

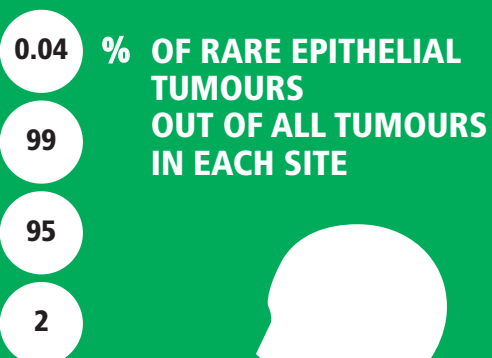
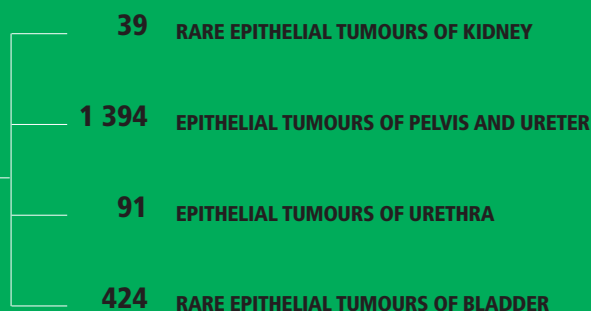
# RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM

**6%**  
OF THE URINARY SYSTEM TUMOURS ARE RARE EPITHELIAL TUMOURS

## INCIDENCE

**1 948**

ESTIMATED NEW CASES  
ITALY, 2015

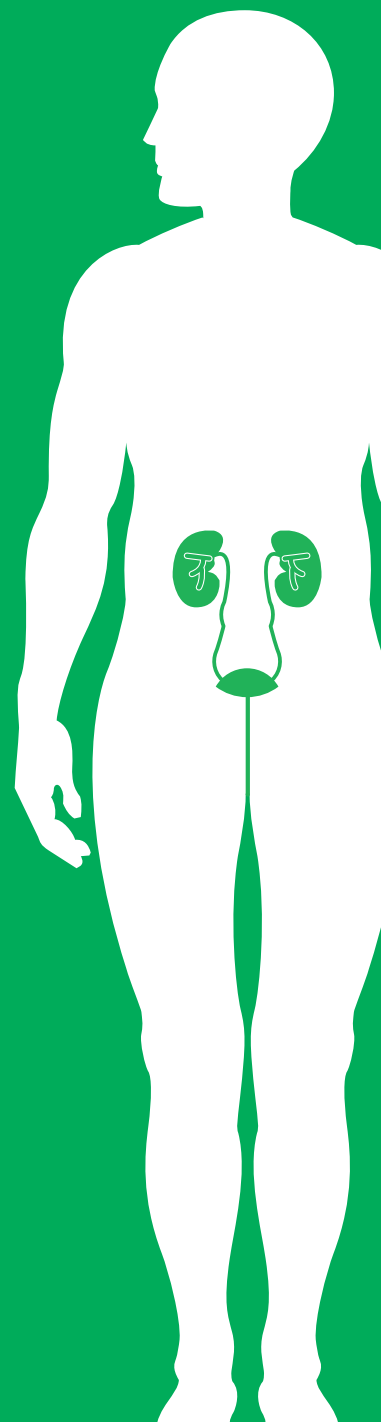
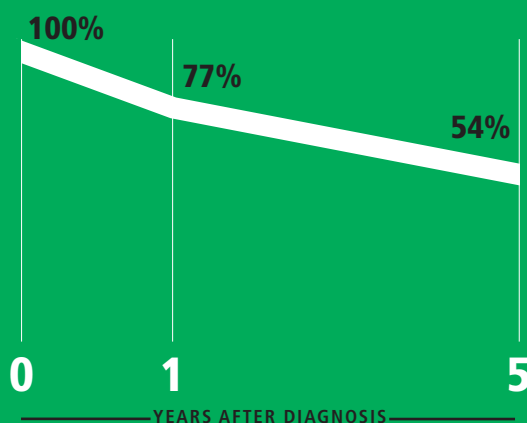


## PREVALENCE

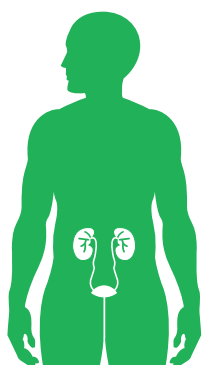
**13 254**

ESTIMATED PREVALENT CASES  
ITALY, 2010

## SURVIVAL



# INCIDENCE



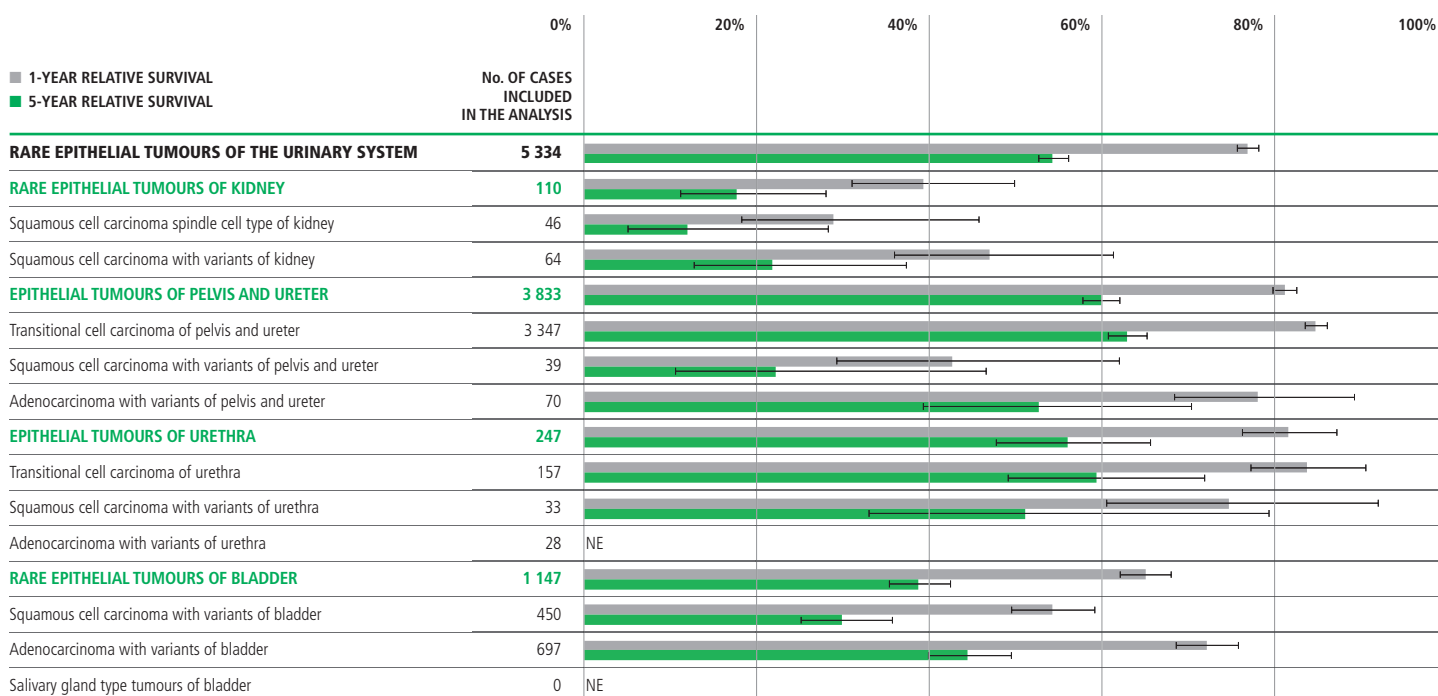
**RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

	AIRTUM POOL (period of diagnosis 2000-2010)														ITALY ESTIMATED NEW CASES 2015
	RATE	95% CI	OBSERVED CASES (No.)	RARE EPITHELIAL CANCERS BY SITE (%)	SEX				AGE						
					MALE		FEMALE		0-54 yrs		55-64 yrs		65+ yrs		
					RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	
<b>RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM</b>	<b>2.88</b>	<b>2.81-2.95</b>	<b>6 394</b>	<b>6%</b>	<b>4.17</b>	<b>4.05-4.29</b>	<b>1.68</b>	<b>1.60-1.75</b>	<b>0.34</b>	<b>0.31-0.37</b>	<b>4.09</b>	<b>3.86-4.34</b>	<b>10.84</b>	<b>10.54-11.15</b>	<b>1 948</b>
<b>RARE EPITHELIAL TUMOURS OF KIDNEY</b>	<b>0.06</b>	<b>0.05-0.07</b>	<b>132</b>	<b>0.04%</b>	<b>0.09</b>	<b>0.07-0.11</b>	<b>0.03</b>	<b>0.02-0.04</b>	<b>0.02</b>	<b>0.01-0.02</b>	<b>0.10</b>	<b>0.07-0.15</b>	<b>0.18</b>	<b>0.14-0.23</b>	<b>39</b>
Squamous cell carcinoma spindle cell type of kidney	0.02	0.02-0.03	50		0.03	0.02-0.05	0.01	0.01-0.02	<0.01	0.00-0.01	0.04	0.02-0.08	0.06	0.04-0.09	15
Squamous cell carcinoma with variants of kidney	0.04	0.03-0.05	82		0.06	0.04-0.07	0.02	0.01-0.03	<0.01	0.00-0.01	0.06	0.03-0.10	0.12	0.09-0.16	25
<b>EPITHELIAL TUMOURS OF PELVIS AND URETER</b>	<b>2.07</b>	<b>2.01-2.14</b>	<b>4 600</b>	<b>99%</b>	<b>2.94</b>	<b>2.84-3.05</b>	<b>1.26</b>	<b>1.20-1.33</b>	<b>0.22</b>	<b>0.20-0.25</b>	<b>3.00</b>	<b>2.80-3.21</b>	<b>7.84</b>	<b>7.58-8.10</b>	<b>1 394</b>
Transitional cell carcinoma of pelvis and ureter	1.80	1.74-1.86	3 989		2.57	2.47-2.66	1.08	1.02-1.14	0.19	0.17-0.22	2.67	2.48-2.88	6.75	6.51-7.00	1 200
Squamous cell carcinoma with variants of pelvis and ureter	0.02	0.02-0.03	50		0.02	0.02-0.03	0.02	0.01-0.03	<0.01	0.00-0.01	0.02	0.01-0.05	0.09	0.07-0.13	15
Adenocarcinoma with variants of pelvis and ureter	0.04	0.03-0.05	83		0.06	0.04-0.07	0.02	0.01-0.03	<0.01	0.00-0.01	0.08	0.05-0.12	0.12	0.09-0.16	25
<b>EPITHELIAL TUMOURS OF URETHRA</b>	<b>0.13</b>	<b>0.12-0.15</b>	<b>292</b>	<b>95%</b>	<b>0.21</b>	<b>0.18-0.24</b>	<b>0.06</b>	<b>0.04-0.07</b>	<b>0.03</b>	<b>0.02-0.04</b>	<b>0.14</b>	<b>0.10-0.20</b>	<b>0.48</b>	<b>0.42-0.55</b>	<b>91</b>
Transitional cell carcinoma of urethra	0.08	0.07-0.10	183		0.15	0.12-0.17	0.02	0.02-0.03	0.01	0.01-0.02	0.08	0.05-0.12	0.32	0.27-0.38	57
Squamous cell carcinoma with variants of urethra	0.02	0.01-0.02	40		0.03	0.02-0.04	<0.01	0.00-0.02	<0.01	0.00-0.01	0.03	0.01-0.05	0.06	0.04-0.08	12
Adenocarcinoma with variants of urethra	0.01	0.01-0.02	33		0.02	0.01-0.03	0.01	0.01-0.02	<0.01	0.00-0.01	0.04	0.02-0.07	0.03	0.02-0.06	10
<b>RARE EPITHELIAL TUMOURS OF BLADDER</b>	<b>0.62</b>	<b>0.59-0.65</b>	<b>1 370</b>	<b>2%</b>	<b>0.93</b>	<b>0.87-0.99</b>	<b>0.33</b>	<b>0.29-0.36</b>	<b>0.07</b>	<b>0.06-0.09</b>	<b>0.85</b>	<b>0.74-0.96</b>	<b>2.34</b>	<b>2.20-2.49</b>	<b>424</b>
Squamous cell carcinoma with variants of bladder	0.24	0.22-0.26	537		0.32	0.29-0.36	0.17	0.14-0.19	0.03	0.03-0.05	0.30	0.24-0.37	0.92	0.83-1.01	168
Adenocarcinoma with variants of bladder	0.38	0.35-0.40	833		0.61	0.56-0.65	0.16	0.14-0.19	0.04	0.03-0.05	0.55	0.46-0.64	1.42	1.31-1.54	256
Salivary gland type tumours of bladder	0.00	-	0		NE	-	NE	-	NE	-	NE	-	NE	-	NE

NE: not estimable because 15 or less incident cases were observed

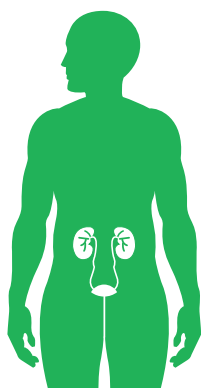
# SURVIVAL

**RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.



NE: not estimable because 30 or less incident cases were observed

# PREVALENCE



**RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration ( $\leq 2$ , 2-5,  $\leq 15$  years) prior to prevalence date (1<sup>st</sup> January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

	AIRTUM POOL								ITALY
	OBSERVED PREVALENCE BY DURATION						COMPLETE PREVALENCE		ESTIMATED PREVALENT CASES 2010
	$\leq 2$ YEARS		2-5 YEARS		$\leq 15$ YEARS		PROPORTION	95% CI	
	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI			
<b>RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM</b>	<b>4.90</b>	<b>4.45-5.39</b>	<b>4.47</b>	<b>4.04-4.94</b>	<b>17.55</b>	<b>16.68-18.45</b>	<b>22.90</b>	<b>21.74-24.06</b>	
<b>RARE EPITHELIAL TUMOURS OF KIDNEY</b>	<b>0.06</b>	<b>0.02-0.13</b>	<b>0.01</b>	<b>0.00-0.06</b>	<b>0.14</b>	<b>0.07-0.25</b>	<b>0.16</b>	<b>0.07-0.25</b>	<b>97</b>
Squamous cell carcinoma spindle cell type of kidney	0.03	0.01-0.10	0.01	0.00-0.06	0.08	0.03-0.17	0.10	0.03-0.17	60
Squamous cell carcinoma with variants of kidney	0.02	0.00-0.08	NE	–	0.06	0.02-0.14	0.06	0.01-0.12	37
<b>EPITHELIAL TUMOURS OF PELVIS AND URETER</b>	<b>3.86</b>	<b>3.46-4.29</b>	<b>3.61</b>	<b>3.22-4.03</b>	<b>14.11</b>	<b>13.33-14.92</b>	<b>18.23</b>	<b>17.20-19.27</b>	<b>10 533</b>
Transitional cell carcinoma of pelvis and ureter	3.39	3.01-3.80	3.38	3.00-3.79	12.95	12.20-13.73	16.64	15.66-17.63	9 599
Squamous cell carcinoma with variants of pelvis and ureter	0.05	0.01-0.12	NE	–	0.06	0.02-0.13	0.07	0.01-0.14	44
Adenocarcinoma with variants of pelvis and ureter	0.14	0.07-0.24	0.05	0.01-0.12	0.28	0.18-0.41	0.31	0.19-0.44	181
<b>EPITHELIAL TUMOURS OF URETHRA</b>	<b>0.31</b>	<b>0.20-0.45</b>	<b>0.15</b>	<b>0.08-0.26</b>	<b>0.80</b>	<b>0.63-1.02</b>	<b>1.03</b>	<b>0.78-1.27</b>	<b>600</b>
Transitional cell carcinoma of urethra	0.22	0.13-0.34	0.11	0.06-0.21	0.56	0.42-0.74	0.71	0.51-0.92	415
Squamous cell carcinoma with variants of urethra	0.06	0.02-0.13	0.02	0.00-0.08	0.13	0.06-0.23	0.15	0.06-0.23	84
Adenocarcinoma with variants of urethra	0.01	0.00-0.06	NE	–	0.03	0.01-0.10	0.04	0.00-0.08	23
<b>RARE EPITHELIAL TUMOURS OF BLADDER</b>	<b>0.67</b>	<b>0.51-0.87</b>	<b>0.70</b>	<b>0.54-0.90</b>	<b>2.52</b>	<b>2.19-2.87</b>	<b>3.48</b>	<b>3.01-3.95</b>	<b>2 025</b>
Squamous cell carcinoma with variants of bladder	0.24	0.15-0.37	0.30	0.20-0.44	0.80	0.62-1.01	1.11	0.84-1.37	640
Adenocarcinoma with variants of bladder	0.43	0.31-0.60	0.40	0.28-0.56	1.71	1.45-2.01	2.36	1.98-2.74	1 376
Salivary gland type tumours of bladder	NE	–	NE	–	NE	–	0.01	0.00-0.04	0

NE: not estimable in observed prevalence if no cases were observed within  $\leq 2$ , 2-5,  $\leq 15$  years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

This group includes the following tumours of the urinary system:

- **rare epithelial tumours of kidney** (squamous cell carcinoma, adenocarcinoma, and spindle cell type squamous cell carcinoma);
- **epithelial tumours of pelvis and ureter** (squamous cell carcinoma, adenocarcinoma and transitional cell carcinoma);
- **epithelial tumours of urethra** (squamous cell carcinoma and adenocarcinoma and transitional cell carcinoma);
- **rare epithelial tumours of bladder** (squamous cell carcinoma, adenocarcinoma, and salivary gland type tumours).

These tumours are usually well defined in terms of morphology, because they are diagnosed by imaging (cystoscopy, urography, or a computerised tomography scan for the kidney) and histopathological examination.

## WHAT DO WE KNOW ABOUT THESE CANCERS?

**Squamous-cell carcinoma** originates from squamous cells. These cells are typical of the epidermis of the skin, but can be found in different body sites for which symptoms at diagnosis, natural history, prognosis, and response to treatment can be extremely heterogeneous.<sup>1</sup> **Adenocarcinoma** is an undifferentiated and consequently malignant cancer of the epithelial tissue, which originates from the glandular epithelium.<sup>2</sup> It includes different histological types: tubulovillous, papillary, mucinous, and non-intestinal. The tubulovillous and mucinous variants are the most frequent and account for over 90% of cases.<sup>3</sup> **Transitional cell carcinoma** (also urothelial cell carcinoma) originates from the urothelium (layer of cells that lines the walls of the urinary tract: renal calices and pelvis, ureter, bladder, proximal urethra).<sup>1</sup> It can be diagnosed in the lower urinary tract (bladder and urethra) or in the upper urinary tract (renal calices, renal pelvis, and ureter). Upper tract urothelial carcinoma (UTUC) is rare and accounts for only 5%-10% of urothelial cancer. The estimated annual incidence of UTUC in Western countries is about two new cases per 100,000 inhabitants.<sup>2</sup> Cancers of the renal pelvis are about two times more common than ureteral tumours.<sup>4</sup> **Spindle cell tumours** of the kidney include a wide range of unrelated neoplasms with overlapping morphologic features and different prognostic/therapeutic implications. Diagnosis is supported mainly by the application of ancillary techniques, such as immunohistochemistry (IH) and in-situ hybridization (FISH). An accurate diagnosis is essential because early management by complete resection and adjuvant chemotherapy improves prognosis dramatically.<sup>5</sup> Tobacco and occupational exposure to certain aromatic amines<sup>2</sup> remain the principal exogenous risk factors for the development of transitional cell carcinomas. For urethral cancers, various predisposing factors have been reported, including urethral strictures, chronic irritation after intermittent catheterisation/urethroplasty, external beam irradiation therapy, radioactive seed implantation, and chronic urethral inflammation/urethritis following sexually transmitted diseases.<sup>6</sup> In female patients, urethral diverticula and recurrent urinary tract infections have been associated with primary carcinoma.<sup>7</sup> For the renal pelvis and ureter, use of laxatives and analgesics are recognised risk factors.<sup>8</sup>

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

All rare epithelial tumours of the urinary system (kidney, renal pelvis, ureter, urethra, and bladder) are more common in males

than females and are typical of the older age groups. The most common rare epithelial tumours of the urinary system are those of the renal pelvis and ureter (72%), followed by rare epithelial tumours of the bladder (21%), urethra (5%), and kidney (2%).

All cancers of the renal pelvis and ureter are rare and the most frequent morphology is transitional cell carcinoma (87%). The other two morphologies are squamous cell carcinoma and adenocarcinoma (1 and 1.8%, respectively). In the bladder, rare epithelial tumours represent only 2% of all bladder tumours and adenocarcinoma is the most frequent morphology (61%). In the AIRTUM database, no cases of salivary gland type cancers of the bladder were observed in Italy in the years 2000-2010; in the European RARECAREnet database ([www.rarecarenet.eu](http://www.rarecarenet.eu)) 7 cases were observed in Europe in the period 2000-2008, confirming the rarity of this entity. All cancers of the urethra are rare and the most frequent morphology is transitional cell carcinoma (63%), followed by squamous cell carcinoma (14%) and adenocarcinoma (11%). The latter two have a very similar incident rate. Finally, rare epithelial tumours of the kidney (squamous cell carcinomas and spindle cell carcinomas) are the rarest of urinary system cancers and represent only 0.4% of all tumours of the kidney. All these tumours, in each site, are more common in males than females and have a peak of incidence in the 70-79-year age groups (data not shown). Epithelial tumours of the urethra show the highest male to female ratio, probably because of the longer length of the male urethra (15-20 cm versus 3-4 cm in females). The male to female ratio of cancer of the renal pelvis and ureter is 2.3 in this study and much lower than for bladder cancer in European data from Globocan (M/F: 4.7).<sup>8</sup> This different male to female ratio suggests a different importance of the various aetiological factors. Smoking is the most important factor for bladder cancer. Although smoking is also a risk factor for cancer of the renal pelvis and ureter, long-term use of analgesics and laxatives, which is a strong risk factor for cancer of the renal pelvis and ureter and which is probably as widespread among females as among males, reduces the male to female ratio.<sup>9</sup> The incidence results described are in line with those observed in Europe in the RARECAREnet database. The incidence of epithelial tumours of the renal pelvis and ureter is slightly higher in Italy than in Europe (2.07 vs. 1.58), but the morphological distribution is the same in the two databases. It is worth mentioning that for cancer of the renal pelvis, ureter or urethra, comparison with other registries outside Italy may be biased by differences in registration and classification practices. In the 9<sup>th</sup> edition of the International Classification of Diseases and the 1<sup>st</sup> edition of the International Classification of Diseases for Oncology, these cancers are grouped together with kidney cancer and many registries still report these cancers combined. Approximately 2,000 cases of rare epithelial tumours of the urinary tract are estimated to be diagnosed in Italy in 2015: 1,394 epithelial tumours of the renal pelvis and ureter, 424 rare epithelial tumours of the bladder, 91 epithelial tumours of the urethra, and only 39 cases of rare epithelial tumours of the kidney.

### Survival

One- and 5-year relative survival (RS) of rare epithelial tumours of the urinary system is 77% and 54%, respectively. Epithelial tumours of the renal pelvis and ureter and epithelial tumours of the urethra are those with the highest RS: 81% after 1

year and 60% (renal pelvis and ureter) and 56% (urethra) after 5 years from diagnosis. Transitional carcinomas are those with the highest RS at 1 and 5 years after diagnosis, followed by adenocarcinoma and squamous cell carcinoma. The RS of rare epithelial tumours of the bladder is the third highest survival rate among urinary system cancers (65% and 39% at 1 and 5 years after diagnosis, respectively), with adenocarcinoma having higher survival than squamous cell carcinoma. Finally, survival of rare epithelial tumours of the kidney is 39% after 1 year and falls to 18% after 5 years from diagnosis. In the kidney, squamous cell carcinoma has higher survival than spindle cell carcinoma.

In Italy, the RS of these tumours is slightly higher than that observed in Europe in the RARECAREnet database. Regarding the survival differences between transitional, squamous cell carcinoma, and adenocarcinoma observed in Italy and in Europe (RARECAREnet database), several studies have pointed out that the stage distribution of squamous cell carcinoma and adenocarcinoma of the renal pelvis and ureter is relatively unfavourable in comparison to transitional cell carcinoma, with consequent poor survival.<sup>10</sup> However, the reason for this unfavourable stage distribution is unclear. Possibly, transitional cell carcinoma causes bleeding at an earlier stage and therefore is discovered earlier.

Considering that roughly half of the patients with these cancers do not survive their illness and that these are very rare cancers, as already suggested at European level, centralisation of treatment to a select number of specialist centres should be promoted.<sup>10</sup>

## Prevalence

Over 13,000 persons were estimated to be living with a diagnosis of rare epithelial cancers of the urinary system in Italy in 2010; 23% of these cases were diagnosed 15 years or more from prevalence date. Most prevalent cases are represented by patients with a previous di-

agnosis of transitional cell carcinoma of the renal pelvis and ureter. Surgery remains the mainstay treatment for renal pelvis and ureter cancer. Conservative surgery of the urethra is technically demanding and, when indicated, requires highly specialised surgeons. Centres that display a high surgical volume of treatment for renal, ureteral, and retroperitoneal tumours and that involve a multidisciplinary team in the decisional process should be contacted for primary care, or at least for a second opinion prior to undergoing treatment. At any rate, as cancer registries come to collect more information on stage and treatment and place of treatment, evaluation of this recommendation should become a priority.

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