Original Article

Patient outcome and prognostic factors of renal cell carcinoma in clinical stage T1-3N1-2M0: a single-institution analysis

CHEN Zhuang-fei, WU Peng, ZHENG Shao-bin, ZHANG Peng, TAN Wan-long, MAO Xiang-ming

Department of Urology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

Abstract: Objective To report our data of patients with clinical stage T1-3N1-2M0 renal cell carcinoma (RCC) and explore the biological behavior of this malignancy. Methods A total of 531 patients with no distant metastatic RCC underwent open radical nephrectomy at our institution between 1988 and 2008, among whom 42 patients with histological nodal metastases had successful surgical tumor resection. The clinical data and outcomes of the 42 patients were analyzed. Results Of those 42 patients, 19.0% had T1, 21.4% had T2, and 59.5% had T3 stage tumors; 42.9% had N1 and 57.1% had N2 stage tumors. Tumor recurred in 30 (71.4%) patients after the surgery, and death occurred in 26 (61.9%) cases at the last follow-up; among the recurrent cases, 83.3% (25/30) had multiple metastases at the initial recurrence. The median cancer-specific survival (CSS) and disease-free survival (DFS) was 23 and 11 months in these cases, respectively. Multivariate analysis demonstrated that Fuhrman grade (P=0.005), N stage (P=0.014) and T stage (P=0.037) were the independent predictors of CSS; Eastern Cooperative Oncology Group (ECOG) performance status (PS) (P=0.002), tumor size (P=0.007), Fuhrman grade (P=0.009) and N stage (P=0.019) were the independent predictors of DFS. Conclusion Patients with T1-3N1-2M0 RCC have poor prognosis. N stage is an independent predictor of both CSS and DFS, suggesting that extended lymph node dissection should be performed when suspicious enlarged nodal disease is found during surgery.

Key words: renal cell carcinoma; prognosis; multivariate analysis; lymph node dissection

Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of adult malignancies and 85% of all primary malignant kidney tumors \(^1\) , and its incidence and mortality rate are still rising worldwide at a rate of approximately 2%-3% per decade \(^2\). The overall risk of lymph node metastasis is approximately 20%, varying significantly in published literature \(^3\) possibly due to patient selection, the extent of lymph node dissection (LND) and the presence or absence of distant metastasis. The rate of nodal metastasis in the absence of distant tumor metastasis is relatively low \(^4\). So far the documentation of the outcome of RCC patients with exclusive lymph node metastasis remains scarce.

Lymph node involvement in RCC is often associated with a poor survival \(^5\). With a highly heterogeneous nature, RCC presents with marked variability in the disease behavior, histology and molecular biology \(^6\). An accurate prediction of the outcome and prognosis after surgical resection is valuable for adjuvant trial design, counseling, and effective scheduling follow-up visits and imaging studies \(^7\). The application of current prognosticators in patients with nodal metastasis in the absence of distant tumor metastasis is controversial. In this study, we report our clinical data of patients with T1-3N1-2M0 RCC and explore the outcome and clinical predictors of the malignancy.

Patients and Methods

With Institutional Review Board approval, a retrospective study was performed based on a chart review of the demographic, clinical and pathological data of patients with RCC. A total of 531 patients without distant metastases underwent open radical nephrectomy (RN) at Nanfang Hospital between January 1988 and December 2008. Of those patients, 45 had histological nodal metastases, including 42 receiving successful radical tumor resection with a negative margin during surgery and 3 without total resection of the primary tumor or/and nodal involvement. The clinical data of the 42 patients with successful total tumor resection were analyzed in this study.

The tumor stage was determined according to the recommendations of the American Joint Committee on Cancer/ UICC TNM classification system (1997) \(^8\). T stage and N stage were defined by pathological examination, and M stage was defined by perioperative radiographic or pathological findings. Tumor grade was determined according to the 4-tiered Fuhrman system. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was determined preoperatively.

All the 42 patients had radical nephrectomy (RN) in conjunction with extended LND for curative intent. For right-sided tumors, the dissection included the hilar,
para-caval, pre-caval, post-caval, interaortocaval and pre-aortic lymph nodes, while for left-sided ones, the hilar, para-aortic, per-aortic, retro-aortic, interaortocaval and pre-caval nodes were dissected. All the surgeries were performed via an abdominal incision. All the nodal involvement was confined to the retroperitoneum as defined by perioperative radiographic imaging (CT or MRI) and pathological examinations.

Regular follow-up examinations were scheduled in all the patients at the end of the first postoperative month, every 3 months in the first and the second years, every 6 months in the third year, and then on an annual basis thereafter. Each follow-up examination consisted of a general physical examination, laboratory examinations, and a chest X-ray. The patients underwent CT scans at 3 months after the surgery, and then once every 6 to 12 months, with additional scans in cases of suspected tumor recurrence. Enhanced CT scan was performed in patients with suspicion of bone metastasis.

Statistical analyses were carried out using SPSS 13.0 statistical software package. The cancer-specific survival (CSS) and disease-free survival (DFS) curves were plotted by the Kaplan-Meier method and compared by the log-rank test. Univariate and multivariable Cox proportional hazard regression analyses were used to assess the effect factors of CSS and DFS in the 42 patients, including age, tumor size, histological subtype, Fuhrman grade, N stage, T stage, adjuvant therapy and ECOG PS. Tumor necrosis was not taken into consideration as the majority of the patients (39/42, 92.9%) showed necrotic foci in the tumor. Two-tailed tests were used for all comparisons, and a P value less than 0.05 was considered to denote a statistical significance.

Results

Clinical characteristics of the patients

Tab.1 shows the clinical and pathological characteristics of the 42 patients with T1-3N1-2M0 RCC, who had a negative margin during surgery. The median tumor size was 9.5 cm (ranging from 5.0 to 20.0 cm). Most of the patients had T3 (59.5%) RCC, followed by T2 (21.4%) and T1 (19.0%). N1 RCC and N2 RCC were found in similar proportions of the patients (42.9% vs 57.1%).

Of the 42 patients, 32 were suspected to have positive nodes before or/and during surgery, and 10 showed no evidence of nodal metastases before and during surgery. Adjuvant therapy was administered in 17 cases after the surgery, which consisted of at least one treatment course of immunotherapy (IL-2 and IFN-α) or chemotherapy (5-Fu, Gemcitabine). None of the patients received targeted therapy.

Cancer-specific survival

The median follow-up time was 15.5 months (ranging from 4 to 130 months). Death occurred in 26 cases (61.9%), and 16 (38.1%) patients completed the last follow-up. The median CSS was 23 months with the 1-, 3- and 5-year CSS rates of 72.3%, 32.0% and 22.4%, respectively (Fig.1a). The CSS did not show significant variations with the tumor size (P=0.081, Fig.1b), T stage (P=0.086, Fig.1c), histological subtype (P=0.593, Fig.1d), ECOG PS (P=0.248, Fig. 1e) or adjuvant therapy (P=0.632, Fig.1f).

Significant differences in CSS were found between patients with different Fuhrman grades (P=0.029, Fig.1g) and N stages (P=0.018, Fig.1h), and also between patients with multiple metastases and solitary metastases at the initial recurrence (P=0.001, Fig.2).

Univariate analysis demonstrated that Fuhrman grade (P=0.036) and N stage (P=0.024) were significant predictors of CSS. Multivariate analysis showed that the Fuhrman grade (G4 vs G2/3, HR 3.4, P=0.005), N stage (N2 vs N1, HR 3.2, P=0.014) and T stage (T3 vs T1, HR 3.7, P=0.037) were independent predictors of CSS. Fuhrman grade was the strongest independent predictor, and patients with grade 4 was 3.4 times more likely to die of the disease than patients with grade 2/3 disease (P=0.005, Tab.2).

Disease-free survival

Thirty (71.4%) patients showed tumor recurrence and 12 (28.6%) had no evidence of recurrence at the last follow-up. In the recurrent patients, 25 (83.3%) had multiple metastases and 5 (16.7%) had solitary metastases at the initial recurrence; 14 had metastases involving more than one organ, including 7 with both lung and bone metastases and 3 with both lung and
retroperitoneal metastases. The most common site of metastases was the lung, occurring in 20 (66.7%) of the patients, followed by the bones (13 cases), retroperitoneum (9 cases, among which only 2 had renal fossa recurrence), brain (1 case), liver (1 case), colon (1 case), and chest wall (1 case).

The median DFS of the patients was 11 months (Fig. 3a). The DFS did not differ significantly with the histological subtype (P=0.059, Fig. 3b), T stage (P=0.056, Fig. 3c) or the administration of adjuvant therapy (P=0.720, Fig. 3d). The DFS varied significantly with the tumor size (P=0.033, Fig. 3e), Fuhrman grade (P=0.041, Fig. 3f), pN stage (P=0.033, Fig. 3g) and ECOG PS (P=0.012, Fig. 3h).

Univariate analysis indicated that the tumor size (P=0.044), N stage (P=0.043) and ECOG PS (P=0.026) were significant predictors of DFS. ECOG PS (P=0.005), Tumor size (P=0.007), Fuhrman grade (P=0.009) and N stage (P=0.019) were identified as the independent predictors of DFS by multivariate analysis. PS1 (HR, 4.1, P=0.018) and PS2 (HR, 7.5, P=0.002) were associated with greater likelihood of recurrence than PS0, and patients with a tumor size ≥9.5 cm were 3.6 times more likely to have recurrence than those with a smaller tumor size (P=0.007, Tab. 4).

**Discussion**

Exclusive nodal metastasis without distant
metastasis is rare in RCC patient, and only a few reports have been available to describe the results of this subset of patients. The incidence of TanyN1-2M0 RCC, according to the published reports, ranges from 1.8% to 14.1%, which is consistent with our data (8.5%). The rates of nodal metastases in M0 RCC in stage T1, T2 and T3 are 1.1%, 4.5% and 12.3%, respectively. TanyN1-2M0 RCC is often associated with a poor...
prognosis, with a 5-year survival rate ranging from 20.9% to 39.3%\(^\text{[4, 12-15, 17]}\) and a median survival of 20 to 27.6 months\(^\text{[16, 12]}\). In our cases, the median survival of the patients was 23 months with a 5-year survival of 22.4%, similar to the reported data.

Researchers have examined the survival predictors of these RCC patients. Canfield et al\(^\text{[5]}\) reported that T stage and N stage were independent predictors of the overall survival, whereas the Fuhrman grade showed no significant predictive value. Karakiewicz et al\(^\text{[4]}\) found that symptom classification contributed the most to the combined predictive accuracy of all the variables (+4.2% , \(P<0.001\)), followed by the Fuhrman grade (+2.3%) and histological subtype (+1.0%), and suggested that patients presenting with systemic symptoms were expected to have an extremely poor survival. Their data showed that T stage was not an informative variable while histological subtype was a predictor of survival. In our study, we found that Fuhrman grade, N stage and T stage were independent predictors of CSS. The discrepancies in these results possibly result from a lack of standard extent of LND, absence of adjuvant therapy data and exclusion of N stage from analysis (as in the two other reports).

Our data show that patients with T1-3N1-2M0 RCC had an early recurrence even a complete resection of the primary tumor and nodal involvement was performed. The median DFS was 11 months after the operation and the recurrent cases often had a high rate of multiple metastases (83.3%) at initial recurrence. A low rate (6.7%) of recurrence in the renal fossa was noted, suggesting the value of a radical tumor resection. This fact also suggested the potential presence of distant metastasis before the operation, as supported by the autopsy data reported by Johnsen et al\(^\text{[14]}\), who found a low rate (5/554) of confined nodal metastases in comparison with a much higher rate of regional nodal involvement with additional metastases (75/554)\(^\text{[18]}\).

To our knowledge, the recurrence data of T1-3N1-2M0 RCC were available only in the study by Canfield et al\(^\text{[5]}\), who examined a cohort of 39 patients and found that pN stage (N2 vs N1, HR, 2.83, \(P=0.039\)) and Fuhrman grade (G4 vs G2/3, HR, 2.57, \(P=0.023\)) were the significant independent predictors of time to recurrence. But ECOG PS and tumor size were not included in their analysis, and they failed to provided specific descriptions of the recurrence site and number of metastatic foci. In the current study, ECOG PS, tumor size, Fuhrman grade and N stage were identified as the independent predictors of tumor recurrence, among which ECOG PS and tumor size were more powerful predictors of recurrence of T1-3N1-2M0 RCC. ECOG PS has also been identified as an independent predictor of survival and recurrence in RCC in a few studies\(^\text{[19-21]}\), and we further demonstrated its value as a powerful predictor of DFS in patients with T1-3N1-2M0 RCC.

The therapeutic value of LND in patients with RCC have remained controversial since 1969, when Robson et al\(^\text{[22]}\) advocated the need for lymphadenectomy for RCC. Some recent studies fail to show any benefit of LND in patients with RCC\(^\text{[5, 10]}\). However, patients undergoing LND at the time of cytoreductive RN for metastatic RCC had reportedly a better survival than those without LND\(^\text{[23, 24]}\). Our data demonstrated that N stage was an independent predictor of both CSS and DFS in T1-3N1-2M0 RCC, and we recommend that extended LND be performed in cases of suspicious nodal enlargement during surgery.

As this present study is based on the single-center data, and due to the rarity of T1-3N1-2M0 RCC, the sample size for analysis is relatively small in this study. But our findings may still provide important insight into the biological behavior of the malignancy.

**Acknowledgments**

We thank Dr. JIANG Yao-dong for his valuable
临床分期T1-3N1-2M0肾细胞癌患者临床分析：单中心研究

陈壮飞，吴凌，郑少斌，张鹏，谭万龙，毛向明
南方医科大学南方医院泌尿外科，广东 广州 510515

摘要：分析临床分期为T1-3N1-2M0肾癌的临床病理及预后资料，探讨其生物学行为特点。方法 1998年至2008年间我院共收治无远处转移肾癌并行开放性肾癌根治术的患者33例，其中42例作局部淋巴结清扫术，对其临床病理及预后资料进行回顾性分析。结果 42例患者中，19.0%为T1期，21.4%为T2期，59.5%为T3期和57.1%为T4期。I期中，19.0%为P0.005，淋巴结转移（P=0.014）和T分期（P=0.037）是CSS的独立影响因素；术前状态（P=0.002），肿瘤大小（P=0.007），病理分级（P=0.009）和淋巴结清扫（P=0.019）是DFS的独立影响因素。结论 T1-3N1-2M0期肾癌患者预后较佳。淋巴结分期是T1-3N1-2M0期肾癌CSS和DFS的独立影响因素，术中出现可疑肿大淋巴结者应行扩大的淋巴结清扫术。

关键词：肾细胞癌；临床分期；预后；多因素分析；淋巴结清扫

中国分类号：R737.11 文献标志码：A 文章编号：1673-4254(2011)05-0749-06