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Nomogram-based Prediction of Overall Survival in Patients with Metastatic Urothelial Carcinoma Receiving First-line Platinum-based Chemotherapy: Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC)

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Abstract

Background: The available prognostic models for overall survival (OS) in patients with metastatic urothelial carcinoma (UC) have been derived from clinical trial populations of cisplatin-treated patients.
Objective: To develop a new model based on *real-world* patients.
Design, setting, and participants: Individual patient-level data from 29 centers were collected, including metastatic UC and first-line cisplatin- or carboplatin-based chemotherapy administered between January 2006 and January 2011.
Intervention: First-line, platinum-based, combination chemotherapy.

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Outcome measurements and statistical analysis: The population was randomly split into a development and a validation cohort. Generalized boosted regression modelling was used to screen out irrelevant variables and address multivariable analyses. Two nomograms were built to estimate OS probability, the first based on baseline factors and platinum agent, the second incorporating objective response (OR). The performance of the above nomograms and that of other available models was assessed. We plotted decision curves to evaluate the clinical usefulness of the two nomograms.
Results and limitations: A total of 1020 patients were analyzed (development: 687, validation: 333). In a platinum-stratified Cox model, significant variables for OS were performance status ($p < 0.001$), white blood cell count ($p = 0.013$), body mass index ($p = 0.003$), ethnicity ($p = 0.012$), lung, liver, or bone metastases ($p < 0.001$), and prior perioperative chemotherapy ($p = 0.012$). The c-index was 0.660. The distribution of the nomogram scores was associated with OR ($p < 0.001$), and incorporating OR into the model further improved the c-index in the validation cohort (0.670).
Conclusions: We developed and validated two nomograms for OS to be used before and after completion of first-line chemotherapy for metastatic UC.
Patient summary: We proposed two models for estimating overall survival of patients with metastatic urothelial carcinoma receiving first-line, platinum-based chemotherapy. These nomograms have been developed on real-world patients who were treated outside of clinical trials and may be used irrespective of the chemotherapeutic platinum agent used.

1. Introduction

After several decades of therapeutic stagnation in the field of urothelial carcinoma (UC), the advent of immunotherapy, that has just revitalized the therapeutic landscape of salvage therapy options, holds promise to also change the paradigm in the first-line metastatic setting [1–4]. Therefore, there is growing interest in developing a new prognostic model that would allow investigators to compare results of experimental and standard therapies and that can be easily used in all patients in clinical practice. Many prognostic factors have been proposed over the last 15 yr, and many of them were derived from clinical trial cohorts or small single-center experiences. These factors included performance status (PS) and the presence of visceral (ie, lung, liver, or bone) metastases [5,6]. Subsequently, these characteristics have been augmented with additional factors like albumin, hemoglobin, leukocyte count, and number of metastatic sites [7,8]. In general, all models have relied on clinical trial populations and included cisplatin-treated patients only. However, we know that almost half of the patients who require systemic therapy for metastatic UC are not considered eligible for cisplatin treatment for many reasons, and carboplatin is used instead, despite its documented inferior efficacy [9,10]. Currently, there are no prognostic models for carboplatin-treated patients, and some investigators are now questioning the need to separate cisplatin-treated patients from carboplatin-treated patients in clinical trials [11].

If available, a unique prognostic model covering both of these therapeutic options would be more applicable in *real-world* practice as well as for better clinical trial planning. An additional benefit would be the possibility of updating the prognostic assessment on the basis of the response to chemotherapy observed in individual patients. The little information that is currently available is one post-treatment nomogram, which is also based on a cisplatin-treated and trial-based patient population [12].

2. Patients and methods

2.1. Patient selection

The Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC) is a retrospective study including individual patient-level data from patients with muscle-invasive or advanced UC or non-UC histology who have received systemic therapy in any clinical setting. This contemporary database includes data gathered from January 1, 2006 to January 1, 2011 from hospitals in the USA, Europe, Israel, and Canada.

At the end of October 2015, data were extracted to select patients who fulfilled the following characteristics: (1) any tumor primary site, (2) predominant UC histology, (3) de novo metastatic UC (including regional lymph nodes or distant metastatic disease) or relapse after radical surgery, and (4) administration of cisplatin- or carboplatin-containing chemotherapy in the first-line metastatic setting. Data analysis was performed at the Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy. The present study was approved by the ethics committees at each participating institution.

2.2. Statistical analyses

The study objective was to determine the prognostic features associated with overall survival (OS) in a large contemporary cohort of patients with metastatic UC treated with platinum-based chemotherapy outside of clinical trials. Accordingly, a nomogram for OS prediction was developed, including selected baseline factors and the platinum agent. An additional aim was to investigate the possible surrogate or prognostic role of the objective response (OR) to first-line chemotherapy to improve nomogram predictions. OR was assessed at each site by the local investigators. Descriptive statistics were used to summarize baseline characteristics, treatments, and outcomes. The Kaplan-Meier method was used for estimation of progression-free survival (PFS) and OS, while the reverse Kaplan-Meier method described by Schemper and Smith [13] was used for follow-up quantification.

The analyses were performed using a split-sampling strategy: the overall sample was randomly split with stratification by center into development and validation cohorts. The former was used for model building, and the latter was used only for model testing purposes.

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