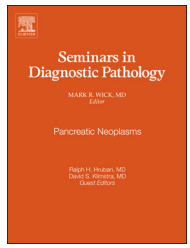
Seminars in Diagnostic Pathology 32 (2015) 172–183

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/semdp



Outcome prediction for patients with renal cell carcinoma

Christine M. Lohse, MS[a], *Sounak Gupta, MD*[b], *John C. Cheville, MD*[b,*]

[a]*Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota*
[b]*Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First St, Southwest Rochester, Minnesota 55905*

ARTICLE INFO

ABSTRACT

Outcome assessment for renal cell carcinoma is somewhat controversial. Despite numerous studies, a very limited variety of features have been recognized as having prognostic significance in clinical practice. In this review, tumor features considered to be of importance in outcome prediction for surgically treated patients with the 3 most commonly encountered morphotypes of renal cell carcinoma (clear cell, papillary, and chromophobe renal cell carcinoma) are evaluated. In particular, we have focused upon histologic subtype, sarcomatoid and rhabdoid differentiation, TNM staging, primary tumor size, tumor grade, and the presence of histologic coagulative tumor necrosis. We have also examined the importance of these prognostic features in a variety of postoperative or outcome prediction models developed by several institutions.

Introduction

Renal cell carcinoma (RCC) was diagnosed in an estimated 32,000 patients in the United States in 2014, with approximately 11,000 estimated deaths.[1] Of note, the incidence and mortality rates for RCC have risen steadily over the past several decades between both genders, trends that are not explained by the increased use of abdominal imaging alone.[2,3] Prognosis for patients with RCC is known to be related to a number of pathologic features, including the TNM classification and grade, which have been incorporated into prognostic models by Memorial Sloan-Kettering Cancer Center, University of California Los Angeles (UCLA), and our own institution.

Herein, pathologic features important in outcome prediction for patients treated surgically for the 3 most common subtypes of RCC are reviewed, including histologic subtype, sarcomatoid and rhabdoid differentiation, the TNM classification, primary tumor size, grade, and histologic coagulative tumor necrosis. We then examine how these features have been incorporated into postoperative prognostic or outcome prediction models developed by several institutions and used in clinical practice. Throughout, the distributions of pathologic features and their impact on patient outcome are summarized using data from 4380 patients in the Mayo Clinic Nephrectomy Registry treated with radical or partial nephrectomy for clear cell ($n = 3521$), papillary ($n = 627$), and chromophobe ($n = 232$) RCC between 1970 and 2009.

Pathologic features used in outcome prediction models

Histologic subtype

In 1997, an international consensus conference on RCC sponsored by the Union Internationale Contre le Cancer

* *Corresponding author.*
E-mail address: cheville.john@mayo.edu (J.C. Cheville).

http://dx.doi.org/10.1053/j.semdp.2015.02.008
0740-2570/

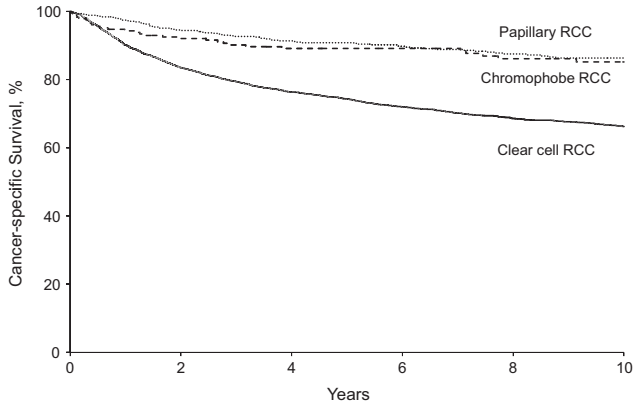


Fig. 1 – Cancer-specific survival rates (95% CI, number still at risk) at 5 years following surgery are 74% (73–76; 2101), 91% (89–93; 448), and 89% (85–93; 157) for patients with clear cell, papillary, and chromophobe RCC, respectively. There are significant differences in outcome among the 3 subtypes ($p < 0.001$) but not between patients with papillary and chromophobe RCC ($p = 0.54$).

(UICC) and the American Joint Committee on Cancer (AJCC) outlined recommendations for the classification of RCC.[4] The UICC/AJCC adopted the classification system originally proposed at the Heidelberg conference in 1996.[5] The participants at both the conferences proposed that RCC be categorized as clear cell, papillary, chromophobe, and collecting duct RCC subtypes. In addition, RCC that does not fall into one of these 4 groups is classified as RCC, not otherwise specified. Since that time, a number of additional less common histologic subtypes have been recognized, yet the 3 most common subtypes of clear cell, papillary, and chromophobe RCC continue to comprise over 90% of RCCs.[6]

Significant differences in pathologic features exist among the 3 most common histologic subtypes. Specifically, patients with clear cell RCC present with higher grade and stage tumors than patients with papillary and chromophobe RCC. In addition, papillary RCC is significantly more likely to be multifocal and exhibit tumor necrosis compared with the other subtypes.

There are also significant differences in outcome among the histologic subtypes.[7–13] The cancer-specific survival rates at 5 years following surgery for patients with clear cell, papillary, and chromophobe RCC in our registry are 74%, 91%, and 89%, respectively (Fig. 1; $p < 0.001$). Patients with clear cell RCC have a worse prognosis compared with patients with papillary and chromophobe RCC, and there is not a statistically significant difference in outcome between patients with papillary and chromophobe RCC ($p = 0.54$). In our experience, clear cell RCC is a significant predictor of metastases and cancer-specific death in multivariable analyses that adjust for tumor size, stage, and grade.[7,8] However, cystic clear cell RCC, which accounts for 4% of clear cell RCC in our registry, is invariably associated with an excellent outcome regardless of the type of surgical intervention.[14]

Given the predominance of clear cell RCC in previous surgical series and the lack of central pathologic review in some contemporary studies, differences in outcome among the histologic subtypes stratified by tumor stage and grade have not been apparent. With larger numbers and standardized pathologic review, significant differences in outcome are evident even after stratifying by stage and grade.[7,8] For example, in our registry, the 5-year cancer-specific survival rates for grade 3 clear cell and papillary RCC are 61% and 84%, respectively ($p < 0.001$), indicating that grade 3 papillary RCC does not follow the same clinical course as grade 3 clear cell RCC. Furthermore, the impact of other prognostic features such as tumor necrosis differs among the histologic subtypes. For example, in our registry, the hazard ratios for the associations of tumor necrosis with death from RCC among patients with clear cell and chromophobe RCC are 5.8 ($p < 0.001$) and 5.0 ($p < 0.001$), respectively, whereas the hazard ratio among patients with papillary RCC is 2.2 ($p = 0.001$), demonstrating that the magnitude of the effect of tumor necrosis on outcome varies by histologic subtype.

Sarcomatoid and rhabdoid differentiation

Sarcomatoid RCC was first described by Farrow et al.[15] as an RCC containing enlarged pleomorphic or malignant spindle cells reminiscent of a sarcoma. In the past, sarcomatoid RCC was considered a distinct subtype; however, this was dropped from the 1997 UICC/AJCC and Heidelberg classification since sarcomatoid differentiation can arise among all histologic subtypes.[4,5]

Previous studies indicate that the presence of sarcomatoid differentiation in RCC is associated with a dismal prognosis, with a median survival following diagnosis of less than 1 year.[16–24] As a result of the small number of patients with sarcomatoid differentiation and the aggressive nature of these tumors, few studies have identified prognostic factors for patients with sarcomatoid differentiation, although TNM stage, performance status, tumor size, tumor necrosis, and presence of metastases have been associated with outcome in various studies.[16–24]

The incidence of sarcomatoid differentiation in RCC in our registry is 4%. Cancer-specific survival rates at 2 years following surgery for patients with clear cell, papillary, and chromophobe RCC with sarcomatoid differentiation are 28%, 56%, and 42%, respectively, compared with 86%, 95%, and 96%, respectively, for patients with clear cell, papillary, and chromophobe RCC without sarcomatoid differentiation. In studies by Ro et al.,[17] de Peralta-Venturina et al.,[21] Mian et al.,[22] and Cheville et al.,[23] the underlying histologic subtype was not significantly associated with outcome among patients with sarcomatoid differentiation, in contrast to the effect of subtype on outcome among patients without sarcomatoid differentiation.

Several studies have shown that metastases at the time of surgery and tumor necrosis are significantly associated with outcome among patients with sarcomatoid differentiation.[17,22,23] Shuch et al.[24] reported that Eastern Cooperative Oncology Group performance status, tumor size, and metastases were independent predictors of outcome in 104 patients with sarcomatoid differentiation; microvascular invasion, percentage of sarcomatoid differentiation, and percentage of tumor necrosis were strongly associated with outcome but were not independent predictors. Similarly, other studies have found a significant association between