified as papillary urothelial neoplasms with low malignant potential (PUNLMPs) and others are classified as low grade (LG); G2 lesions are classified as LG or high-grade (HG) urothelial carcinomas; G3 lesions as HG urothelial carcinomas (Fig. 1). Recently, an update of the 2004 WHO grading classification was published without substantial changes, so the 2004 WHO classification is now known as 2016 WHO classification [9].

By eliminating the heterogeneous moderately differentiated (G2) category of the 1973 system, the 2004/2016 classification was expected to provide a more reproducible stratification of patients with differing prognoses and well-defined recommendations for treatment and follow-up. However, several studies have shown considerable interobserver variability and its anticipated superior prognostic value is still a matter of debate [6,10].

This systematic review compares the prognostic performance and reproducibility of the 1973 WHO and 1998 ISUP/2004 WHO/2016 WHO grading systems for NMIBC.

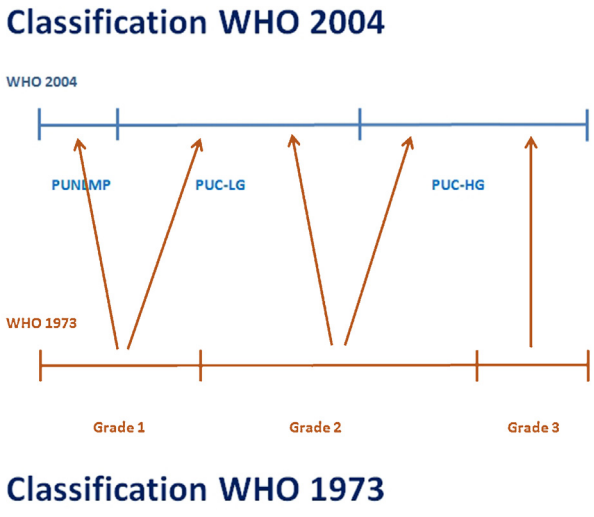

Fig. 1 – Stratification of tumours according to grade in the 1973 and 2004 WHO classifications. PUNLMP = papillary urothelial neoplasm with low malignant potential; PUC-LG = papillary urothelial carcinoma—low grade; PUC-HG = papillary urothelial carcinoma—low grade; WHO = World Health Organization.