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Evaluation of the Importance of Advanced Age for Histopathological Prognostic Data in Patients with Kidney Tumor

Böbrek Tümörlü Hastalarda Histopatolojik Prognostik Veriler Açısından İleri Yaşın Öneminin Değerlendirilmesi

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Öz

Böbrek tümörleri erkeklerde daha fazla görülen ve sıklıkla ileri yaş tümörleri kategorisinde yer alan tümörlerdendir. Bu çalışmada histolojik alt tür yanı sıra birçok tanımlanmış histopatolojik prognostik parametrenin bulunduğu böbrek tümörleri için histopatolojik prognostik veriler açısından yaşın öneminin değerlendirilmesi amaçlanmıştır. 2010-2020 yılları arasında nefrektomi uygulanarak böbrek kanseri tanısı almış 75 yaş üzerinde olan 24 hasta çalışmaya dahil edilmiştir. Tümör histolojik alt tipi, tümör derecesi, lenfovasküler invazyon (LVI), perinöral invazyon (PNI), nekroz varlığı, hiler yağ doku ve perirenal yağ doku invazyonu ile cerrahi sınırların durumunu içeren histopatolojik bulguların yaş ile ilişkisi belirlenmiştir. Tümörlerin 23'ü renal hücreli karsinom (RCC), birisi düşük malignite potansiyelli multiloküler kistikrenal hücreli neoplazm olarak sınıflandı. RCC'nin histopatolojik alt tipleri sırasıyla; şeffaf hücreli RCC (n=19), kromofob RCC (n=2), Tip 1 papiller RCC (n=1) ve Tip 2 papiller RCC (n=1) idi. İncelenen histopatolojik veriler arasında renal ven invazyonunun sağkalım açısından istatistiksel anlamlılık gösterdiği saptanmıştır (p=0,002). Ayrıca artan tümör derecesi ile LVI arasında anlamlı ilişki gözlenmiştir (p=0,009). Tümör boyutu, tümör derecesi, nekroz varlığı, lenf nodu metastazı varlığı, perirenal yağ doku invazyonu ve renal ven invazyon varlığı RCC için prognostik belirteçler arasında yer almaktadır. Ancak ileri yaş olgulardan oluşan serimizde; yalnızca renal ven invazyonununun sağkalım açısından prognostik önemli olduğu, diğer tanımlanan belirteçlerin bu yaş gurubunda belirgin etkisinin olmadığı görülmüştür. Bu durum; ileri yaş tümörlerinin diğer yaş gruplarındaki tümörlerden farklılık gösterebileceğine ve rutin kullandığımız verilerin hastaların gidişatını ön görmekte yetersiz kalabileceğine işaret etmektedir.

Anahtar Kelimeler: Renal Hücreli Karsinom, Renal Hücreli Karsinomun Histopatolojik Alt Tipleri, Renal Hücreli Karsinomun Prognostik Parametreleri, Yaşlıların Böbrek Tümörleri

Abstract

Kidney tumors are more common in males, and are often considered to be in the category of older-age tumors. In this study, it was aimed to evaluate the importance of age in terms of histopathological prognostic data for kidney tumors, with many defined histopathological prognostic parameters. Twenty–four patients >75 years, who were diagnosed with kidney cancer with nephrectomy between 2010 and 2020, were included in study. The relation between histological features as histological subtype, grade of the tumor, presence of lymphovascular, perineural, hilar and perirenal adipose tissue invasion, necrosis, and the state of surgical margins were determined. Twenty-three tumor samples were classified as renal cell carcinoma (RCC). One sample was classified as multilocular cystic renal cell neoplasm with low malignancy potential. The histopathological subtypes of RCC were; clear cell RCC (n=19), chromophobe RCC (n=2), Type 1 papillary RCC (n=1), and Type 2 papillary RCC (n=1), respectively. Among the histopathological data, renal vein invasion showed statistical significance in terms of survival (p=0.002). In addition, a significant relationship was observed between increasing tumor grade and LVI (p=0.009). Tumor size, and grade, presence of necrosis, lymph node metastasis, perirenal adipose tissue and renal vein invasion are among the prognostic markers for RCC. However, in our series of advanced age cases, only renal vein invasion was found to be prognostic for survival, while other identified markers did not have a significant effect on this age group. This phenomenon indicates that advanced age tumors may differ from tumors in other ages, and the data used routinely may therefore be insufficient to predict the course of the disease.

Keywords: Renal Cell Carcinoma, Histopathologic Subtypes Of Renal Cell Carcinoma, Prognostic Parameters Of Renal Cell Carcinoma, Renal Tumors Of Elderly

Introduction

Various factors play a role in the development of cancer, which is currently a serious health issue. Since carcinogenesis is a long process, it is expected that cancer will occur more frequently at older ages. Prolonged exposure to carcinogens, DNA damage accumulation, tumor suppressor gene defects, impaired cellular repair mechanisms, oncogenic activation, and weakening of the immune system are among the mechanisms thought to be responsible for cancer incidence in older individuals (1).

Kidney tumors are also more frequently seen at an advanced age, and the average age of onset is 64 years according to the Epidemiology, and End Results (SEER) database in the United States (2). Based on statistics from the Directorate of Cancer Department of Public Health Agency of Turkey for 2014, kidney cancers are among the most common cancer types in the 70 and overage group. It is seen in 1.3% of men, and ranks among the most frequent 10 cancer types for men, but not for women (1).

In this study, it was aimed to investigate the histopathological subtypes, and histomorphological features of the tumor and the relationship between

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these features and prognosis of tumors that demonstrate diagnostic significance due to their heterogeneity in patients over 75 years of age diagnosed with kidney cancer.

Material and Method

Ethics committee approval was obtained from the Ethics Committee of Health Sciences University Tepecik Training and Research Hospital, Izmir with the decision dated 13/11/2019 and numbered 2019/16-16. The participants were 24 patients over the age of 75, with available clinical follow up data who were diagnosed with kidney cancer between 2010 and 2020, after examining specimens of partial/radical nephrectomies performed at the Tepecik Training and Research Hospital of Izmir University of Health Sciences. Data on patients' age, and gender, tumor size and location, and recurrence/metastasis and survival data were obtained from the patient files. Hematoxylin & eosin-stained sections of the tumor specimens stored in the pathology archive were re-evaluated, taking into account the 2016 World Health Organization classification. Histological subtype, and grade of the tumor, presence of lymphovascular (LVI), perineural (PNI), hilar adipose tissue and perirenal adipose tissue invasion, necrosis, and the state of the surgical margins were recorded.

Statistical Package for the Social Science (SPSS) version 24.0 was used for statistical evaluation. The relationship between age and histomorphological data was evaluated by chi-square test. The relationship between data and survival was evaluated using Kaplan Meier analysis, and a p value of less than 0.05 was considered statistically significant.

Results

Twenty-four cases underwent either radical (n=16) or partial (n=8) nephrectomy. Fourteen cases were male and 10 were female, with a median age of 80.2 (min77-max88) years. Nine cases survived, and 15 cases exited. The mean follow-up period was 32.5±30.9 months (range = 1-104 months), and no case of recurrence and/or metastasis was detected during the follow-up period. The median tumor diameter was 6.2 cm (min3.5-max13.5 cm). Tumor specimens had diameters of ≤7 cm (n=20) or more than 7 cm (n=4). Histopathologically, 23 tumor specimens were classified as renal cell carcinoma (RCC) and one as multilocular cystic renal cell neoplasm with low malignancy potential. Histopathological subtypes of RCC were as follows; clear cell RCC (n=19), chromophobe RCC (n=2), Type 1 papillary RCC (n=1), and Type 2 papillary RCC (n=1). According to WHO/ISUP grading system, tumors were of Grade 1 (n=4), 2 (n=4), 3 (n=10) and 4 (n=4). WHO/ISUP grading was not applied to 2 cases with chromophobe RCC, as it was not recommended.

Necrosis was observed in 11, LVI in 7, PNI in 1, kidney capsule invasion in 11, perirenal adipose tissue invasion in 7, hilar adipose tissue invasion in 10, renal vein invasion in 1, and surgical margin positivity in 2 tumor specimens (Table 1). WHO/ISUP tumor grade was compared with histopathologic data by chi-square analysis (Table 2).

LVI was not seen in Grade 1 (n=4) and 2 (n=4) tumor specimens while LVI was observed in 3 of 10 of Grade 3, and all of Grade 4 (n=4) tumor specimens. A statistically significant relationship was found between tumor grade and LVI (p = 0.009).

Regarding the relationship between tumor grade and necrosis, necrosis was observed in 3 of 4 Grade 4, in 7 of 10 Grade 3, and 1 of 4 Grade 4 tumors. Necrosis was not seen in Grade 1 (n= 4) tumors. There was no statistically significant relationship between tumor grade and necrosis (p = 0.068).

There was no statistically significant relationship between tumor grade and PNI, perirenal, hilar or adipose tissue invasion (p=0.560, p=0.945, p=0.259, respectively).

Necrosis was observed in 7 of 20 tumors with a diameter of ≤7 cm, and in all 4 tumors with a diameter of >7 cm. There was a statistically significant relationship between necrosis and tumor size (p=0.037).

Survival and histopathological data were compared across all patients with the Kaplan Meier test. Renal vein invasion was present in one of the patients who died. A statistically significant relationship was found between renal vein invasion and survival (p=0.002).

A statistically significant relationship was not seen between survival, and gender (p=0.330), LVI (p=0.360), tumor grade (p=0.850), perirenal adipose tissue invasion (p=0.930), hilar adipose tissue invasion (p=0.980), tumor diameter (p=0 067), surgical margin positivity (p=0.800) and necrosis (p=0.180).

Discussion

Kidney cancer accounts for about 2% of all cancer diagnoses and cancer-related deaths worldwide. Its incidence increases with age, and is more common in men (2,3). Renal cell carcinoma is a heterogeneous cancer group originating from renal tubular epithelial cells and constituting more than 90% of cancers in the kidney (2). The most common RCC subtype is clear cell RCC (2,4,5).

In renal cell carcinoma, tumor size, presence of lymph node metastasis, grade, and stage of tumor are considered to be related to clinical course and prognosis (6).

Table 1. Clinical and Histopathological Features of Our Cases

Clinical and Histopathological Findings	Category	n
Median age of years (range)	80.2 (min77- max88)	24
Tumor size	6.2 cm (min3.5- max13.5 cm)	24
Gender	Male	14
	Female	10
Survival	Live	9
	Ex	15
Histopathological types	Clear cell RCC	19
	Chromophobe cell RCC	2
	Type 1 papillary RCC	1
	Type 2 papillary RCC	1
	Multilocular cystic renal cell neoplasm with low malignancy potential	1
Tumor Grade	Grade 1	4
	Grade 2	4
	Grade 3	10
	Grade 4	4
	Grading is not applicable*	2
Lymphovascular invasion	Absence	16
	Presence	7
Perineural invasion	Absence	22
	Presence	1
Tumor Necrosis	Absence	12
	Presence	11
Perirenal adipose tissue invasion	Absence	16
	Presence	7
Hilar adipose tissue invasion	Absence	13
	Presence	10
Renal vein invasion	Absence	22
	Presence	1
Renal capsule invasion	Absence	12
	Presence	11
Surgical Margins	Negative	21
	Positive	2

*Grading is not applicableto 2 cases with chromophobe RCC

Table 2. The Association of Grade with lymphovascular invasion,perineural invasion, perirenal adipose tissue invasion, and hilar adipose tissue invasion (chi-square test)

	LVI (+/-)	PNI (+/-)	Necrosis (+/-)	PRATI (+/-)	HATI (+/-)
Grade 1	0/4	0/4	0/4	1/3	2/2
Grade 2	0/4	0/4	1/3	1/3	0/4
Grade 3	3/7	0/10	7/3	3/7	5/5
Grade 4	4/0	4/3	3/1	2/2	3/1
Chromophobe RCC	0/2	0/2	0/2	0/2	0/2
p value	0.009	0.565	0.068	0.945	0.259

*WHO/ISUP grading was not applied to 2 cases with chromophobe RCC. LVI: Lymphovascular invasion, PNI: Perineural invasion, PRATI: Perirenal adipose tissue invasion, HATI: Hilar adipose tissue invasion

The identification of histopathological subtypes in kidney tumors provides guidance in terms of prognosis and treatment planning. Therefore, in the most recent WHO classification (WHO 2016), new histological subtypes continue to be defined as separate entities. Among the recently-defined entities according to histomorphological features are clear cell papillary RCC and tubulocystic RCC.

Chromophobe cell RCC is known to have a better prognosis than other RCC histological subtypes; however, the tubulocystic RCC, defined as a new entity, is also reported to be a slowly progressing clinical RCC with rare metastasis and recurrence (4,7-10). Two large-scale studies conducted by Teloken PE et al. (11) and Leibovih BC et al. (12) demonstrated that histopathological subtypes were independent prognostic markers for RCC, while

metastasis and cancer-related deaths are more frequent than in clear cell RCCs chromophobe and papillary cell RCC subtypes, (11-13).

In the study of Nguyen DP et al., the histopathological subtypes of RCC were reported to be associated with survival, regardless of the pathological stage and surgical method used (13).

In the study by Özbir S et al., in 174 RCC patients, cases were categorized as either, aged <70 or ≥70 years, for comparison of disease-specific survival and overall survival rates. Although there was no statistically significant difference in disease-specific survival between groups, overall survival rates were reported to be statistically significantly lower in the age group of ≥70 years. In the same study, clear cell RCC was found to be the most common renal cancer (73.2%) in the ≥70-year-old patient group, followed by chromophobe RCC (11.3%) and papillary cell RCC (7%) (14).

In the study by Panian J et al., overall survival (OS) in 4736 metastatic RCC patients did not differ among three age groups (<50 years, 50-70 years, and >70 years), but progression-free survival (PFS) in the youngest group (<50 years) was found to be shorter (15).

In the literature, other publications indicate that the incidence of clear cell RCC (16), and also papillary RCC (17) increases with age. In addition, according to a 2-center study of 2941 patients by Wu J et al., clear cell RCC (90.2%) was most frequently reported in patients over 60 years of age, followed by papillary RCC (5.5%) and chromophobe RCC (4.3%) (18).

In our 75-year-old RCC case series, the most common histological subtype was clear cell RCC (n=19), while equal rates were observed for chromophobe RCC (n=2) and papillary RCC (n= 2).

In determining the stage which is the most important indicator of clinical course and prognosis in renal cell carcinomas, the key features are tumor size, perirenal adipose tissue or hilar adipose tissue invasion, presence of lymph node metastasis and distant organ metastasis (2).

It was reported that perirenal adipose tissue invasion directly affects disease-specific survival, especially in tumors larger than 7 cm, and the presence of perinephric adipose tissue invasion is associated with poor prognosis, regardless of tumor size (6). However, the prognosis was reported to be worse in tumors over 7 cm, than in tumors measuring 4-7 cm, and smaller than 4 cm (6).

In the study of R. Houston Thompson et al., metastasis was detected in 162 of 2691 RCC patients. The rate of metastasis was around 2% in patients whose tumor size is less than 4 cm, increasing to 17% in tumors over 7 cm (18).

In this context, studies so far have focused on the comparison of treatment procedures for ≤4 cm tumors in RCC cases over 75 years of age, determination of molecular subtypes of tumor in advanced age patients with synchronous metastasis, and the target therapy. However, identification of histopathological features still remains as an important issue, and related studies are ongoing (19,20). In our study, the cases were grouped according to tumor diameter (≤7 cm, and >7 cm) and there was no significant difference in terms of overall survival. Thus, it is doubtful whether tumor size in patients aged >75 years is an effective variable on overall survival.

In the literature, independent prognostic parameters affecting survival in RCCs have been defined as tumor size, tumor grade, tumor necrosis, presence of lymph node metastasis, perirenal adipose tissue invasion, and renal vein invasion (21-25). In our series, a statistically significant relationship was found between renal vein invasion and overall survival in advanced age. The latest American Joint Committee on Cancer (AJCC) pathological staging guidelines (8th Edition) emphasized that in pTNM, renal vein invasion is associated with changes in the stage, regardless of size, and that the tumor is considered to be at least pT3a in the presence of renal vein invasion (26).

The patient with renal vein invasion were 78 years old at the diagnosis and he had 2 months survival after diagnosis. The histopathological findings of the grade 3 and 12 cm tumor were lymphovascular invasion, capsular invasion, renal capsular invasion, necrosis, perirenal and hilar adipose tissue invasion in addition to renal vein invasion. No perineural invasion or surgical margin positivity was observed.

In a retrospective study of 672 patients conducted by Gaove et al., the cases were divided into 3 groups as <40, 40-75, and ≥75 years of age. According to the results, the age of ≥75 was considered as an independent risk factor on overall survival (3).

In our study, no significant relationship was found between overall survival in patients aged >75 years and gender, LVI, tumor grade, capsule invasion, perirenal adipose tissue invasion, hilar adipose tissue invasion, tumor diameter, surgical margin positivity, and necrosis.

In a comprehensive systematic review and meta-analysis of printed articles by Zhang L et al. (27), tumor necrosis was detected in 4452 of 14,084 (31.6%) cases. Tumor necrosis in RCC cases was associated with low cancer-specific survival (CSS), overall survival (OS), recurrence-free survival (RFS) and progression-free-survival (PFS) rates.

In addition to this study, in studies by Khor et al. (28) and Ito et al. (29), the presence of necrosis was accepted as an independent prognostic factor, and found to be associated with low survival rates. In contrast to the literature, in our study, there was no statistically significant relationship between the presence of necrosis and overall survival in RCC cases aged >75 years. However, in our study,

necrosis was observed more frequently in Grade 3 and 4 tumors. Although there was a numerically significant relationship between tumor grade and necrosis, this could not be shown statistically, possibly due to the inadequate number of cases.

According to the WHO/ISUP grading system, based on predominant nucleolar features, it is accepted that the classification of RCCs has also prognostic significance. However, in the study by Delahunt et al. (30), it was recommended that the presence of microscopic necrosis in the clear cell RCCs should be added to the WHO/ISUP grading system to provide more robust information about survival. In this study, tumor necrosis was seen in only 1 case with ISUP Grade 1, but in 4.2% of cases with ISUP Grade 2. In contrast, in a study by Klatte et al. (31) necrosis was detected in approximately 50% of cases of Grade 1 and 2, and no relationship was found between the presence of necrosis and grade in a multivariate model. Because of the differences in results across studies, it has been suggested that the determination of necrosis may differ according to institution, and therefore, a reproducible grading system including necrosis should be formulated.

In our study, we observed that LVI was not seen in Grade 1 or 2 tumors, while the frequency of LVI increased with increasing grade of the tumor. LVI was observed in approximately 30% of Grade 3, and all Grade 4 tumors with a statistically significant intergroup difference (p=0.009).

Different types of mutations have been identified in the subtypes of RCC that is defined as a heterogeneous group. The most common molecular changes identified in clear cell RCC, which constitutes the majority of the cases in the literature include 3p loss and inactivation of the von Hippel Lindau "VHL" gene (32).

The prognostic and clinical significance of many of the mutations in RCC has been defined. These mutations include the genes such as PBRM1, SETD2, BAP1, KDM5C, TP53, TERT, PTEN, ERBB2, CDK8, TSC1, SPEN (33-35). Among these genes, mutations in BAP1, PTEN, ERBB2, TP53, CDK8, TSC1, SETD2 and SPEN were associated with poor prognosis as the results of The Cancer Genome Atlas cohort (34). The defined somatic mutations of SETD2, KDM5C, TP53, and TERT in RCC, have prognostic significance, especially in patients who receive standard treatment for metastatic disease (33). Furthermore, some genes were associated with metastatic disease, some with recurrence, some with the histopathological features of the tumor, and some with disease-free survival (34). The mutations in PBRM1, SETD2, BAP1 and also KDM5C were shown to associate with aggressive clinical features (35).

VHL/HIF pathway dysregulation and activation of targets of mTOR signals were detected in RCC. This has resulted in the development of VEGF and mTOR targeted therapies (32,35). In addition to this; immunotherapeutic agents targeting the cytotoxic T lymphocyte antigen 4 and programmed cell death protein 1 are also among the preferred targeted treatment options (32,35).

In our study, no bilaterality, metastasis, or resistance to treatment was found in any of our patients, and additional treatment was not required. Molecular pathological examination was not performed in our patients of our retrospective study during the routine diagnosis and treatment process.

In the recent days after the definitions of the molecular changes underlying the disease, new targeted therapies are used to treat patients. These treatments are especially applied in metastatic and advanced disease. There are promising studies on novel targeted therapies in the literature.

The main limitation of this study is the limited number of patients and only reflects a single center experience. This study could be done with a multicenter and with larger number of cases. In addition, molecular studies cannot be applied due to financial constraints.

In the literature, tumor size, tumor grade, presence of necrosis, lymph node metastasis, perirenal adipose tissue and renal vein invasion are defined as prognostic markers for RCCs.

In our series consisting of advanced age cases, it was observed that renal vein invasion alone was a prognostic marker in terms of survival, and other identified markers had no significant effect on this age group. Furthermore, a significant correlation was found between increased tumor grade and lymphovascular invasion, and a numerically significant relationship was found between increased tumor grade and presence of necrosis.

This phenomenon indicates that advanced age tumors may differ from tumors in other ages, and the data used routinely may therefore be insufficient to predict the course of the disease.

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