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# A clinical prognostic model compared to the newly adopted UICC staging in an independent validation cohort of P16 negative/positive head and neck cancer patients

Jacob H. Rasmussen[a,*], Katrin Håkansson[b], Gregers B. Rasmussen[b], Ivan R. Vogelius[b], Jeppe Friborg[b], Barbara M. Fischer[c], Søren M. Bentzen[d], Lena Specht[b]

[a] Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Denmark
[b] Department of Oncology, Section of Radiotherapy, Rigshospitalet, University of Copenhagen, Denmark
[c] Department of Clinical Physiology, Nuclear Medicine & PET, PET & Cyclotron Unit, Rigshospitalet University of Copenhagen, Denmark
[d] Division of Biostatistics and Bioinformatics, University of Maryland Greenebaum Cancer Center, and Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, USA

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ABSTRACT

*Objectives:* A previously published prognostic model in patients with head and neck squamous cell carcinoma (HNSCC) was validated in both a p16-negative and a p16-positive independent patient cohort and the performance was compared with the newly adopted 8th edition of the UICC staging system.

*Materials and methods:* Consecutive patients with HNSCC treated at a single institution from 2005 to 2012 were included. The cohort was divided in three. 1.) Training cohort, patients treated from 2005 to 2009 excluding patients with p16-positive oropharyngeal squamous cell carcinomas (OPSCC); 2.) A p16-negative validation cohort and 3.) A p16-positive validation cohort. A previously published prognostic model (clinical model) with the significant covariates (smoking status, FDG uptake, and tumor volume) was refitted in the training cohort and validated in the two validation cohorts. The clinical model was used to generate four risk groups based on the predicted risk of disease recurrence after 2 years and the performance was compared with UICC staging 8th edition using concordance index.

*Results:* Overall 568 patients were included. Compared to UICC the clinical model had a significantly better concordance index in the p16-negative validation cohort (AUC = 0.63 for UICC and AUC = 0.73 for the clinical model; $p = 0.003$) and a borderline significantly better concordance index in the p16-positive cohort (AUC = 0.63 for UICC and 0.72 for the clinical model; $p = 0.088$).

*Conclusion:* The validated clinical model provided a better prognostication of risk of disease recurrence than UICC stage in the p16-negative validation cohort, and similar prognostication as the newly adopted 8th edition of the UICC staging in the p16-positive patient cohort.

## Introduction

Various treatment approaches are available for patients with non-metastatic head and neck squamous cell carcinoma (HNSCC) including radiation as monotherapy or in combination with systemic therapy and/or surgery. Currently, several trials testing treatment de-intensification in low risk patients are in progress [1] and a few phase I trials testing treatment intensification in patients with assumed high risk of recurrence has been conducted [2–4]. In both cases, it is important to select the appropriate study population for each trial. To this end, the TNM classification from the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) staging system is still the primary prognostic tool for patients with HNSCC [5].

Prior to the 8th edition of UICC, the AJCC/UICC staging system included anatomical information but did not consider other prognostic information such as smoking and alcohol [6,7] or associated tumor biology assessed with immunohistochemical [8–11] or functional imaging [12–14] biomarkers. Currently, the most important prognostic subgroup in HNSCC is the human papilloma virus (HPV) related

* Corresponding author at: Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet F-2074, Blegdamsvej 9, 2100 Copenhagen, Denmark.
*E-mail addresses:* jacob.hoeygaard.rasmussen.01@regionh.dk (J.H. Rasmussen), katrin.elisabet.haakansson@regionh.dk (K. Håkansson), dr.gregers@gmail.com (G.B. Rasmussen), ivan.richter.vogelius@regionh.dk (I.R. Vogelius), jeppe.friborg@regionh.dk (J. Friborg), barbara.malene.fischer@regionh.dk (B.M. Fischer), sbentzen@som.umaryland.edu (S.M. Bentzen), lena.specht@regionh.dk (L. Specht).

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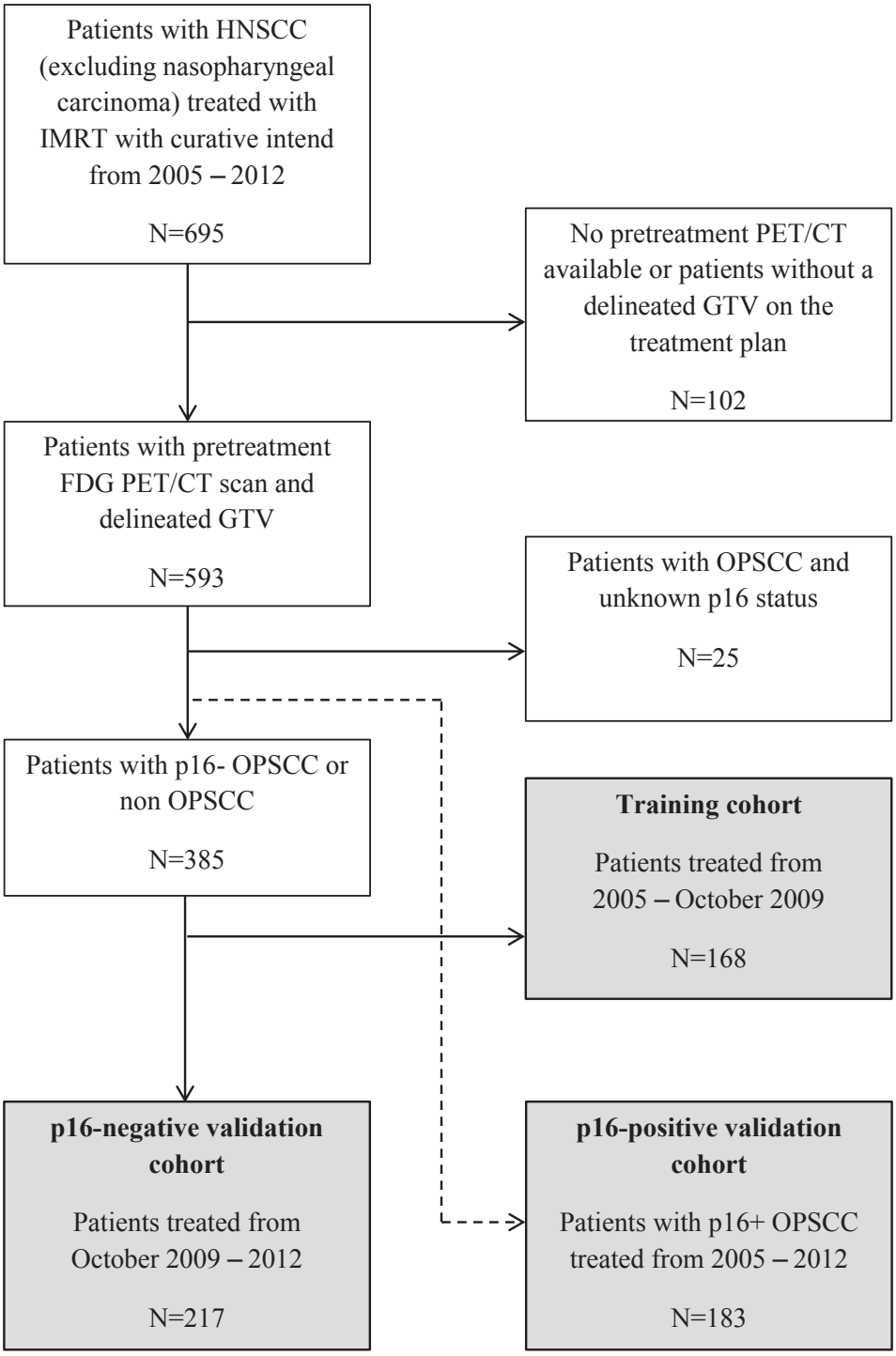


**Fig. 1.** Flowchart of patient's inclusion in the three cohorts.

oropharyngeal carcinoma usually assessed by p16 status [15,16]. The incidence of HPV related OPSCC is increasing [17,18] and numerous studies have shown that patients with p16-positive oropharyngeal squamous cell carcinomas (p16-positive OPSCC) have a much better prognosis thus challenging the traditional UICC staging system [19,20]. This has led to a change in the 8th edition of UICC with a new classification for p16-positive OPSCC as suggested amongst others by the International Collaboration on Oropharyngeal cancer Network for Staging [21]. Except for the p16-positive selection this new classification is an anatomical staging system and does not include other prognostic information [22,23]. The AJCC/UICC staging algorithms are built on survival as the sole endpoint. However, far from all HNSCC patients die from their cancer, and especially in p16-negative patients some deaths are related to lifestyle associated comorbidities. Hence, disease recurrence remains an important endpoint in HNSCC.

Evidently, the paradigm of personalized medicine could be furthered by individualized prognostication beyond p16 status and UICC stage. Even though several studies in HNSCC have tested the prognostic importance of both imaging [24] and biologic biomarkers [25] using other endpoints than survival, none of these are broadly implemented in the clinic for a variety of reasons [26], such as lack of demonstrated clinical utility, validation, and documented superiority over