Clinical Study

Pathological upstaging of renal tumors and its impact on the therapeutic and follow-up decision

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Abstract

Introduction and Objectives. This study aimed to assess the incidence of pathological upstaging of renal tumors in relation to the surgical technique (radical/partial nephrectomy) or approach (laparoscopic/open) as well as its potential associations of clinical and/or pathological factors.

Materials and Methods. We retrospectively reviewed patients who underwent any type of nephrectomy (radical/partial or open /laparoscopic) for renal tumors between January 2018 and December 2020. Among 175 eligible patients, 139 patients were available for our analysis. We conducted a comparative analysis according to clinical and pathological characteristics of two groups: upstaged group (n = 17) and the non-upstaged group (n = 122).

Results. Pathological upstaging was found in 17 patients (12.23%) with a majority of pT3a (13 patients, 76%). Patients in the upstaging group exhibited a higher proportion of cT1b stage (65% (11) vs. 47% (57), p=0.01), pT3a stage (76% (13) vs. 14% (17), p <0.0001) as well as a higher Fuhrman grade (Grade 3 and 4) (47% (8) vs. 25% (30), p=0.001).

Conclusions. Pathological upstaging occurred more frequently in patients with radical nephrectomy as well as in patients that benefited from open surgery. Tumor size and high Fuhrman grade were related to upstaging, exerting an influence on patient follow-up protocol.

Key-words. Fuhrman grade, kidney cancer, nephrectomy, upstage

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Introduction and Objectives

Renal cell carcinoma (RCC) affects approximately 300.000 patients worldwide annually and is responsible for over 100.000 deaths each year. The incidence of RCC varies worldwide, the highest being in North America (11.7 per 100.000) followed by Western Europe (9.8) [1; 2]. With widespread abdominal imaging, the incidence of RCC has increased in recent decades by almost 3% annually from 1975 to 2007 [3].

According to the American Urological Association (AUA) [4], the American Society of Clinical Oncology (ASCO) [5], and the European Association of Urology (EAU) [6] guidelines, clinical TNM staging remains the most accepted system for treatment decision in renal tumors. Partial nephrectomy (PN) is recommended as first-line treatment for clinical T1 (cT1) renal tumors whenever this intervention is feasible. Laparoscopic Radical Nephrectomy (LRN) is recommended for T2 renal tumors or T1 tumors not treatable by PN [6].

Computer Tomography (CT) may accurately distinguish T1 (<7cm) from T2 (> 7cm) renal tumors. Overall, CT had the median diagnostic sensitivity and specificity of 87% and 74.5%, while Magnetic Resonance Imaging (MRI) displayed the median sensitivity of 90% and specificity of 75% [7]. However, depending on tumor location, preoperative CT occasionally cannot detect tumor expansion in the renal sinus, renal vein, or perirenal tissue (T3a) [8-10]. Therefore, a tumor upstaging may exist if the renal tumor was diagnosed clinically as T1 or T2, but revealing a pT3a after surgery. Some studies have shown that among patients undergoing surgical treatment for cT1 tumors, up to 30% may have different final pathological stages compared to initial clinical diagnosis [11-14].

This study aimed to assess the incidence of pathological upstaging of renal tumors related to the surgical technique (radical/partial nephrectomy) or approach (laparoscopic/open). Furthermore, we investigated if upstaging could be associated with clinical and/or pathological factors.

Materials and Methods

We retrospectively reviewed patients who underwent radical or partial nephrectomy for renal tumors at the Department of Urology, Mureș County Hospital, Târgu Mureș, Romania, during January 2018 and December 2020. Both types of surgical approaches (open and laparoscopic) were analyzed. The surgeons certified preoperative clinical staging according to the patient's CT or MRI investigation. Clinical staging was per-

Table I. The American Joint Committee on Cancer (AJCC) TNM Staging System for Kidney Cancer [10]

Primary tumor (T)	
T1	Tumour ≤7 cm in greatest dimension, limited to the kidney.
T1a	Tumour ≤4 cm.
T1b	Tumour >4 cm but ≤7 cm.
T2	Tumour >7 cm in greatest dimension, limited to the kidney.
T2a	Tumour >7 cm but ≤10 cm.
T2b	Tumour >10 cm.
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia.
T3a	Tumour grossly extends into the renal vein or its segmental branches, or tumour invades perirenal and/or renal sinus fat but not beyond Gerota fascia.
T3b	Tumor grossly extends into the vena cava below the diaphragm.
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava.
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland).
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Regional lymph node metastases.
Distant Metastasis (M)	
M0	No distant metastasis.
M1	Distant metastasis.

Table II. Fuhrman nuclear grades[15]

Grade	Description
1	Tumors are composed of cells with small (~10 μ), round, uniform nuclei with inconspicuous or absent nucleoli.
2	Tumors had larger (~15 μ) nuclei with irregular outlines and nucleoli that were visible under high-power (400X) microscopy.
3	Tumors had even larger nuclei (~20 μ) with obviously irregular outlines and prominent nucleoli even under low-power (100X) microscopy.
4	Tumors exhibited features similar to those of Grade 3 tumors but also had bizarre, often multilobed nuclei and heavy chromatin clumps.

formed using the TNM classification system (see Table I). All patients were clinically diagnosed with RCC either as T1 (T1a or T1b), T2 (T2a or T2b), T3 (T3a or T3b), T4, NX or N0, and M0. For pathological details, we analyzed all the patients' histopathological reports.

However, among 175 patients treated for renal tumors the following were excluded: patients with benign tumors (n = 9; 5.1%), recurrent renal tumors (n = 1; 0.5%), bilateral renal tumors (n = 1; 0.5%), and tumors with regional lymph node metastases (N1) (n = 11; 6.2%) or distant metastases (M1) (n = 10; 5.7%). We also excluded patients with insufficient data for analysis (n = 4; 2.2%). There were 139 patients with localized tumors available for our analysis.

We classified the patients into two groups: group 1- clinical upstaged group (n = 17) after partial or radical nephrectomy (RN) and group 2- not upstaged group (n = 122).

We evaluated patients' demographics (age, gender), clinical (date of surgery, clinical staging) and pathological characteristics (tumor size, Fuhrman grade, complete histopathological diagnosis), as well as surgery details (PN or RN, open or laparoscopic, operation time).

The Fuhrman nuclear system distinguishes 4 degrees of malignancy of renal cell carcinomas and refers to the characteristics (size, number, shape) of nuclei, nucleoli, and chromatin (see Table II).

We performed descriptive statistics with means and medians for continuous variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the distribution of collected data. Continuous variables were compared using the non-parametric Mann–Whitney test or the Student t-test. For categorical variables, which were expressed as numbers or percentages, we performed the comparison using either Pearson's χ 2 (chi-square) test or Fisher's exact test. Statistical significance was achieved at $p<0.05$. All data were statistically analyzed using GraphPad Prism 8.4.2.679 (x64) software.

Results

From our cohort of 139 patients, who underwent either PN or RN for RCC, upstaging was found in 17 patients (12.23%). Downstaging of renal tumors was also noted in 3 (2.1%) of included patients. A comparison of demographic, clinical, and pathological characteristics of patients is presented in Table III and Table IV.

Table III. Demographic and surgical characteristics of patients included in the study group.

Variable	Upstaging group (n=17)	No upstaging group (n=122)	p-value
Age (years), mean±SD	64.80±10.51	62.17±12.99	0.48
>70 (%)	35	25	0.12
Sex (%)			
Men	59	57	>0.05
Women	41	43	>0.05
Nephrectomy type (%)			
PN	24	39	0.02
RN	76	61	
Surgical type (%)			
Open	82	49	<0.0001
Laparoscopic	18	51	

Table IV. Clinical and pathological parameters of included patients presented in relation to pathological upstaging.

Variable	Upstaging group (n=17)	No upstaging group (n=122)	p-value
Clinical stage (%)			
T1a	24	21	0.61
T1b	65	47	0.010
T2a	12	10	0.65
T2b	0	3	N/A
T3a	0	15	N/A
T3b	0	3	N/A
T4	0	2	N/A
Pathological T stage (%)			
T1a	0	20	N/A
T1b	0	48	N/A
T2a	12	9	0.64
T2b	12	5	0.12
T3a	76	14	<0.0001
T3b	0	2	N/A
T4	0	1	N/A
Histology (%)			
Clear cell	88	85	0.53
Chromophobe	6	11	0.31
Papillary	6	4	0.74
Fuhrman grade (%)			
1	12	48	0.001
2	41	27	
3	29	22	0.001
4	18	3	

The mean age at diagnosis was 64.80 ±10.51 for the upstaging group and 62.17±12.99 for the non-upstaging group. There was no significant difference in gender type between the two groups.When compared with the not upstaged group, the upstaged group had a greater proportion of patients with clinical T1b tumors: n=11 (65%) vs. n=57 (47%), p=0.01. The upstaged group also exhibited a higher proportion of pT3a stage after surgery, compared to the not upstaged group: n= 13 (76%) vs. n=17 (14%), p<0.0001 (see Figure 1). High-grade tumors (Fuhrman grade 3 and 4) were significantly more frequent in the upstaged group: n=8 (47%) vs. n=30 (25%), p=0.001) (see Figure 1).

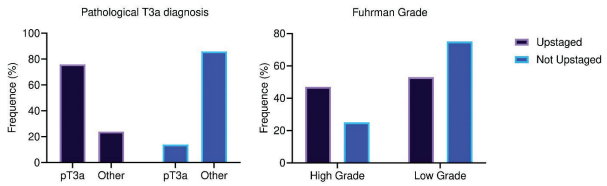


Figure 1. The proportion of pT3a diagnosis and Fuhrman grade tumors.

According to the tumor histology type, there was no significant difference between the groups.

With regards to surgical techniques, RN was performed more frequently in the upstaged group than in the non-upstaged group (76% (13) vs. 61% (75), p = 0.02) (see Figure 2). Additionally, the upstaging group exhibited higher open approaches compared to the non-upstaging group (82% (14) vs. 49% (60), p <0.001) (see Figure 2).

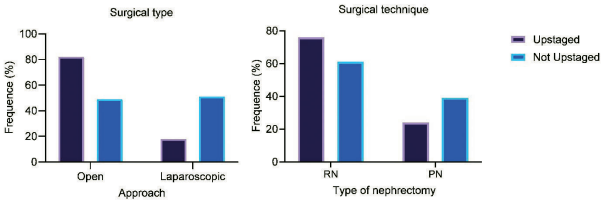


Figure 2. The frequency of surgical techniques and approaches.

Discussions

Previous studies have reported a poor prognosis in RCC patients with upstaged tumors compared to patients with non-upstaged ones. Nayak GJ et al. analyzed a large database of 1448 patients with clinical T1 RCC and reported a recurrence-free survival at 3-years of 76% in the upstaged group: 134 patients (9%) compared to 93% in the non-upstaged group: 1314 patients (87%) [11]. Chen et al., in a recent meta-analysis, which included follow-up studies for 23 months and over 60 months, highlighted upstaging as an unfavorable prognostic factor with a negative impact on patient survival. However, the surgical technique does not influence negatively the prognostic significance of tumor upstaging, and surgeons should not avoid PN because of concerns about upstaging [16].

TNM staging typically determines the treatment options, follow-up protocol, and prognosis. In addition, Fuhrman nuclear grade is an independent prognostic factor [17]. According to the UCLA Integrated Staging System (UISS) that incorporates the TNM staging system, a person's overall health and the Fuhrman grade divided patients with localized RCC into three groups: low-risk, intermediate-risk, and high-risk. For localized RCC, the five-year cancer-specific survival rates

Table V. Surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy [20].

Risk profile	Surveillance				
	6 months	1 year	2 years	3 years	over 3 years
Low	US	CT	US	CT	CT once every 2 years
Intermediate/High	CT	CT	CT	CT	CT once every 2 years

CT- computed tomography of chest and abdomen, alternatively use magnetic resonance for the abdomen;
US- ultrasound of abdomen, kidneys and renal bed.

are 91%, 80%, and 55% for low-, intermediate-, and high-risk groups, respectively. Therefore, defining risk groups is efficient for counseling patients, individualizing follow-up, and choosing treatment options [18-19]. EAU guidelines propose baseline imaging after surgery at 6 months follow-up, with the imaging modality adjusted to the patient's risk profile [20] (see Table V).

Our analysis found that the proportion of upstaging was 12.23% with 76% of cases being pT3a after surgery. Other series report that patients with PN or RN performed for cT1 RCC had pathological upstaging to T3a in variable percentages between 4.8-31% [11-13]. However, the studies that included only patients who underwent PN for cT1 renal masses showed tumor upstaging to pT3a only in 5% of cases [14].

In a retrospective study, Jeong S-H et al. analyzed 987 patients who underwent partial or radical nephrectomy for cT1 RCC, with 9.2% cases upstaging to pT3a. They found no difference between the type of nephrectomy and tumor recurrence rate in the upstaging group [21]. Similarly, Shah et al. found that patients who had undergone PN have inferior recurrence-free survival rates relative to those who undergo radical nephrectomy as well as a higher risk of tumor recurrence in the upstaged group for PN than for RN [22]. However, our study revealed a higher incidence of RN and open approach in the upstaging group.

In our study, increasing age determined a differentiation between groups, but not statistically significant. Many studies have associated several demographics and clinico-pathological characteristics with an upstaged group. Lee H, et al. observed that older age, larger tumor size, and hilar location were significantly associated with the risk of pathological upstaging [23]. Moreover, Nayak GJ et al. have shown that increased patient age, tumor size, and Fuhrman grade are predictors of pathological upstaging, which can also be appreciated by a preoperative biopsy [11].

Our analysis revealed that a high Fuhrman grade was significantly associated with an increased incidence of upstaged tumors. This is similar to the findings of Mouracade et al. who demonstrated that patients in the upstaged group were more likely to have the following clinical (high R.E.N.A.L nephrometry score, large hilar tumors, male gender) and pathological (high tumor grade, clear cell type, and positive surgical margins) features [24]. This is also supported by the work of Lai et al. who performed an analysis of 476 patients with RN or PN performed for T1N0M0 tumors and revealed that high Fuhrman grade, pathological upstaging, and large tumor size are predictive factors of tumor recurrence [25].

The present study has several limitations. First, it was a single-center retrospective study, with the corresponding inconveniences. Another limitation consists in the various surgical methods (PN and RN) as well as the surgical approaches (open and laparoscopic) for our patients. Unfortunately, no data on long-term recurrence free-survival of upstaged patients was available for the study team. However, to the best of our knowledge, this is the first study in a Romanian hospital that provides details about the incidence of pathological upstaging of renal cancer as well as its relation to various clinical and pathological characteristics.

Conclusions

Our study found that pathological upstaging was a relatively frequent event that was more likely to occur in patients that had radical nephrectomy and/or open surgery. Although with no influence on surgical planning, pathological upstaging has a decisive role on tailoring follow-up programs for these patients.

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