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Corresponding Author	Family Name	Antonelli
	Particle	
	Given Name	**Alessandro**
	Suffix	
	Division	Department of Urology
	Organization	University of Brescia, Spedali Civili Hospital
	Address	Piazzale Spedali Civili 1, Brescia, 25123, Italy
	Email	alxanto@hotmail.com
Author	Family Name	Simeone
	Particle	
	Given Name	**Claudio**
	Suffix	
	Division	Department of Urology
	Organization	University of Brescia, Spedali Civili Hospital
	Address	Piazzale Spedali Civili 1, Brescia, 25123, Italy
	Email	
Author	Family Name	Cunico
	Particle	
	Given Name	**Sergio Cosciani**
	Suffix	
	Division	Department of Urology
	Organization	University of Brescia, Spedali Civili Hospital
	Address	Piazzale Spedali Civili 1, Brescia, 25123, Italy
	Email	

Abstract	Despite the significant increase in early diagnoses that took place in recent years, thanks to the increase in popularity of imaging techniques (ultrasonography and CT), the kidney neoplasm is still the urologic cancer with the highest mortality rate [1] due to the significant number of cases with distant metastases for which no systemic treatment with curative potential exists. The disease has a variable and often highly unpredictable biological behavior and recurrence is possible also after radical treatment of organ-confined disease. The most common sites of relapse are lung, adrenal, liver, bone, brain, lumbar fossa, and contralateral kidney, but the literature documents that kidney carcinoma can metastasize to virtually any organ. The absence of effective systemic therapy can justify adoption of the most accurate follow-up plan available to diagnose a relapse as quickly as possible and surgically remove it. As a matter of fact, surgical metastasectomy, wherever technically feasible, can be curative and/or lead to an increase in survival duration [2].

Keywords (separated by '-')	Nonmetastatic kidney cancer - Kidney - Nephrectomy - Surveillance - Papillary carcinoma

74 Renal Cancer Follow-up Counterpoint: Europe

Alessandro Antonelli, Claudio Simeone, and Sergio Cosciani Cunico

Keywords
Nonmetastatic kidney cancer • Kidney • Nephrectomy • Surveillance • Papillary carcinoma

Despite the significant increase in early diagnoses that took place in recent years, thanks to the increase in popularity of imaging techniques (ultrasonography and CT), the kidney neoplasm is still the urologic cancer with the highest mortality rate [1] due to the significant number of cases with distant metastases for which no systemic treatment with curative potential exists. The disease has a variable and often highly unpredictable biological behavior and recurrence is possible also after radical treatment of organ-confined disease. The most common sites of relapse are lung, adrenal, liver, bone, brain, lumbar fossa, and contralateral kidney, but the literature documents that kidney carcinoma can metastasize to virtually any organ. The absence of effective systemic therapy can justify adoption of the most accurate follow-up plan available to diagnose a relapse as quickly as possible and surgically remove it. As a matter of fact, surgical metastasectomy, wherever technically feasible, can be curative and/or lead to an increase in survival duration [2].

Several clinical, biochemical, anatomic pathological, and molecular factors have been analyzed for their prognostic value but today anatomic pathological staging according to the TNM system remains the most important single prognostic factor. In order to increase its accuracy, several authors have proposed some integrated staging systems in which the TNM stage is combined with other prognostic factors [3].

In our institution, over the last two decades, we have surgically treated more than 1,500 patients with renal cell carcinoma. In cases where radical surgery was applied to a nonmetastatic neoplasm (pN0/Nx M0), patients are followed with a surveillance plan independent of the disease stage. Periodic controls are done with blood tests (complete blood count, kidney and liver function tests), abdominal imaging examinations (ultrasonography or CT) and chest examinations (plain X-rays or CT) once each 6 months in the first 2 years after surgery and then again every year for an indefinite time. Additional examinations (brain CT and bone scintigraphy) have been, in general, used only in the presence of specific symptoms. In light of this experience, which has allowed us to monitor these patients continuously, we have recently reviewed the results obtained and retrospectively applied an integrated staging system to assess which cases might require more intense surveillance and which cases might well be served by less intense surveillance [4].

Among the many integrated staging systems available, we have chosen the one developed at UCLA (UCLA Integrated Staging System, UISS [5]), which is based on two anatomic pathological factors (the stage according to TNM 1997 [6] and the cytonuclear grading according to Fuhrman [7]) plus a clinical factor (the performance status as defined by the ECOG score [8]) (see Table 74.1). The widespread availability of this information makes this staging system applicable in all institutions, which is one of its greatest assets. The combination of the three factors permits assignment to three risk classes, i.e., low risk (LR), intermediate risk (IR), and high risk (HR) (see Table 74.2).

We have reviewed data on 814 patients with nonmetastatic kidney cancer (pN0/Nx M0), 158 of which had undergone nephron-sparing surgery, the remaining 656 had undergone nephrectomy. Average follow-up duration for all patients was 76 months (minimum 24 months). Relapses have occurred in 193 cases, corresponding to 24% of the total. According to UISS, 140 cases were LR, 420 IR, and 254 HR. Relapse rate in the follow-up for the three risk

A. Antonelli (✉) • C. Simeone • S.C. Cunico
Department of Urology, University of Brescia, Spedali Civili Hospital, Piazzale Spedali Civili 1, Brescia 25123, Italy
e-mail: alxanto@hotmail.com

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Table 74.1 Prognostic systems

TNM 1997		
pT1	Tumor <= 7 cm in the greatest dimension, limited to the kidney	
pT2	Tumor >7 cm in the greatest dimension, limited to the kidney	
pT3	Tumor extends into major veins or directly invades the adrenal gland or perinephric fat tissues but not beyond the Gerota's fascia	
pT4	Tumor directly invades beyond Gerota's fascia	
Fuhrman's grading		
G1	Tumor cells with small (~10 μm) round uniform nuclei without nucleoli	
G2	Tumor cells with larger nuclei (~15 μm) with irregularities in outline nucleoli when examined under high power (400)	
G3	Tumor cells with even larger nuclei (~20 μm) with obviously irregular outline prominent larger nucleoli even at low power (100)	
G4	Tumor cells with bizarre, multilobed nuclei heavy clumps of chromatin	
ECOG score		
0	Fully active, able to carry on all predisease performance without restriction	
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work	
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours	
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	

Table 74.2 UISS definitions

UISS risk class	pT	G	ECOG
Low risk	1	1–2	0
Intermediate risk	1	1–2	>0
	1	3–4	Any
	2	Any	Any
	3	1	Any
	3	>1	0
High risk	3	>1	>0
	4	Any	Any

Table 74.3 Site of relapse

	latency (months)	All patients (%)	LR (%)	IR (%)	HR (%)
Operated kidney	23.4	4.1	11.6	5.4	0
Contralateral kidney	71.8	10.9	30.1	10.1	4.0
Local recurrence	26.4	11.9	3.9	7.6	20.0
Distant metastasis	29.5	73.0	53.8	76.1	76.0
Abdomen	32.8	15.6	7.2	17.1	15.8
Chest	29.5	48.3	35.7	50.0	49.1
Bone	14.9	11.3	21.4	12.9	7.0
Others	41.4	9.9	21.4	8.6	8.8
Multiple sites	24.1	14.9	14.3	11.4	19.3

Recurrence sites and time, as a percentage of asymptomatic patients, and the distribution of different types of recurrence in UISS risk groups (LR low risk, IR intermediate risk, HR high risk; the sum of percentages of each site of distant metastasis is 100%)

classes was 10, 22, and 54%, respectively, with an average latency after surgery of 54, 36, and 30 months, respectively. The most common type of relapse was distant metastasis (73%), followed by local relapse (12%) and by the appearance of a new kidney neoplasm in the contralateral kidney (11%) or in the remaining kidney after nephron-sparing surgery (4%). Table 74.3 shows the distribution of relapses, with onset times, in the different UISS risk classes. It is easy to note that the risk of relapse via a new renal neoplasm decreases gradually over time among the three risk classes (LR, IR, and HR) while the chance of local relapse or distant metastasis increases from LR to IR to HR class. From a biological point of view relapses in the kidney deserve to be viewed and dealt with differently from distant metastases or local relapses. Indeed, the development of a neoplasm in the kidney undergoing nephron-sparing surgery may be explained by the presence of unrecognized multifocal disease or by the lack of adequate surgical margins while a neoplasm in the contralateral kidney can be considered a new primary cancer. Patients with a relapse in the contralateral kidney, in the ipsilateral kidney after nephron-sparing surgery, with distant metastasis, and local recurrence have a 12-month survival rate after diagnosis of 96, 86, 70, and 44%, respectively. Figures 74.1 and 74.2 show the time distribution of the three risk classes of relapses in the chest and in the abdomen, including abdominal metastases, local relapses, and kidney relapses. Disease relapse in LR patients in the first 5 years of follow-up occurs chiefly at abdominal level, while the risk of lung recurrence is less serious. On the other hand, IR patients in the first 5 years after surgery have a higher risk of relapse in the lung, especially in the first 24–36 months, while risk of relapse in the abdomen is lower; the same happens, albeit at a significantly lower rate, for the subsequent 5 years. HR patients, during the earliest years of follow-up, show a high risk of relapse in the abdomen and a lower risk of lung metastasis. This risk, though still significant, decreases in the subsequent 5 years. All risk classes, after 10 years of follow-up, feature only rare relapses, chiefly in the abdominal area and in the contralateral kidney. As regards the imaging methods to be used for monitoring the chest and abdomen, from a cost/benefit point of view, it is preferable

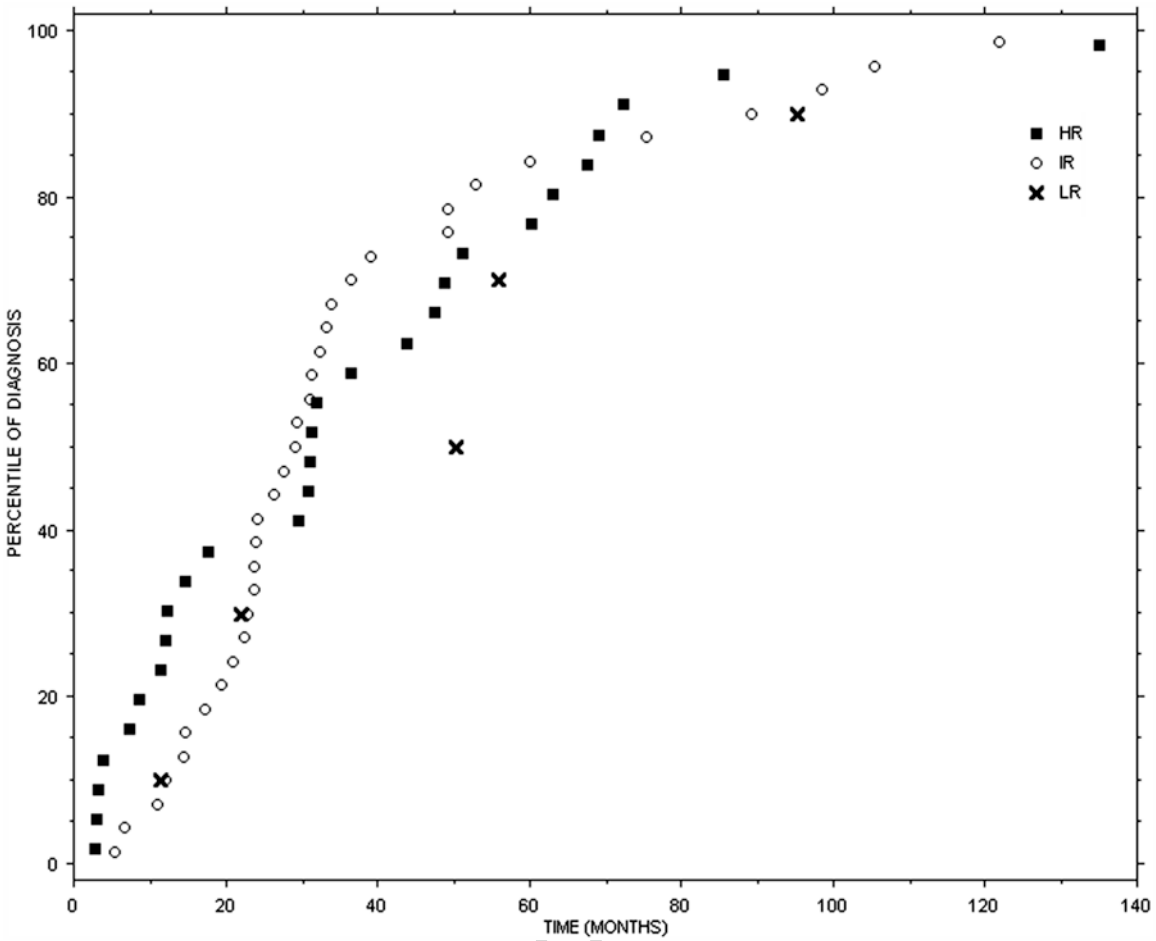

Fig. 74.1 Time distribution of thoracic relapses (LR low risk, IR intermediate risk, HR high risk; marks represent the events of recurrence as percentiles on overall recurrences in each specific site; zero point is the time of treatment of primary tumor)

to use cheaper and safer (for the patient) techniques like abdominal ultrasonography and chest radiography for lower-risk patients, using CT only for higher-risk patients. The risk of bone metastases is limited. It is higher in the time period closer to the surgery and it also pertains chiefly to HR cases. In light of these data, we think it is possible to offer different surveillance plans, depending on risk classes, as shown in Tables 74.4, 74.5, 74.6.

There is no significant difference in risk and relapse mode between patients subjected to nephrectomy and those subjected to nephron-sparing surgery. There is consequently no need to modify surveillance according to this factor.

One factor not included in the UISS but, in our opinion, worthy of consideration is the tumor histological subtype. Currently, according to the classification drafted in the Heidelberg and Rochester consensus conferences, there are four main histological subtype of kidney carcinoma: clear cell (80% of cases), papillary (in turn divided in type 1 and type 2), chromophobe, and collecting duct [9]. Although the independent prognostic role of the histotype has not been clearly demonstrated, it is quite evident that patients suffering with chromophobe and type 1 papillary renal cell carcinomas usually have a highly favorable prognosis, whereas patients with collecting duct carcinoma have an extremely unfavorable prognosis and the prognosis of patients with type 2 papillary carcinoma or conventional renal cell carcinoma is somewhere in between the extremes [10, 11]. Consequently, we propose to manage follow-up of patients with favorable histotype (chromophobe and type 1 papillary renal cell carcinoma) with the plan proposed for LR class patients and to apply the HR follow-up plan for patients with the unfavorable histotype (collecting duct carcinoma). The follow-up of patients with type 2 papillary carcinoma can be decided by stratification with the UISS.

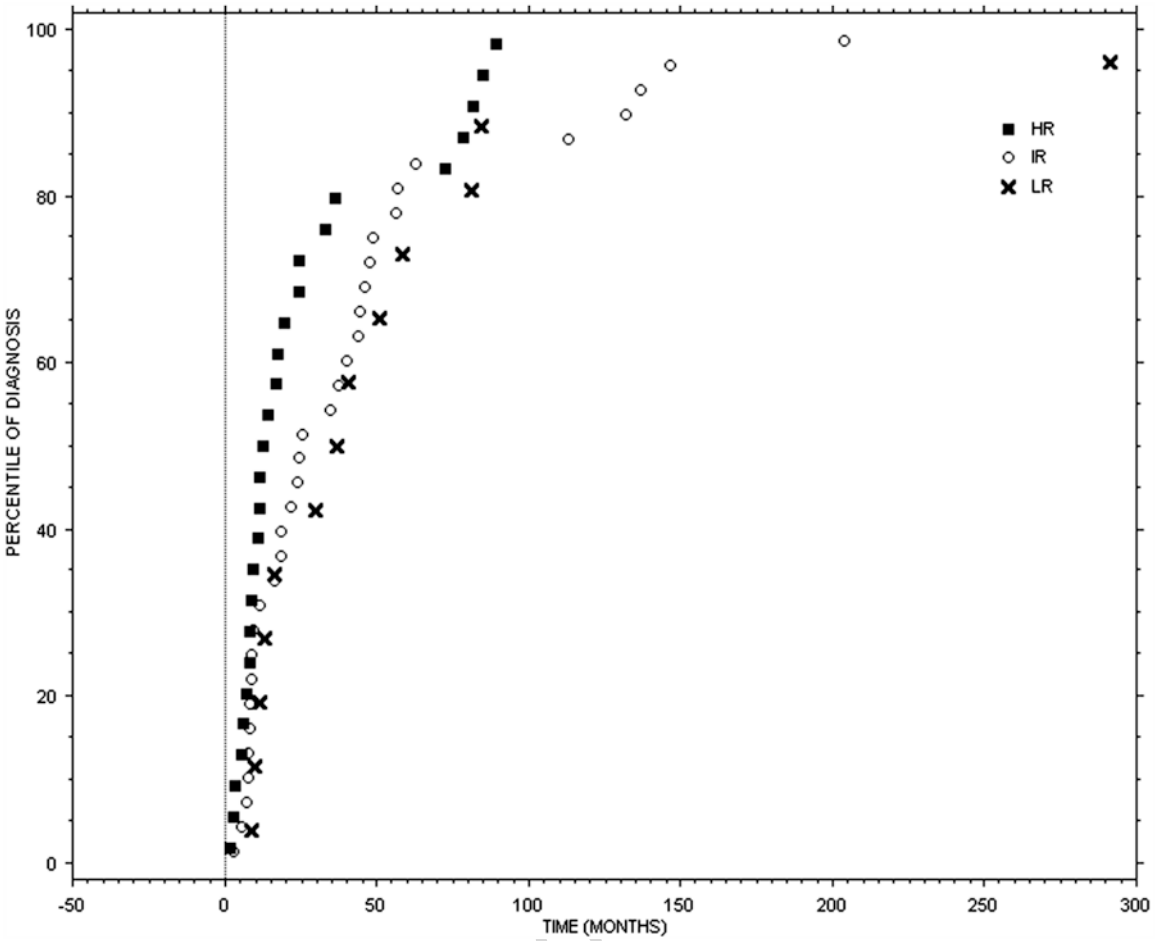

Fig. 74.2 Time distribution of abdominal relapses (LR low risk, IR intermediate risk, HR high risk; marks represent the events of recurrence as percentiles on overall recurrences in each specific site; zero point is the time of treatment of primary tumor)

t4.1 **Table 74.4** Surveillance after curative-intent treatment for renal cancer for LR patients at Spedali Civili Hospital

	years posttreatment						
	1	2	3	4	5	5–10	>10
Chest X-ray	0	1	0	1	0	0	0
Abdomen US	1	1	1	1	1	2	1
Abdomen CT	0	0	0	0	0	0	0
Chest CT	0	0	0	0	0	0	0
Bone scan	0	0	0	0	0	0	0

The number in each cell is the number of times a particular examination is recommended in a particular posttreatment year (LR, low risk)

t5.1 **Table 74.5** Surveillance after curative-intent treatment for renal cancer for IR patients at Spedali Civili Hospital

	years posttreatment						
	1	2	3	4	5	5–10	>10
Chest X-ray	1	1	2	1	1	5	0
Abdomen US	1	1	2	1	1	5	1
Abdomen CT	1	1	0	0	0	0	0
Chest CT	1	1	0	0	0	0	0
Bone scan	0	0	0	0	0	0	0

The number in each cell is the number of times a particular examination is recommended in a particular posttreatment year (IR intermediate risk)

t6.1 **Table 74.6** Surveillance after curative-intent treatment for renal cancer for HR patients at Spedali Civili Hospital

	years posttreatment						
	1	2	3	4	5	5–10	>10
Chest X-ray	0	1	1	2	2	5	0
Abdomen US	0	1	1	2	2	5	1
Abdomen CT	2	1	1	0	0	0	0
Chest CT	2	1	1	0	0	0	0
Bone scan	0	1	0	0	0	0	0

The number in each cell is the number of times a particular examination is recommended in a particular posttreatment year (HR high risk)

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