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Original article

Statin use is associated with improved survival in patients undergoing surgery for renal cell carcinoma

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Abstract

Purpose: To determine whether statin use at time of surgery is associated with survival following nephrectomy or partial nephrectomy for renal cell carcinoma (RCC). Statins are thought to exhibit a protective effect on cancer incidence and possibly cancer survival in a number of malignancies. To date, no studies have shown an independent association between statin use and mortality in RCC.

Methods: A retrospective cohort study of 916 patients who underwent radical or partial nephrectomy for RCC from 2000 to 2010 at a single institution was performed. Primary outcomes were overall (OS) and disease-specific survival (DSS). Univariable survival analyses were performed using the Kaplan-Meier and the log-rank methods. Multivariable analysis was performed using a Cox proportional hazards model. The predictive discrimination of the models was assessed using the Harrell *c*-index.

Results: The median follow-up of the entire cohort was 42.5 months. The 3-year OS estimate was 83.1% (95% CI: 77.6%–87.3%) for statin users and 77.3% (95% CI: 73.7%–80.6%) for nonstatin users ($P = 0.53$). The 3-year DSS was 90.9% (95% CI: 86.3%–94.0%) for statin users and 83.5% (95% CI: 80.1%–86.3%) for nonstatin users ($P = 0.015$). After controlling for age, American Society of Anesthesiology class, pT category, pN category, metastatic status, preoperative anemia and corrected hypercalcemia, and blood type, statin use at time of surgery was independently associated with improved OS (hazard ratio = 0.62; 95% CI: 0.43–0.90; $P = 0.011$) and DSS (hazard ratio = 0.48; 95% CI: 0.28–0.83; $P = 0.009$). The multivariable model for DSS had excellent predictive discrimination with a *c*-index of 0.91.

Conclusions: These data suggest that statin usage at time of surgery is independently associated with improved OS and DSS in patients undergoing surgery for RCC.

Keywords: Statins; Nephrectomy; Partial nephrectomy; Renal cell carcinoma

1. Introduction

Nearly 65,000 new cases of renal cell carcinoma (RCC) are diagnosed each year in the United States, and it is expected to account for almost 13,500 deaths in 2012 [1]. Surgery, by nephron-sparing approaches or radical nephrectomy, is the

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mainstay of curative treatment for RCC [2]. Several predictors of mortality after nephrectomy for locoregional RCC have been identified, including age, race, gender, stage, grade, tumor size, nutritional status, performance status, and ABO blood type [3–6]. Although these risk factors may provide important prognostic information, with exception to nutritional status, most provide little potential for intervention to alter the course of the disease.

Supported by a number of epidemiologic risk studies, there has been an increasing interest in the antineoplastic properties of statins in recent years [7–13]. Statins are widely used cholesterol-lowering medications that act by inhibiting 3-hydroxy-3-methyl glutaryl-coenzyme A reductase, the rate-limiting enzyme of the mevalonate pathway. Disruption of this pathway is thought to inhibit cancer growth and metastasis by affecting critical cellular functions, including cell proliferation, maintenance of membrane integrity, cell signaling, protein synthesis, and cell-cycle progression [14].

Despite plausible mechanistic links for a protective role of statins in the development of cancer, epidemiologic studies evaluating the association between statin use and cancer risk have been controversial [14–18]. Although earlier studies had suggested an increased risk of cancer associated with statin use, other studies have reported a neutral effect, and the remaining have described protective effects for some cancers of up to a 50% relative risk reduction in cancer incidence [7,8,10,18,19]. Results from the evaluation of statin use and cancer-related mortality have been mixed as well, although a recent, well-performed nationwide study of patients with cancer in the Danish population found a 15% reduction in cancer-related mortality associated with statin use [13,18,20].

A limited number of studies have evaluated statin use and the risk of developing RCC, with conflicting results [7,11,12,21,22]. A nested case-control study of almost 500,000 veteran patients in the south-central United States found a 48% risk reduction of RCC associated with statin use [11]. More recently, a smaller, prospective population-based study of 2 cohorts of US health professionals confirmed this protective effect of statins on the risk of developing RCC, but only in women without a history of hypertension [12]. In regard to statins and prognosis after surgery for RCC, a recent single-institution study suggested a significant association between statin use at time of surgery and RCC progression (defined as development of metastases or RCC-specific death), although this result was not statistically significant when modeling statin usage as a time-dependent postoperative variable and when accounting for those who initiated statin therapy after surgery for RCC [23]. Furthermore, statin use at time of surgery for RCC was not independently associated with overall survival (OS), and no independent analysis of disease-specific survival (DSS) was reported. Therefore, although statin use has been associated with reduced cancer-related mortality in other malignancies, its effect on RCC prognosis following surgical treatment has not been definitively established [13,23]. We therefore sought to evaluate whether statin use is associated with survival following surgery for RCC. Given the evidence supporting a protective effect of statins in cancer as well as the presumed metabolic nature of RCC, we hypothesized that current statin use at time of surgery would be associated with improved OS and DSS in patients undergoing radical or partial nephrectomy for RCC [24].

2. Patients and methods

We performed a retrospective cohort study of 916 consecutive patients with information on statin use who underwent radical or partial nephrectomy for RCC of all stages from 2000 to 2010. All RCC histologic subtypes were included. All surgeries were performed at Vanderbilt University Medical Center, with preoperative evaluation and postoperative care standardized to institutional protocol. Follow-up was at the discretion of the treating physician. Cause of death was determined by the treating physicians, death certificate, and medical chart review.

A staff surgical pathologist evaluated all surgical specimens. Stage and grade were assigned according to the 2010 American Joint Committee on Cancer guidelines and Fuhrman grading system, respectively. Clinical, pathologic, and survival data were collected prospectively and were supplemented by medical chart review. Institutional review board approval was obtained for the creation of a prospective database and for retrospective analysis of this cohort.

The primary outcome measures in this study were OS and DSS. The duration of follow-up was the time from surgery to the date of death or last clinic visit. Patients who were alive at last follow-up were censored for OS and DSS analysis; those who died of causes other than RCC were censored for DSS.

We evaluated clinical and pathologic variables including age, sex, race (white vs. nonwhite), American Society of Anesthesiology (ASA) physical status classification system, body mass index, preoperative anemia (hematocrit $<41\%$ for men and $<36\%$ for women), preoperative hypoalbuminemia (albumin <3.5 g/dl), preoperative corrected hypercalcemia ([preoperative calcium $=$ 0.707 * (preoperative albumin $=$ 3.4)] >10 mg/dl), Fuhrman nuclear grade (I–II vs. III–IV), pathologic T category, node status, presence of metastasis, tumor histology (clear cell vs. non–clear cell), procedure performed (radical vs. partial nephrectomy), red blood cell transfusion status, ABO blood group (type O vs. non-O), and statin use at time of surgery. Patients without radiographic or palpable evidence of lymphadenopathy generally did not undergo lymphadenectomy (Nx) and were grouped with patients with N0 lesions for analysis.

2.1. Statistical analysis

The relationship between statin use and clinicopathologic variables was assessed using the chi-square tests. Univariable survival analyses were performed using the